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Choline-stabilized orthosilicic acid, applications of an oral supplement in dermatology


Maria Rosa Gaviglio


Mario Remi Calomme

Maria Rosa Gaviglio, Mario Remi Calomme

SUMMARY

Several clinical trials have investigated the use of choline-stabilized orthosilicic acid as an oral supplement to improve the quality of skin, hair and nails. This specific complex of orthosilicic acid and choline was shown to stimulate collagen synthesis and protect the collagen network in connective tissue. Women with photoaged skin, who took choline-stabilized orthosilicic acid were found to have improved skin microrelief and elasticity. But also, nail brittleness and tensile properties of hair have been shown to improve after the use of choline-stabilized orthosilicic acid. Other benefits of choline-stabilized orthosilicic acid have been reported in clinical trials that are related to bone, joint and gum health.

KEYWORDS
collagen, choline-stabilized orthosilicic acid, aging, skin, hair, nails, bone, joints, gum.

Maria Rosa Gaviglio
Studio Dermatologico Gaviglio
20121 Milan ITALY

Mario Remi Calomme
Bio Minerals N.V.
Research & Development
B-9070 Destelbergen
BELGIUM

INTRODUCTION

Choline-stabilized orthosilicic acid (tradename ch-OSA®) is a specific complex of choline with orthosilicic acid which is used in dietary supplements. The health benefits of ch-OSA® have been documented in clinical trials and are supported by animal studies.

These studies show that the ch-OSA® complex activates biological pathways that generate and protect collagen. Collagen is a fibrous protein, essential for the structural integrity and biomechanical properties of connective tissue and is present in high amounts in skin, bone, and joints. Starting at age 21, collagen in skin decreases linearly with 1% per year (1) resulting in a decline of skin thickness and elasticity (2).

Post-menopausal changes are even more dramatic with a loss of 30% skin collagen in the first 5 years (3) and an annual decline in skin elasticity of 0.55% (4).

Elasticity is correlated with the depth of wrinkles, suggesting that the formation of wrinkles primarily results from the loss of elasticity (5). Importantly, the postmenopausal decrease in skin collagen correlates with the age-related decrease in bone mineral density (6).

The present article discusses the potential use of ch-OSA® as an oral supplement in dermatology, its mechanisms of action and other health benefits outside the field of dermatology.

Application of ch-OSA® in dermatology

Several clinical studies report positive anti-aging effects of ch-OSA® on skin, hair and nails when administered as an oral supplement **(table 1).**

Skin

A clinical trial was undertaken by the University of Brussels in Belgium (7) to evaluate the effect of ch-OSA® on photo-aged skin. Photo-aging is the result of chronic exposure to ultraviolet radiation (e.g., sun, sunbeds) superimposed on chronobiological (intrinsic) ageing. Photo-aged skin is characterized by major changes in the dermis i.e., a marked decrease in collagen, glycosaminoglycans and proteoglycans combined with a degeneration of elastic fibers (elastosis) resulting in a rough leathery skin surface with many fine and coarse wrinkles. Typically, decreased elasticity is found in photo-aged skin because of the degraded mesh of collagen and elastin fibers in the dermis. Over time these changes also occur in normal, chronobiogical ageing, therefore photo-aging is a valuable model to study anti-aging products. In the clinical trial, fifty healthy women, aged between 40 and 65 years, with clear signs of photo-aging were randomized in a ch-OSA® and a placebo group. Participants were instructed not to change their daily dietary and cosmetic regimen during the study. In addition, any dermatological or anti-aging therapy was prohibited.

Non-invasive, validated methods were used to evaluate skin roughness with skin replicas (Visiometer, Courage-Khazaka, Germany) and skin elasticity by measuring mechanical anisotropy (Reviscometer, Courage-Khazaka, Germany). Quantifying skin microrelief is a standard method to measure the depth of fine lines and wrinkles and include typical parameters such as maximum roughness (Rm) i.e., the depth of the main wrinkle (8).

Mechanical anisotropy of skin is an indirect parameter of skin elasticity (9). The participants also scored the severity of hair and nail brittleness on a 4-point numeric scale. After 20 weeks, the depth of the main wrinkle improved significantly in the ch-OSA® group by 19% but continued to decline in the placebo group by 11%, resulting in an overall improvement of 30% **(figure 1a).** Skin microrelief in young skin is characterized by a multi-directional pattern of lines. When skin ages, the lines become both deeper and more oriented in a dominant, single direction (8). These changes in microrelief reflect the ongoing deterioration with age of the underlying collagen framework in the dermis. Women who took ch-OSA® were found to have after 20 weeks a more multidirectional pattern of skin lines compared to the start of the study (baseline), resembling "younger" skin because of a denser collagen framework in the dermis **(figure 2).**

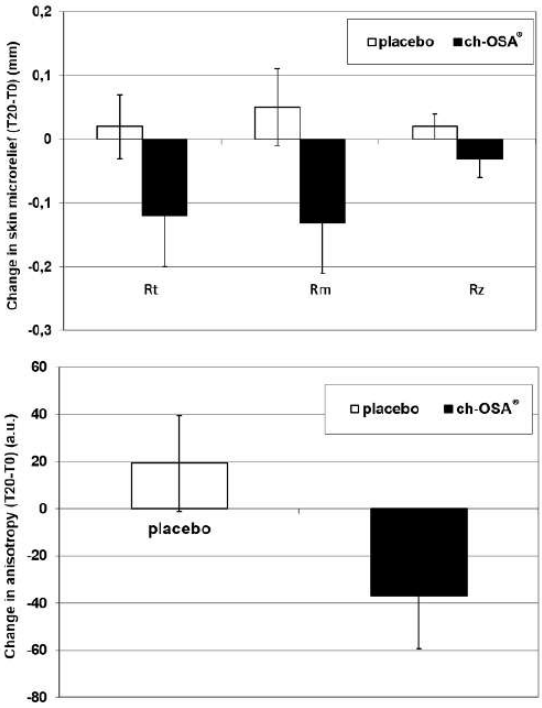
Skin elasticity, measured as mechanical amiso-tropy, increased significantly in the ch-OSA® group compared to the placebo group i.e., 89% improvement was observed in the ch-OSA® group over placebo **(figure 1b).**

The investigators explained the reduction in fine lines and the improvement in skin elasticity as a regeneration or de novo synthesis of collagen fibers i.e., the activation of collagen pathways by ch-OSA® resulting in a denser collagen framework in the dermis and better skin quality. Supporting evidence is found in an animal study from the University of Antwerp, Belgium (10). Young animals were given ch-OSA® or a placebo in their diet and randomly chosen skin biopsies were analyzed for the hydroxyproline content.

Hydroxyproline is a specific component of collagen i.e., it can be used as a marker of collagen content.

A significant 12.5% higher hydroxyproline content was found in skin of animals on the ch-OSA® diet compared to skin of placebo controls.

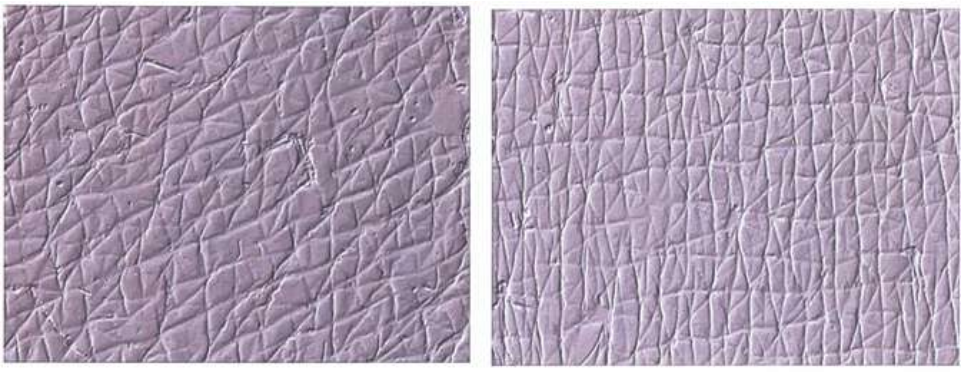
Figure 1
The effect of ch-OSA®, an oral supplement, on skin microrelief and skin elasticity in women with photoaged skin (7).



1 A
Change in depth of roughness (Rt, -24% vs. placebo), maximum roughness (Rm, -30% vs. placebo), and mean depth of roughness (Rz, -12% vs. placebo) after 20 weeks supplementation (mean values ± SE are shown).

1 B
Change in mechanical skin anisotropy, an indirect measurement of elasticity, after 20 weeks supplementation (-89% vs. placebo). Improvement in skin elasticity is observed as a decrease in anisotropy.
(Mean values ± SE are shown, T0: baseline, T20: after 20 weeks) (SE: standard error)

Figure 2
Skin microrelief of a patient with photoaged skin, at baseline (left) and after 20 weeks supplementation with ch-OSA® (right): a more multidirectional pattern of shallow lines resembling younger skin is observed after 20 weeks compared to placebo because of a denser collagen network in the dermis (7).



Additionally, physiological concentrations of orthosilicic acid were also reported to stimulate the synthesis of collagen type I in human skin fibroblast cell cultures (11).

In an open label, single arm study which was conducted in India, women with photodamaged skin (12) took ch-OSA® for 5 months. The patients were followed up for additional 3 months. Compared to baseline, skin hydration improved significantly already after 2 months, whereas both dyschromia and skin roughness improved significantly after 5 months.

Nails

The study of Barel et al. (7) in women with photoaged facial skin, also investigated brittleness of nails. It was found that brittleness decreased significantly in the ch-OSA® group whereas no significant change was observed for women in the placebo group.

More recently, a team led by professor Piraccini, presented a study (13) on nail fragility.

Ten female patients aged 52-65 years (mean age: 59,2 y) took for 6 months ch-OSA®, and nail quality was evaluated by clinical pictures and a video-dermatoscope at baseline, and after 3- and 6- months study. Both the patients and the investigators rated the change in the quality of nails on a 4-point, numeric scale. At baseline all patients had rough nails, 70% had longitudinal ridges of the nail plate, and 30% had onychoschizia.

The investigators scored after 6 months study that 44% of the patients had completely normal nails, i.e., full recovery of the nail disorder, and in 56% of the patients the quality of the nails showed good improvement. In fact, the clinical pictures showed an improvement in roughness of the nail plate and onychoschizia in all patients, as well as an improvement in longitudinal ridges in 83% of the patients.

Dermatoscopic results, confirmed these findings as nail plate characteristics after 6 months study improved in all patients.

Evaluation by the patients indicated in 78% of the cases a full recovery and in 22% a slight improvement.

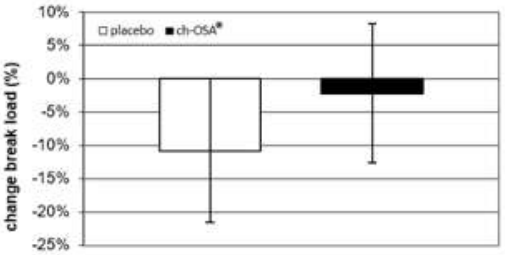
In a small open label study in India (12), 10 women between 40-65 years with brittle nails on both hands and feet took for 5 months ch-OSA® and were followed up for an additional 3 months. Nail roughness improved significantly after 2 months study, whereas the percentage of broken nails (baseline 53%) and discolored (yellow) nails (baseline 50%) completely normalized after 3 and 8 months of study respectively.

Hair

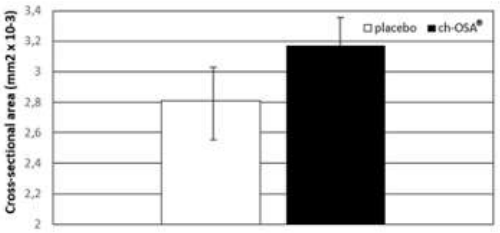
The effect of ch-OSA® on hair quality was investigated in a collaborative study led by Professor Randy Wickett of the University of Cincinnati and the Dr. Schrader Institute (Germany) (14). Forty-eight women aged between 18 and 65 years, with thin, fine hair were randomized in a ch-OSA® and a placebo group. Hair morphology and tensile properties were evaluated with validated methods. Investigated tensile properties included the elasticity of the hair (elastic gradient, elastic modulus) and the force needed to break hair fibers (break load, break stress). After 36 weeks the hair elasticity decreased significantly in the placebo group but remained unchanged in women who took ch-OSA®.

The break load was found 13.1% higher in women taking ch-OSA® compared to women in the placebo group. With respect to hair morphology, women who took for 36 weeks ch-OSA® had a 12.8% bigger cross-sectional area of hair fibers compared to women taking placebo. Several mechanisms of action were suggested by the investigators to explain these results. A direct interaction with keratin-associated proteins is possible considering that silanol groups in ch-OSA® form complexes with amino acids and peptides.

Figure 3
The effect of ch-OSA®, an oral supplement, on hair quality in women with fine, thin hair (14).



3 A Change in tensile strength measured as break load, after 36 weeks study remained stable in patients who took ch-OSA®, whereas a significant decrease was observed in the placebo group (net difference of 13.1% between groups).



3 B Hair morphology measured as the cross-sectional area, was found significantly higher in patients who took ch-OSA® compared to the placebo group (net difference of 12.8% between groups).(Mean values ± SD are shown, T0: baseline, T20: after 20 weeks) (SD: standard deviation)

Such an interaction could change the biomechanical properties of hair since keratin is the major constituent of hair. The increase in cross-sectional area suggests that ch-OSA® has a structural influence on keratin fibers or on the hair follicle. Since the hair follicle is embedded in a collagen rich matrix and serviced by collagen rich blood vessels, stimulation of collagen synthesis by ch-OSA® will improve the flow of nutrients to the hair follicle resulting in more keratin formation. While most of the hair structure arises from epidermal keratinocytes, a specialized population of fibroblasts called the dermal papilla controls hair growth and hair volume. Increased collagen synthesis by ch-OSA® in fibroblasts of the dermal papilla, will increase the volume of the dermal papilla resulting in a bigger cross-sectional area of the newly formed hair shaft.

These same factors could also explain the significative reduction of hair brittleness after 20 weeks measured by self report VAS scores.

An open label, pilot trial was done in the Philippines (15), to investigate the effect of ch-OSA® on abnormal hair loss. In total 19 patients were included between 17-54 years (10 men and 9 women). Eight patients with male pattern hair loss (stages 2-5) and 11 patients with alopecia (2 men, 9 women) took for 6 months ch-OSA®. Semi-quantitative rating scales and clinical pictures were used to evaluate the treatment. After 6 months study, the scores for hair regrowth and hair loss significantly improved.

The investigator observed an improvement in 89% of the patients of which in 28% a slight improvement, 55% moderate and in 5% of the patients a marked improvement. Most of the patients (95%) observed an improvement in hair loss, of which 33% a marked improvement.

Similar results were observed in another pilot trial in India (12). Nine alopecia patients between 17-54 years (5 men, 4 women) took for 5 months ch-OSA®, and the hair density measured with a non-invasive trichoscopic device (Medicam 1000,

FotoFinder Systems GmbH) improved significantly compared to baseline.
The study of Barel et al. (7) in women with photoaged facial skin, also investigated brittleness of hair. It was found that brittleness decreased significantly in the ch-OSA® group whereas no significant change was observed for women in the placebo group.
Interestingly, in a review article of the Memorial Sloan-Kettering Cancer Center on side effects by cancer treatments and nursing care (16), the dietary supplement Biosil® which contains ch-OSA® is recommended together with other supplements to help ameliorate nail changes and hair loss, during or after anticancer treatment. In dermatological practices similar recommendations have been made for the use of ch-OSA® in patients who experience nail brittleness and hair loss following or during anticancer treatment (17).

Health benefits of ch-OSA® outside the field of dermatology

The effect of ch-OSA® on other collagen-depending tissues such as bone, cartilage, and gums, has also been investigated in clinical trials **(table 2).**

Bone

The effect of the ch-OSA® on markers of bone turnover and bone mineral density was investigated in a clinical trial at the St Thomas Hospital in London (18). One hundred and eighty-four osteopenic and osteoporotic, but otherwise healthy women with a T-score at the lumbar spine of < -1.5 were randomized in ch-OSA® and placebo groups. All the subjects took 1000 mg calcium and 20 mcg cholecalciferol daily. Biochemical markers of bone formation and bone resorption were measured, and bone mineral density (BMD) was assessed by Dual-Energy X-Ray Absorptiometry.
Overall, there was a trend for ch-OSA® to have a positive effect on bone formation markers. In particular, the procollagen marker PINP (procollagen type I N-terminal propeptide) increased significantly after 12 months in women who took ch-OSA® compared to women in the placebo group. PINP is known as the most sensitive marker for bone collagen formation and an early marker of bone formation. Women on ch-OSA® who were osteopenic for both the lumbar spine and the hip were found to have a 2% higher BMD at the critical hip region compared to women in the placebo group. This difference in BMD was not only statistically significant but also clinically relevant since 1% differences with placebo is generally accepted as the threshold for clinical relevance. Supporting evidence that ch-OSA® promotes bone health can be found in two animal studies. In an animal model for postmenopausal osteoporosis (19) it was found that ch-OSA® increased the femoral BMD with 3 to 7% in ovariectomized animals with a high bone turnover. Ovariectomy causes estrogen deficiency comparable to what happens in postmenopausal women. This condition will dramatically increase bone resorption and result in bone loss. This animal study demonstrates that ch-OSA® helps to prevent post-menopausal bone loss. In another experiment, it was shown in young, developing birds that ch-OSA® increased femoral BMD by almost 6% and marginally improved the biomechanical properties of the femur (20).
The fact that ch-OSA® increases bone collagen formation means that it can help improve bone quality. In fact, the soft framework of bone collagen fibers is essential for bone flexibility and fixation of calcium phosphate in the bone. This combination of collagen and calcium makes bone both flexible and strong, which in turn helps bone to withstand stress (21).

Table 1
Dermatological applications of choline-stabilized orthosilicic acid (ch-OSA®), reported in clinical trials. ch-OSA® was administered as an oral supplement, i.e., twice daily one capsule containing 5 mg of silicon and 100 mg choline as ch-OSA® (Bio Minerals NV, Belgium).

	Author, study design	Study population	Observations
Skin	Barel et al. (7) Placebo-controlled, randomized, double-blind.	50 women with photoaged skin. (Age: 40-65 years)	Decreased roughness (-30% vs. placebo, and increased elasticity (+89% ch-OSA® group versus placebo group) after 20 weeks.
	Chandrashekar et al. (12) Open label, single-arm.	10 women with photodamaged skin. (Age: 40-65 years)	Improved hydration, dyschromia, and roughness (versus baseline) after 5 months.
Hair	Wickett et al. (14) Placebo-controlled, randomized, double-blind.	48 women with fine hair. (Age: 18-65 years)	Improved tensile strength (+13,1%, versus placebo) and increased hair cross-sectional area (+12,8% ch-OSA® group versus placebo group) after 36 weeks.
	Chan (15) Open label, single-arm.	8 patients with male pattern hair loss and 11 patients with alopecia. (2 men, 9 women) (Age: 17-54 years)	Improved hair re-growth and reduced hair loss (versus baseline) after 6 months.
	Chandrashekar et al. (12) Open label, single-arm.	9 alopecia patients (5 men, 4 women) (Age: 17-54 years)	Increased hair density (versus baseline) after 5 months.
Nails	Barel et al. (7) Placebo-controlled, randomized, double-blind.	50 women with photoaged skin (Age: 40-65 years)	Decreased nail and hair brittleness (versus baseline) after 20 weeks.
	Bruni et al. (13) Open label, single-arm.	10 women with fragile nails (hand). (Age: 18-65 years)	Improvement in nail roughness, onychoschizia, and longitudinal ridges (versus baseline) after 6 months.
	Chandrashekar et al. (12) Open label, single-arm.	10 women with brittle nails both on hands and feet. (Age: 40-65 years)	Improvement in nail roughness, the number of broken and discolored nails (versus baseline) after 5 months.

Table 2
Other health benefits of ch-OSA®, reported in clinical trials. ch-OSA® was administered as an oral supplement, i.e. twice daily one capsule containing 5 mg of silicon and 100 mg choline as ch-OSA® (Bio Minerals NV, Belgium) or ch-OSA® containing drops (once daily 6 drops containing 6 mg of silicon and 120 mg choline as ch-OSA®).

	Author, study design	Study population	Observations
Bones	Spector et al. (18) Placebo-controlled, randomized, double-blind.	184 osteopenic women. (Age: 18-79 years)	Improvement of bone formation biomarkers, e.g. increased bone collagen formation (+1%) increased bone mineral density in the hip (+2%) (ch-OSA® /calcium/vitamin D3 group versus calcium/vitamin D3) after 1 year.
Joints	Geusens et al. (22,23) Placebo-controlled, randomized, double-blind.	166 patients (46 men and 120 women) with knee osteoarthritis. (Age: 34-77 years)	Improvement in symptoms (pain, stiffness, mobility) and biomarkers of cartilage degradation (CTX-II, COMP) in men (ch-OSA® group versus placebo group) after 12 weeks.
Dental	Teughels et al. (26) Placebo-controlled, randomized, double-blind.	73 patients (34 men and 39 women) with severe periodontitis. (Age: 20-67 years)	Improved pocket depth of teeth with a pre-stage of periodontitis, and less bleeding of gums (ch-OSA® group versus placebo group) after 6 months.
	Teughels et al. (27) Pilot, placebo-controlled, randomized, double-blind.	21 peri-implantitis patients (10 men and 11 women). (Age: 32-68 years)	Improved gum recession and stabilization of bone loss at per-implantitis sites (ch-OSA® group versus placebo group) after 12 months.

Joints

The effect of ch-OSA® on joint health was investigated in a multicenter, randomized, double-blind, placebo-controlled, single joint study in patients with painful knee osteoarthritis (OA) (22, 23). Over 12 weeks, one hundred sixty-six patients with documented knee OA (K&L grade II and III) and a baseline knee pain score of moderate or moderately severe on a 5-point Likert scale, completed the study. The patients were randomized in a ch-OSA® group and a placebo group. The mean age of the patients was 61.9 years and 72% were women of which 98% were post-menopausal. Patients were allowed to take rescue medication (paracetamol) up to 48 hours prior to each clinical investigation.

Symptoms of OA were evaluated in the target knee with the validated WOMAC questionnaire which measures joint pain, joint stiffness, and physical function.

Patient Global Assessment was measured on a 100 mm scale. Biochemical markers of cartilage degradation i.e., C-telopeptide fragments of type II collagen (CTX-II) and cartilage oligomeric matrix protein (COMP) were analyzed respectively in urine and serum.

The investigators found no differences between the two groups in the total study population but did found a significant improvement in men taking ch-OSA® compared to men in the placebo group after 12 weeks, respectively for total WOMAC (ch-OSA®: -43% vs. placebo: -17%), WOMAC pain (ch-OSA®: -48% vs. placebo -22%), WOMAC stiffness (ch-OSA®: -48% vs. placebo: -13%) and WOMAC physical function (ch-OSA®: -41% vs. placebo: -16%).

A similar trend was observed in patient global assessment (ch-OSA®: -50% vs. placebo: -34%).

The change in biochemical markers for cartilage degradation was also significantly different in men for both CTX-II (ch-OSA®: +20% vs. placebo: +45%) and COMP (ch-OSA®: -2% vs. placebo: +17%), i.e., significantly less cartilage degradation was found in patients who took ch-OSA® compared to placebo. Baseline levels of CTX-II were higher in women compared to men indicating more cartilage breakdown in women at the start of the study. Patients (women and men) with moderate baseline knee pain and K&L grade II, showed a significant improvement in WOMAC after 6 weeks supplementation (ch-OSA®: -55 % vs. placebo: -22 %).

This study demonstrated that ch-OSA® reduces joint pain and stiffness and improves physical function of the knee joint already after 12 weeks of supplementation in men with painful knee OA. This clinical improvement was associated with decreased cartilage degradation as demonstrated by reduced levels of biochemical markers in both serum and urine.

The difference in response to ch-OSA® supplementation between men and women was explained by previously reported gender differences in the incidence and severity of knee OA (24) including higher levels of cartilage degradation products (25) in women compared to men. The investigators therefore suggested that longer ch-OSA® supplementation may be needed in women to obtain a similar clinical improvement as is observed in men.

Dental

Recently two clinical studies have been presented, which investigate a potential role of ch-OSA® in dental health. In fact, the oral cavity is characterized by collagen-rich gingiva, but also the alveolar bone in which both natural teeth and dental implants are integrated is dependent on an optimal collagen network for adequate biomechanical strength. In a first randomized, placebo-controlled double-blind study, 72 patients with severe, generalized periodontitis completed a 6-month study (26). Periodontitis starts with an inflammatory condition of gums resulting in the formation of so called "pockets" around the affected teeth.

This inflammation results in swollen, painful, bleeding gums and may lead to bone loss and

ultimately loss of teeth. The investigators found that for teeth with a pre-stage of periodontitis, observed as "shallow" pockets, the pockets became less deep, and the gums had less bleeding in patients who took ch-OSA® compared to the placebo group. In a second study 21 patients with peri-implantitis were randomized in ch-OSA® or placebo groups and followed for 1 year (27). Peri-implantitis, starts also with inflammation of gums, resulting in swollen, painful gums and leads to receding gums, bone loss and ultimately loss of the implant. The investigators observed after 1 year a decrease of receding gums and a stabilization of the alveolar bone loss in patients who took ch-OSA® compared to patients taking placebo.

Mechanism of action of ch-OSA®, its impact on collagen biosynthesis.

Collagen synthesis is a complicated biochemical process that comprises several chronological steps and various enzymes **(table 3).**

Choline-stabilized orthosilicic acid was suggested to have an impact on the activity of four enzymes, that are required in different steps of collagen biosynthesis.

The impact on these enzymes is in part related to (a) ch-OSA's silicon component orthosilicic acid, (b) from its choline component, and (c) from the complex as a whole.

Experiments in animals have shown that insufficient dietary intake of bioavailable silicon (e.g., orthosilicic acid) result in connective tissue abnormalities including bone defects and lowered concentration of collagen. Low dietary intake of bioavailable silicon has been found to reduce the activity of the enzyme ornithine aminotransferase which catalyzes the biochemical production of proline from ornithine (28). Proline is together with glycine and lysine, a major amino acid in the primary structure of collagen.

Prolyl hydroxylase is the enzyme which converts proline in the collagen peptide into hydroxyproline, a collagen specific amino acid. In fact, two types are known for postranslation prolyl hydroxyalation in collagen synthesis, i.e. prolyl 4-hydroxylase and prolyl 3-hydroxylase (29). The in-vitro activity of prolyl hydroxylase in bone explants of chick embryos was found to be dependent on the concentration of silicon in the culture medium (30). In vivo, young animals which were supplemented with ch-OSA® in their diet, were found to have 12.5% higher hydroxyproline content in the dermis compared to controls without ch-OSA® supplementation (10). Physiological concentration of orthosilicic acid were found in cell cultures of human fibroblasts, to increase m-RNA and protein expression of lysyl hydroxylase, the enzyme which converts lysine in the collagen peptide into hydroxylysine (31). A significant increase in the procollagen marker PINP (procollagen type I N-terminal propeptide), an early marker of bone formation was reported for osteopenic women who took ch-OSA® compared to women in the placebo group (17), which directly illustrates that ch-OSA® stimulates collagen formation in man.

Proper cross-linking is critical for normal collagen structure and optimal mechanical properties of the connective tissue in which the collagen fibers are embedded (32). Beside lysyl oxidase, at least 9 different enzymes are involved in the maturation process of collagen which also includes non-enzymatic reactions. Proper cross links formed by lysyl oxidase shouldn't be confused with the distriputive cross links that collagen molecules are susceptible over time by the undesirable reactions of reducing sugars, particularly glucose ("glycation") and lipid oxidation products resulting in "aged" collagen fibers which result in connective tissue with poor mechanical properties.

Lysyl oxidase is also responsible for the formation of cross-links in elastin, the second

most important fibrous protein in connective tissue. Collagen and elastin together determine the biomechanical properties of skin.

Accumulation of homocysteine was found to have a negative impact on collagen metabolism, as it was reported to interfere with lysyl oxidase's synthesis and its enzymatic activity **(table 4).**

In animals and man, hyperhomocysteinemia has been shown to correlate with poor quality of bone collagen (33) and altered bone morphology. In man, blood levels of homocysteine correlate with the collagen cross-links ratio in bone forming areas (34). Recently, a meta-analysis and systematic review of the literature demonstrated that homocysteine significantly increased the risk of fracture (35).

Choline, a component of ch-OSA®, functions as a precursor of betaine, a compound which is used as a methyl donor in the biochemical conversion of homocysteine to methionine by the enzyme betaine-homocysteine methyltransferase. The dietary choline intake is inversely associated with plasma homocysteine i.e., a high choline intake correlates with low plasma homocysteine levels and choline depletion tends to increase the homocysteine level in blood. In addition, human intervention studies show that choline supplementation results in a significant decrease of plasma homocysteine levels. The European Food Safety Authority (EFSA) has confirmed (36) that a cause-and-effect relationship is established between the consumption of choline and contribution to normal homocysteine metabolism which resulted in the authorization of the health claim "choline contributes to normal homocysteine metabolism". Homocysteine can also be trans-sulphurated to cysteine, which requires vitamin B6 as a co-factor.

Cysteine is an important sulfur-containing amino acid used in the production of keratin, the structural protein of hair and nails, and is used by the body to make glutathione, a powerful antioxidant that protects cellular components against oxidative damage via the glutathione peroxidase pathway.

The above illustrates that a balanced homocysteine metabolism is important for optimal health i.e., relatively low levels of homocysteine are needed since it is used as a precursor for other amino acids (methionine, cysteine) but accumulation will cause connective tissue related health problems such as cardiovascular, skin and bone defects due to the negative impact on collagen metabolism.

The intake of the choline containing ch-OSA® complex, contributes to a healthy homocysteine metabolism and protects collagen against homocysteine mediated denaturation.

Table 3
The different steps in the biosynthesis of collagen. ch-OSA® has a positive impact on key enzymes that are needed in collagen biosynthesis: ornithine transferase and 3 post-translation enzymes, i.e., prolyl hydroxylase, lysyl hydroxylase, and lysyl oxidase.

1 - Amino acid synthesis	**Ornithine transferase converts ornithine into proline, a major amino acid in collagen.**
2 - Transcription	**Genes (DNA) encoding the collagen molecule must be turned on and transcribed into messenger RNA.**
3 - Translation	**Messenger RNA leaves the nucleus and is translated by ribosomes in a pro-peptide which is basically a chain of amino acids.**
4 – Post-translation	▪ **Several modifications such as hydroxylation of lysine and proline residues in the pro-peptide by the enzymes lysyl hydroxylase and prolyl hydroxylase.** ▪ **Association of three pro-peptides into a triple helix (procollagen).** ▪ **Peptidase enzymes cleave the N- and C- terminal pro-peptides, which then assemble into a tropocollagen triple helix.** ▪ **The enzyme lysyl oxidase is responsible for the formation of cross-links between tropocollagen molecules which then generates collagen fibrils.** ▪ **Additional cross-linking occurs between different fibrils to form strong collagen fibers.**

Table 4
Hyperhomocysteinemia negatively impacts collagen metabolism by several mechanisms. Choline, which is present in ch-OSA®, contributes to a normal homocysteine metabolism i.e. it helps prevent hyperhomocysteinemia.

Inhibits lysyl oxidase	**Homocysteine thiolactone, a derivative and by product of homocysteine metabolism inhibits lysyl oxidase activity directly (37). An inverse correlation was found between the homocysteine concentration and the lysyl oxidase activity in vitreous specimens of patients with proliferative diabetic retinopathy (38).**
Down regulation transcription	**Homocysteine interferes indirectly by down-regulation the expression of lysyl-oxidase's messenger RNA and other genes involved in collagen cross-linking (39).**
Interacts with cross-linking	**Homocysteine reacts chemically with collagen thereby interfering with collagen cross-linking. In bone samples of orthopedic patients, about 50 % of the bone homocysteine is bound to collagen plus an association was found between altered bone morphology and bone homocysteine concentration (40).**

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