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Potential synergy of vitamin MK-7 and silica in cardiovascular health

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Abstract

Silica – the second most prevalent element after oxygen – is required in the human body for synthesis of structural materials necessary in connective tissue, bone and cardiovascular system functionality, e.g. securing elasticity of blood vessels. Vitamin K2 is similarly important in its multitasking role based on a particular family of 18 (and growing), vitamin K-dependent proteins with matrix GLA protein (MGP) potentially reversing arterial calcification and safeguarding arterial elasticity. One of the most important synergistic roles of silica and vitamin K2 is in preventing age-related deterioration of the cardiovascular system. Based on epidemiological, preclinical and clinical studies the potential synergy between these two nutrients may be based on alleviating chronic inflammation in diverse conditions including cardiovascular disease.

SILICA AND ITS BIOLOGICAL ROLE

Silica is ubiquitous in all living organisms and is required for the production of structural materials in simple organisms as well as higher plants and animals (1). Silica is a multifunctional mineral found throughout the body, entering into the simplest and most complex structures in microscopic and macroscopic forms, from cellular cytoskeletons to the body skeleton. It participates in biosynthesis and posttranslational modification, e.g., phosphorylation of mucopolysaccharides, proteoglycans, and proteins like collagen, basic for connective tissue composition and function. Silica plays a critical role in molecular condensation reactions giving molecular structures a direction in formation of connective tissue, organs and systems. One of the important biological functions of silica is to form the blood vessel walls making them more flexible, regulating their permeability and accelerating their regeneration and healing processes. Silica also functions to detoxify body, e.g. chelating and removing toxic metals like aluminum, prevents molecular aging processes, enhances immunity and prevents infections.

Chemically, silica is an oxide of silicon or silicon dioxide which is insoluble in water. When associated with metals or minerals the family of silicates is formed. There are several water-soluble forms of silica referred collectively to as silicic acid (ortho-, meta-, di-, and tri-silicates), which are present in surface and well waters in concentration of 1-100 mg/L. Orthosilicic acid is the form predominantly absorbed by humans and is found in numerous tissues including bone, tendons, aorta, liver and kidney.

Silica is considered essential for health although recommended daily intake (RDI) for this mineral has not been established. However, deficiency of silica is associated



with skeletal deformities in the skull and peripheral bones (e.g. vertebrae and femoral bones), poorly formed joints, and reduced contents of cartilage and collagen. In addition, while silica is rich in the normal human aorta its levels decrease with age and such decline is often associated with the development of atherosclerosis. The toxicological studies indicate a No Observed Adverse Effects Level (NOAEL) of 50,000 ppm (mg/L) for dietary silica (1).

CARDIOVASCULAR ROLE OF SILICA

The science on silica in maintaining overall health, healthy bones, cartilage, connective tissue and healthy cardiovascular function is relatively new and stems from traditional sources, epidemiological studies and preclinical studies. Traditional and historical use of grains like millet produced folk stories and adages highlighting health benefits of, what we know now, were foods rich in silica. For example, glowing and youthful skin, strong and shiny hair and healthy nails were credited in folklore wisdom to consumption of millet. Nutritional analysis has found that the husk of millet contains up to 5% of silica in form of silicic acid, which builds and supports the all important connective tissue (Figure 1). Silica plays a key role in optimal connective tissue formation, especially needed for skin and bone health (2-4). An important evidence for this association has been provided in epidemiological studies showing relationships between dietary silica intakes and bone mineral density in the US (5) and UK cohorts (6). Because of the biological significance of silica in the body, much of the scientific research has been focused on its potential role in cardiovascular system function. The preclinical studies of silica indicate its growing importance in cardiovascular health, i.e. in preserving vascular elasticity, normalizing elevated blood pressure, improving blood lipids and blood rheology or blood composition for its efficient flow and nutrient delivery. The 8-week supplementation of silica to spontaneously hypertensive rats lowered significantly systolic blood pressure as compared to animals receiving a control diet sans supplemental silica (7). In the follow-up *in vitro* study

of rats, silica increased by 177% the magnesium uptake by aortic smooth muscle cells, as compared to cell cultures with no silica addition.

Magnesium helps to relax the smooth muscles in blood vessels, which allows them to dilate and accommodate efficient blood flow. Supplemental magnesium has been effective in people who have high blood pressure. Further, silica suppressed aortic cells' gene expression for angiotensin, a hormone that elevates blood pressure, as well as the growth factors related to inflammation and vascular remodeling which may distort blood vessel walls and impede blood flow; it also stimulated expression of peroxisome proliferator-activated receptor- γ (PPAR- γ), a biological molecule with anti-inflammatory and blood pressure lowering effects. These combined experimental findings suggest that the antihypertensive mechanism of silica may depend on regulation of cardiovascular uptake of magnesium and the epigenetic regulation of the cardiovascular inflammation and hormonal play leading to vascular bed constriction and high blood pressure.

Further insight into the cardiovascular role of silica derives from the study of the effects of dietary silica on nitric oxide synthase (eNOS) and nitric oxide (NO) in regulation of blood vessels' elasticity and wall hemodynamic properties (8). The nitric oxide produced by blood vessel endothelial cells regulates the vascular play helping blood delivery to the tissues when it is produced in the physiological amounts. The experiments evaluated functional changes in the endothelial and smooth muscle cells in the aorta of rats supplemented with silica in drinking water for eight days. As a result of supplementation the endothelial cells from silica-treated animals were found to have reduced endothelial eNOS expression, were more responsive to vascular relaxants like nitric oxide, and resulted in attenuated arterial smooth muscle cell response to nitric oxide. Silica supplementation



Figure 1. Millet's individual ingredients.





reduced the NO-associated hyper-responsiveness of blood vessels and potentially reduced cardiovascular pathology in response to excessive cardiovascular action of NO.

The beneficial cardiovascular role of dietary silica can also be credited to its regulatory role of blood lipids. In one experiment 52 rabbits were submitted for two months to an arterial plaque (atherogenic)-promoting cholesterol-rich diet with or without silica administered by intravenous injection (9). Out of the 26 rabbits receiving the cholesterol-rich diet alone, 23 developed arterial plaque lesions, and out of the 26 rabbits receiving the cholesterol-rich diet with silica, only eight had arterial plaque lesions. The arachidonic acid, involved in lipid peroxidation, which is an additional cardiovascular risk factor to elevated blood cholesterol levels, decreased in the silicon-treated rabbits as compared to the group receiving the cholesterol-rich diet alone. The plasma levels of arachidonic acid are positively correlated with arterial injury and arterial plaque formation. It has also been postulated that supplemental silicon may stimulate endothelial production of heparan sulfate proteoglycans that inhibit the cardiovascular disease process, leading to thickening, stiffening and narrowing blood vessels (10).

Epidemiological studies indicate that regions that have food and water rich in silica enjoy populations that age in good health (11,12). One important parameter of health status with aging is cognitive decline which usually depends on cardiovascular health and factors preventing chronic inflammation and neurodegeneration. In a study conducted on a population 65 years or older residing in southern France, associations between exposure to aluminum or silica from drinking water and risk of cognitive decline, dementia, and Alzheimer's disease among elderly subjects was followed for 15 years (1988-2003). A total of 1,925 subjects who were free of dementia at baseline and had reliable water assessment data were analyzed. The cognitive decline with time was greater in subjects with a higher daily intake of aluminum from drinking water. Conversely, an increase of 10 mg/day in silica intake was associated with a reduced risk of dementia (11).

The objective of a similar design study was to investigate the potential association between the composition of drinking water and the

level of cognitive function in a population of 1,462 French women 75 years old and older who were taking part in the osteoporosis study and followed up for at least seven years for incidence of Alzheimer's disease (12). During follow-up, the diagnosis of dementia was made by a geriatrician and a neurologist. A multivariate analysis including potential confounding factors showed that women who developed Alzheimer's disease had lower intake of silica. This study concluded that silica in drinking water may reduce the risk of developing Alzheimer's disease in elderly women.

The discussed preclinical and epidemiological findings indicate combined effects of dietary silica in prevention of chronic inflammation in both the cardiovascular and central nervous systems which collectively may alleviate these degenerative conditions.



BIOLOGICAL ROLE OF VITAMIN K2

In a similar way that silica has been re-discovered by science as a versatile mineral, vitamin K came from a relative obscurity as a single-function "homeostasis vitamin" to be re-discovered as a "multi-functional vitamin" and arguably the most fascinating of all vitamins (Shearer M.J., Schurgers L.J., Newman P.; DeGruyter, 2011) (Figure 2).

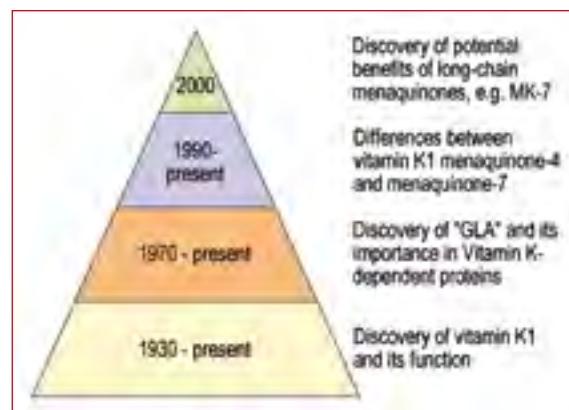


Figure 2. Vitamin K-research: multitasking vitamin.

The importance of menaquinone-7 (vitamin MK-7 or MK-7) as a multitasking vitamin has been clearly illuminated in the last five years, despite the fact that vitamin K has more than an 80-year-old history since its discovery. In 1929, at the Biochemical Institute of Copenhagen University, the experimental studies on chicks fed a very low-fat diet led to the discovery of the existence of Vitamin K, which denotes a fat-soluble vitamin that occurs in two biologically active forms, phylloquinone (vitamin K1) and menaquinone (vitamin K2). Vitamin K1 is produced by plants and algae, and vitamin K2 is predominantly of microbial origin and comprises a family of molecules distinguished from K1 by unsaturated side chains of isoprenoid units varying in length from 1 to 14



repeats (hence, menaquinone-4 represents short chain, and menaquinone-7 long chain menaquinones etc.). The major dietary form of vitamin K has been considered to be K1, whose most abundant source is green and leafy vegetables. In contrast, K2 is found in animal products, meat, dairy, eggs and fermented food, e.g. cheese, yogurt and natto, as well as in the colon, where K2 is synthesized by the intestinal microflora.

Vitamin K is a coenzyme for glutamate carboxylase, the enzyme which converts (carboxylates) the inactive form of K-dependent proteins to its active forms, e.g. bone-building osteocalcin or matrix Gla protein (MGP) preventing arterial calcification. Vitamin K, especially K2, mediates the conversion of glutamate moiety on the respective proteins to gamma-carboxyglutamate (Gla). The gamma-carboxylation of the Gla proteins is essential for the proteins to attract calcium and fulfill their biological roles; the under-carboxylated protein, e.g. unMGP, usually reflects a low nutritional status of vitamin K2.

The nutritional role of menaquinones and especially long-chain menaquinone-7 or MK-7 is increasingly recognized and distinguished from the biological role of vitamin K1 or phyloquinone as well as other menaquinones, e.g. short-chain MK-4. At this point 18 vitamin K-dependent proteins have been discovered playing critical roles in blood coagulation, muscle and skeletal health, cardiovascular health and metabolic health. Menaquinone-7, with the half-life in circulation significantly longer than that of vitamins K1 and MK-4, plays an important role as a co-substrate to activate K-dependent proteins. Menaquinones, especially MK-7, play a particularly important role in cardiovascular health since menaquinones have been shown to be a ligand for the specialized receptor in the body, steroid xenobiotic receptor (SXR), which stimulates synthesis of matrix Gla protein or MGP. As previously mentioned, MGP belongs to the family of vitamin K-dependent proteins that prevent calcification in the body and especially calcification in the arterial walls. As a clear example, MGP knockout mice that cannot produce MGP die within eight weeks of birth from ruptures of the large blood vessels due to massive vascular calcification (13).

HEART HEALTH

VITAMIN K2 IN CARDIOVASCULAR HEALTH

The nutritional status of vitamin K on cardiovascular disease was evaluated in the Rotterdam study (Figure 3) (14). The study enrolled 16,057 perimenopausal and postmenopausal women, 49 to 70 years old, free of cardiovascular disease at the baseline. After 10 years follow-up, there were 480 cases with diagnosed coronary heart disease. The mean intake of vitamin K1 and K2 in

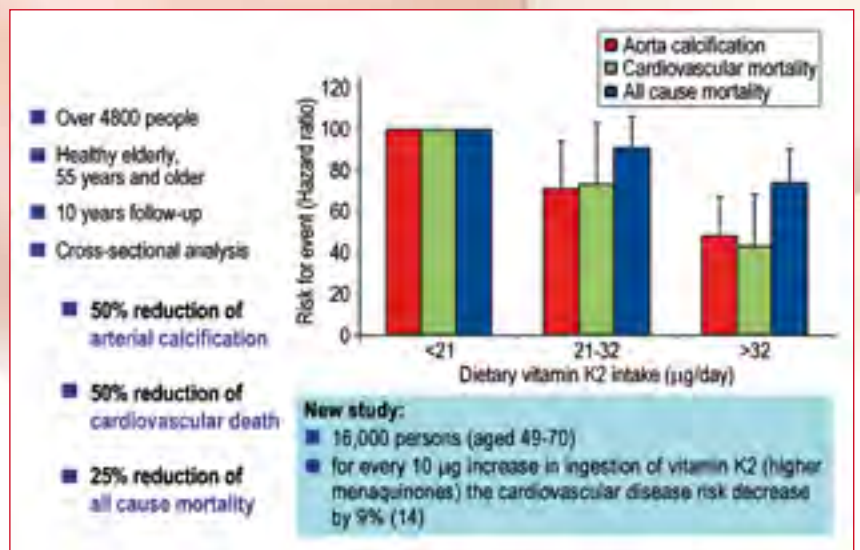


Figure 3. The Rotterdam Study: Importance of vitamin K2.

this studied population was 211.7 mg and 29.1 mg per day, respectively. After adjustment for traditional risk factors and dietary factors, the study showed a drop in risk of developing coronary heart disease per each 10 mg of vitamin K2 intake. This association was mainly due to intake of long-chain menaquinones, particularly menaquinone-7. The dietary intake of vitamin K1, on the other hand, was not significantly related to prevention of cardiovascular disease.

Vitamin K is critical for efficient metabolism of calcium in the body. Calcium is crucial for the maintenance of a strong skeletal system and teeth but also for nerve transmission, blood clotting, vascular tone, blood pressure, muscle contraction, enzyme activation, and hormone regulation.

Sufficient dietary calcium may lower the risk of colorectal cancer and lower risk of cardiovascular disease due to lowering blood lipids and when taken in moderation it has a tendency



Heart Health



to lower blood pressure. Calcium supplements, with or without vitamin D, have been widely used for the prevention and treatment of osteoporosis and general health support of an aging population. However, when nutritional vitamin K intake is low, the K-dependent proteins (like previously discussed MGP) is unavailable in its active carboxylated form and uncontrolled mineralization of calcium in arterial walls has been shown to contribute to cardiovascular disease.

The paradox of calcium as both hero and villain has been highlighted by the results of a 2013 *JAMA* published study by Xiao *et al* (15). The report discusses the outcome of the National Institutes of Health (NIH)–AARP Diet and Health Study, which evaluated the role of supplemental calcium on cardiovascular health. This prospective study involved a large cohort of 219,059 men and 169,170 women followed up for 12 years to ascertain their health status. The outcome of the study revealed that intake of 1,000 mg per day of supplemental calcium from multivitamins or individual calcium supplements were associated with significant increase in heart disease death in men but not in women; there were reported 7,904 and 3,874 deaths in men and women, respectively.

Although the *JAMA* study indicates that supplemental calcium may affect adversely cardiovascular health in men only; other studies indicate that supplemental calcium intake puts women at cardiovascular risk as well, e.g. the WHI CaD Study reporting an increased risk of CVD in women allocated to a calcium supplementation group (16). In addition, use of calcium supplements with or without vitamin D was associated with a significant 24% increase in risk of coronary heart disease in a cohort of 10,555 Finnish women (17).

These epidemiological findings suggest that guidelines for calcium supplements may have to be revised, and calcium and vitamin D supplements may need to be complemented with vitamin K2 intake for efficient delivery of calcium to ensure effective performance of the body's physiological functions.

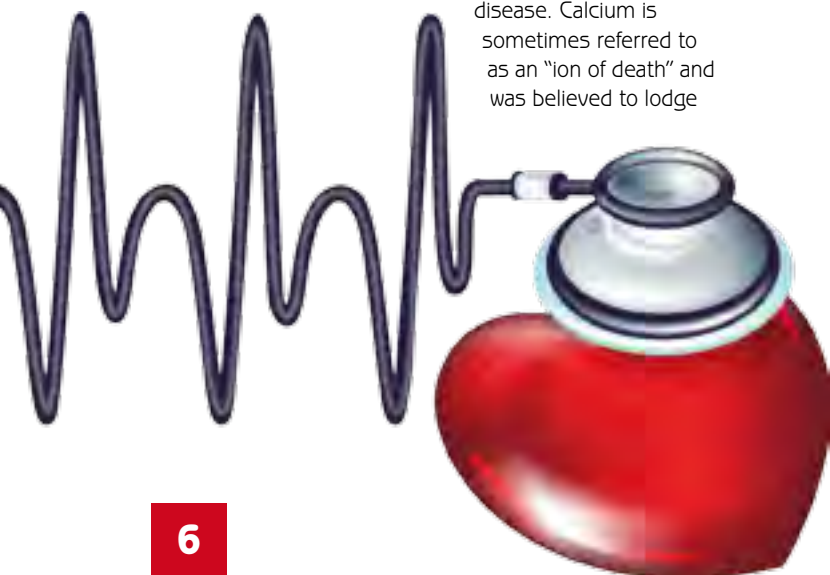
Until recently arterial calcification was thought of as a passive process and the end stage of cardiovascular disease. Calcium is sometimes referred to as an "ion of death" and was believed to lodge

irreversibly in damaged blood vessel walls causing arterial calcification, loss of vascular elasticity and irreversible loss of function – which could partially be restored only in a surgical procedure. However, recently, it has been shown in clinical studies that dietary vitamin K, especially K2, may be actively involved in prevention and possibly reversal of arterial calcification.

In a recently published study, vascular calcification was evaluated in patients on hemodialysis who typically have low levels of active MGP and a high degree of arterial calcification (18). The hemodialysis patients received supplemental MK-7 (MenaQ7®) for six months in a dose of 45 µg, 135 µg and 360 µg daily for six weeks. This therapy resulted in a dose-response increase of the active or carboxylated form of MGP levels, which might prevent or reverse arterial calcification. The response rates in the improvement of MGP status were 77% and 93% in the groups receiving 135 µg and 360 µg of menaquinone-7, respectively. Even the lowest dose of 45 µg showed some degree of improvement in the MGP status. This study provides a compelling rationale for vitamin K2 therapy to potentially decrease vascular calcification in hemodialysis patients (18).

A 2012-completed clinical study, which was a double-blind randomized clinical trial, evaluated a three-year regular intake of 180 µg menaquinone-7 (MenaQ7®) daily by a group of 244 healthy post-menopausal Dutch women, 55 to 65 years old. This study showed for the first time the nutritional dose of vitamin K providing clinically statistically significant protection of the vertebrae and the hip against osteoporosis and bone fracture and protection against cardiovascular deterioration with aging. Importantly, the trial showed that supplementation with menaquinone-7 prevented statistically significantly the age-related stiffening of arteries (typically due to arterial calcification) as evaluated by the speed of pulse wave velocity (PWV) and as compared to the placebo receiving group. One of the most important findings from the study was that clinically relevant improvement became evident no sooner than after two and three years of MenaQ7 supplementation. This finding explains for the first time why shorter studies (12 months and less) typically failed to show benefits of vitamin K on bone health and cardiovascular health. Establishing a correlation between length of administration and efficacy of menaquinone-7 intake is a clinically significant "breakthrough" for clinically relevant use of vitamin K2 in the potential prevention and reversal of arterial calcification and CVD (19).

The combined evidence from cardiovascular research of vitamin K, and especially MK-7, indicates that vitamin K may influence the enduring process of arterial calcification only with protracted and regular daily intake of nutritional dose of MK-7, reversing cardiovascular disease and underlying chronic inflammatory process aggravated by aging.





APPROACH TO CHRONIC INFLAMMATION

The phenomenon of chronic inflammation should be addressed with a nutritional approach in aging populations, especially in relation to cardiovascular health.

Inflammation is often treated with a “band-aid” type approach to quell discomfort or immediate pain. However it is inflammation as a lingering, rather than an acute, process that is increasingly attracting attention. It is considered as the root-cause of many diseases that remain poorly understood or treated. Cardiovascular disease, a leading cause of mortality in the world, is no longer considered a disorder of blood lipids, but rather a disease process characterized by low-grade inflammation of the vascular lining (endothelial cells) and an inappropriate “wound healing response” of the blood vessels. Osteoporosis is also considered due to deterioration of the immune functions with aging. Similarly, the devastating neurodegenerative disorder, Alzheimer’s, is hypothesized as being caused by dysfunction of the immune system reacting to chronic inflammation of the central nervous system.

Silica and vitamin K and their apparent nutritional efficacy in cardiovascular disease, osteoporosis and other degenerative conditions point to a potential synergistic mechanism and rationale for a combined nutritional use to address a common denominator of health deterioration with aging – chronic inflammation.

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