VITAMINS D3 AND K2 – Another Dynamic Duo!

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Introduction

In my last article "Vitamin D: An Underestimated Ally", I summarised the science behind the many benefits of Vitamin D and how in the light of this accumulating scientific support that no-one can afford to be deficient in this important hormone. And yet evidence would indicate that as many as 70% of us may be deficient or have too low levels of this God-given molecule.
People are becoming aware of this and although they may not have checked their blood levels, have taken it upon themselves to large doses of vitamin D3. Whilst undoubtedly there are benefits to correcting your vitamin D deficiency, there lies a hidden danger in taking large doses of Vitamin D3 without its sister vitamin, Vitamin K2.

This article aims to clarify the synergy between these two important molecules and explain why we need them both together for optimum bone and cardiovascular health.

To reiterate, Vitamin D has been shown to influence dozens of conditions, including: Cancer, Hypertension, Heart Disease, Obesity, Rheumatoid Arthritis, Autism, Type 1 and Type 2 Diabetes, Osteoporosis, Multiple Sclerosis, Crohn's and other Inflammatory Bowel disease, Flu, Tuberculosis, Dementia and Alzheimers, Eczema and Psoriasis, Muscle pain, Peridontal disease, Macular degeneration, Pre-eclampsia, Infertility, Asthma, Cystic Fibrosis, Migraines, Depression, Schizophrenia and Seizures. Some of these have been discussed in more detail in my previous article referenced above.

The RDA for vitamin D remains at a measly 600 IUs. This is despite the overwhelming evidence showing that vitamin D is extremely important for a wide variety of health conditions besides bone health, and that most people may need about **ten times this amount** or more.

Vitamin K may very well end up being as important for you as vitamin D. Research continues to illuminate the many benefits for your health. Vitamin K itself may prove to be as important as vitamin D.

Dr. Kate Rheaume-Bleue says in her book *Vitamin K2 and the Calcium Paradox: How a Little Known Vitamin Could Save Your Life "K2 is really critical for keeping your bones strong and your arteries clear* ". (1)

The picture that has emerged is that whilst vitamin D is crucial for adequate calcium absorption, it is vitamin K that directs calcium to your skeleton, to prevent the calcium from being deposited in the wrong areas.

Also, taking calcium in isolation without complimentary nutrients like magnesium, vitamin D, and vitamin K can have adverse effects, including the build-up of plaque in coronary arteries and heart attacks.

Dr. Reinhold Vieth has studied the question of D3 toxicity extensively and states categorically that there is no published evidence for this causing toxicity in adults taking 10,000 IU of a daily D3 supplement.

Much new research is now focusing on the synergy between vitamin K (specifically, vitamin K2) and vitamin D3, particularly in terms of bone strength and cardiovascular health.

Taking vitamin D3 on its own is potentially a health hazard, but if taken with adequate vitamin K2 then one can benefit from healthy bones and a healthy heart. There are numerous studies that have shown this to be true. (2,3,4,5)

Another common misconception is that human beings do not need vitamin K2 in their diet, since they have the capacity to convert vitamin K1 to vitamin K2. The amount of vitamin K1 in typical diets is ten times greater than that of vitamin K2. It has been shown that intake of K2 is inversely associated with heart disease in humans while intake of K1 is not (Geleijnse et al., 2004, Ref 6).

The Calcium paradox

It may come as a surprise that Vitamin D3—cholecalciferol—is also used as a rodenticide. If given in a high enough dose over a short enough period of time it can effectively kill rodents and it does this by causing massive hypercalcinosis of their organs. However, in order to reach the LD50 dose, that subject would need to consume over 3,500 of the 50,000 IU D3 caps in a 24 hour period (146 capsules an hour) in order to have a 50% chance of dying. This is equivalent to 175 million units a day.

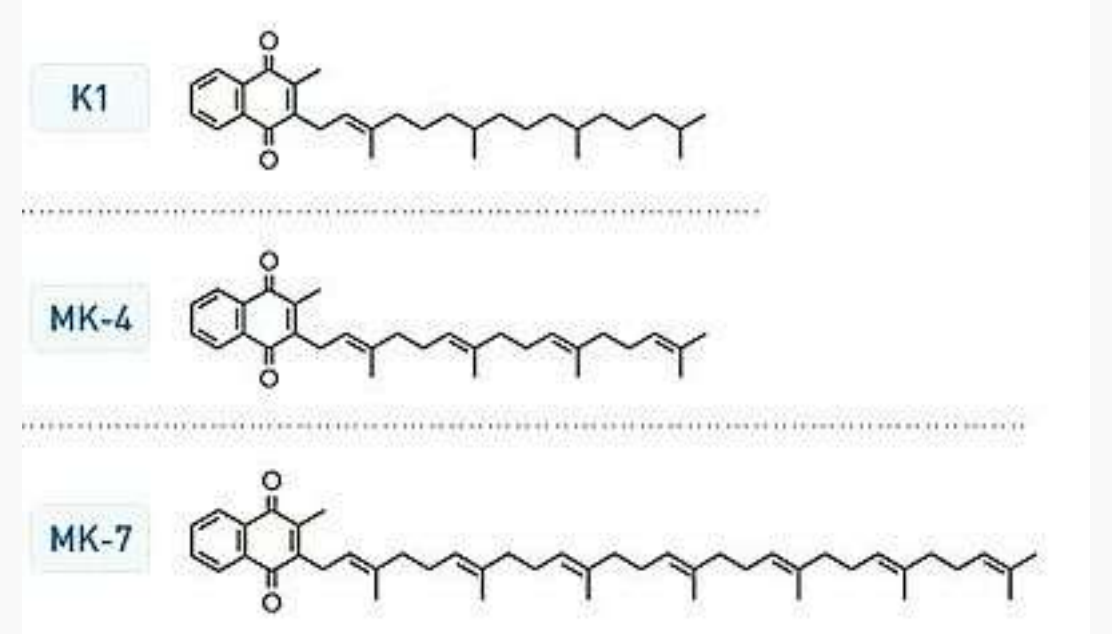
Without Vitamin K2, the body cannot direct calcium to the bones where it's needed; instead, the calcium resides in soft tissue (like the arteries)—leading to a combination of osteoporosis and atherosclerosis, or the dreaded "calcium paradox."

Vitamin K2 deficiency is actually what produces the symptoms of vitamin D toxicity, which includes inappropriate calcification that can lead to hardening of your arteries.

Dr Rheaume-Bleue warns *"There are so many people on the vitamin-D-mega-dose bandwagon, taking more and more of vitamin D. And it could absolutely be causing harm if you are lacking the K2 to complete the job to get the calcium where it's supposed to be."*

The net consequence of this "Calcium Paradox," is that too little calcium is utilized by the bones, resulting in weak bones, while excess calcium accumulates in the arteries, making them stiff and inelastic.

Types of Vitamin K2



Vitamin K structures. MK-4 and MK-7 are both subtypes of K_2. MK-4 and MK-7 are the two most significant forms of K2 and act very differently in your body. MK-7, is a newer agent with more practical applications because it stays in your body longer; its half-life is three days. Unlike vitamin K1 that is obtained largely from the diet, Vitamin K2 isn't produced by plants like K1, but rather by an array of bacteria (7). Both Mk-4 and Mk-7 inhibit osteoclast formation (bone breakdown) and promote osteoblast formation (bone forming cells) (8).

K2 functions

One biological role of vitamin K2 is to help move calcium into the proper areas in the body, such as your bones and teeth. It also helps remove calcium from areas where it should not be, such as in your arteries and soft tissues.

Vitamin K2 deficiency may predispose to a number of chronic diseases, including:

- Osteoporosis
- Heart Disease
- Heart attack and Stroke
- Inappropriate calcification, from heel spurs to kidney stones
- Brain degenerative disease
- Cancer

Another main role of K2 seems to be to activate proteins that control cell growth suggesting that K2 has a very important role to play in cancer protection (1).

Another, published in the journal Science (9) , found that vitamin K2 serves as a mitochondrial electron carrier, thereby helping maintain normal ATP production in mitochondrial dysfunction, such as that found in Parkinson's Disease.

When vitamin D is taken, the body creates vitamin K2-dependent proteins, the proteins that will move the calcium around. These proteins have many potential health benefits but until the K2 comes is present to activate these proteins, the benefits are not realized. There are currently 17 different vitamin K-dependent proteins known.

One of these proteins is a hormone called osteocalcin, produced by osteoblasts, which is needed to bind calcium into the matrix of your bone. Osteocalcin also appears to help prevent calcium from depositing into your arteries. Carboxylation of osteocalcin is another regulation feat of vitamin K which keeps bones properly mineralized with a strong protein matrix. Activated osteocalcin also stimulates adiponectin, a potent fat metabolism stimulator which helps to maintain normal weight.

Activation of the vascular GMP protein is crucial in preventing calcification of coronary and carotid arteries. This explains the 50+% reduction in heart disease in regular vitamin K users

Vitamin K was identified some 40 years ago as essential for the synthesis of sphingolipids, which are present in high concentrations in brain cell membranes and are now known to possess important cell-signaling functions. Vitamin K-dependent proteins are now known to play key roles in the central and peripheral nervous systems. Notably, protein Gas6 has been shown to be actively involved in cell survival cell growth. Further, Parkinson's patients have several genetic defects, including PINK 1 and Parkin mutations that lead to reduced mitochondrial activity. But vitamin K2 plays a role in the energy production of defective mitochondria (9). The Neuroscientist Patrik Verstreken, succeeded in undoing the effect of one of the genetic defects that leads to Parkinson's using vitamin K2 – a discovery that gives hope to Parkinson's patients.

In recent years, various reports have shown that vitamin K2 has anti-oncogenic effects in various cancer cell lines, including leukemia, lung cancer, ovarian cancer, and hepatocellular cancer. Previously, Nimptsch et al (10) showed an inverse relationship between dietary intake of vitamin K2 and risk of prostate cancer. Interestingly, serum under-carboxylated osteocalcin , a biomarker of vitamin K status, is inversely associated with vitamin K2 intake and the development of advanced prostate cancer. Moreover, vitamin K2 is also shown to enhance the chemotherapeutic efficacy of conventional anticancer drug Sorafenib in the most common type of liver cancer, hepatocellular carcinoma.

Researchers have hypothesized the molecular mechanism of MK-7 insufficiency in chronic inflammation fueled by pro-inflammatory cytokines. Tumor necrosis factor-α (TNF-α) exemplifies the pro-inflammatory cytokine, implicated in the process of vascular calcification and osteoporosis (12). The results show that vitamin K2 inhibits the production of pro-inflammatory mediators by human and mouse macrophages in vitro.

Osteoporosis

Osteoporosis is a disease characterized by loss of bone mineral density. According to the World Health Organization (WHO), osteoporosis currently affects some 200 million people globally. Worldwide, one in three men are expected to suffer from osteoporotic fractures in the future, whereas lifetime risk of fracture for women is nearly one in two.
Women are more vulnerable due to 1) having less bone mass then men, and 2) the annual bone mass in women accelerates after menopause.

As a general principle, as long as the bone-forming activity (absorption) is greater than the bone-breakdown (resorption), the process of maintaining healthy bones is kept under control. Osteoblasts produce a vitamin K2-dependent protein called osteocalcin, which helps bind calcium in the bone matrix, leading to increased bone mineral content.

Over three thousand elderly French women were given 1200mg of calcium ion and 800IU of vitamin D3 for 3 years and the result was that there was a decrease in hip fractures by 43% (13). When there is insufficient intake of calcium in the diet the parathyroid gland begins to stimulate osteoclasts which are cells that break down bone and inhibits the osteoblasts that build up bone, this is at the cost of calcium being withdrawn from bones to subsidize the calcium level in the blood (14,15).

First indication that K2 is important for bone mineral density came from patients with femoral neck fractures, who demonstrated an extremely low level of circulating vitamin K_2.

A meta-analysis of 19 randomized controlled trials. The results showed that Vitamin K2 might play a role in maintaining the bone mineral density (BMD) and in reducing the incidence of fractures for postmenopausal women with osteoporosis, and were published in *Osteoporosis International*.

It has been found that vitamin K_2 deficiency results in a decreased level of active osteocalcin, which in turn increases the risk for fragile bones (16,17).

Natto, a traditional breakfast dish made of fermented soybeans. Increased intake of MK-7 from natto seems to result in higher levels of activated osteocalcin and a significant reduction in fracture risk (18,19). Even more striking is the research finding, reported in 2001, that there seems to be an inverse correlation between the amount of natto consumed, in different regions of Japan, and the number of hip fractures. In regions of the country where natto is not part of the daily diet, hip fractures are more common (20).

A 3-year study of a vitamin K2 as MK-7 ingredient on 244 women showed for the first time clinically statistically significant protection of the vertebrae and the hip (femoral neck) against osteoporosis. This was achieved with only 180 mcg daily of vitamin K2, which is considered a “nutritional dose,” meaning it is much more easily obtainable through supplementation and the right diet than pharmaceutical doses used in previous studies. The K2 group showed significantly increased circulating active osteocalcin, a well-established biomarker for bone and vitamin K status.

After 3 years of supplementation, improvements in both bone mineral content and bone mineral density were statistically significant in the vitamin K2 group. Further, bone strength was statistically improved, demonstrating therapeutic benefits for the K2 group as compared to the placebo group. This study appears in the January 2013 issue of Osteoporosis International, validating the credibility of the research findings.

A 2008 published study showed that improving vitamin-K status in children over a 2-year period resulted in stronger and denser bones. One year later, the same group of researchers demonstrated that in healthy, pre-pubertal children, modest supplementation with vitamin K2 as MK-7 increased osteocalcin carboxylation (activating inert osteocalcin).

The best way to evaluate vitamin K deficiency is to determine the decrease in the circulating undercarboxylated form of the vitamin K-dependent proteins in the blood (e.g., the level of carboxylated osteocalcin or MGP).

Recent studies found a clear association between long-term anticoagulant treatment and reduced bone quality due to reduction of active osteocalcin. Oral anti-coagulation therapy might lead to an increased incidence of fractures, reduced bone mineral density/bone mineral content, osteopenia, and increased serum levels of undercarboxylated osteocalcin (21).

A note on bisphosphonate drugs.
Bones are made up of minerals in a collagen matrix. Whilst minerals give your bones rigidity and density, collagen gives bones flexibility. Without good flexibility, they become brittle and break easily. Bone density does not necessarily equate with bone strength. Drugs like Fosamax build up a lot of minerals and make the bone LOOK very dense, but in reality, they are extremely brittle and prone to fracture. This is why there have been so many cases of hip fracture among people taking these drugs.

A note on Calcium and bone mineral density.

Countries with the highest calcium consumption have the highest rates of osteoporosis -- namely, the U.S., Canada and Scandinavian countries. This is commonly known as the "calcium paradox."

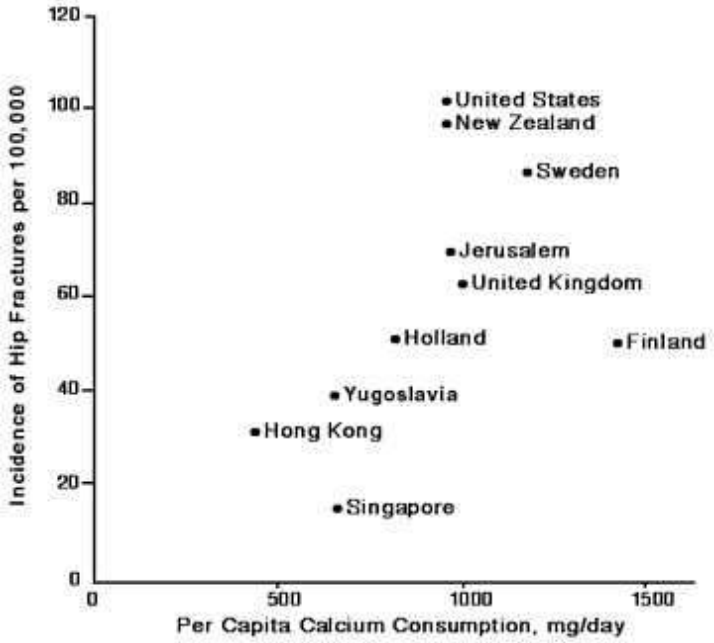
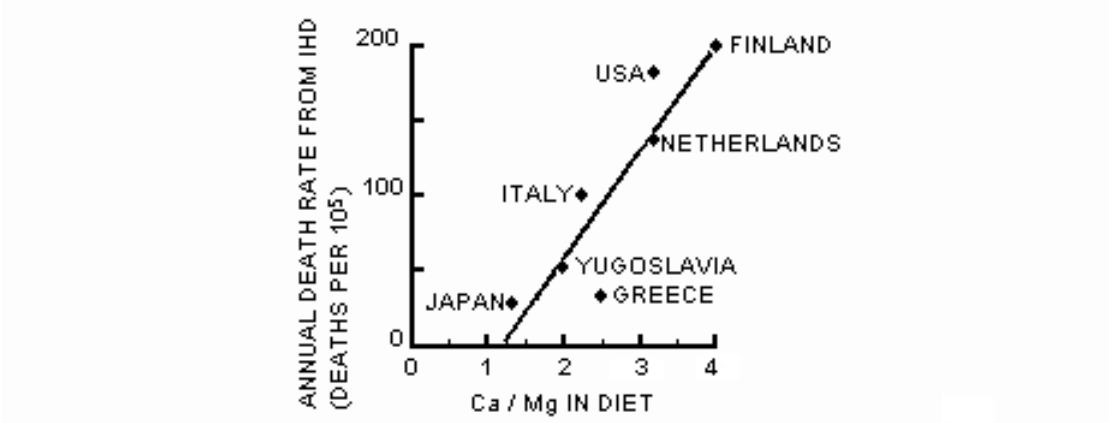


Figure: Hip fractures per calcium consumed.

From: Hegsted DM. Calcium and osteoporosis. Adv Nutr Res 1994;(9);119-28, ...

It is also interesting to note from the graph below that higher calcium/magnesium ratios are associated with greater risk of ischaemic heart disease and this suggests that the whole story of calcium alone being good for health and bone strength needs to revisited. More,

that people are likely being harmed by this dogma that is still prevalent in mainstream medical thinking.



Ischemic heart disease rates correlated with dietary calcium/magnesium ratios. [From H Karpannen et al.: Advances in Cardiology, Vmanninen and Halonen (Eds), S. Karger, Basel, 1978, pp 9-24]

A recent meta-analysis linking calcium supplements to heart attacks (22).

K2 and Cardiovascular Disease

Globally, cardiovascular diseases (CVD) are responsible for nearly 1 in 3 deaths.

Studies in Japan show that vitamin K2 is linked to a reduction of cardiovascular diseases. These populations have a regular intake of nutritional doses of Mk-7 from natto.

A large epidemiological study from the Netherlands also illustrates this point well. The researchers collected data on the vitamin K intakes of the subjects between 1990 and 1993 and measured the extent of heart disease in each subject, who had died from it and how this related to vitamin K2 intake and arterial calcification. They found that calcification of the arteries was the best predictor of heart disease. Those in the highest third of vitamin K2 intakes were 52 percent less likely to develop severe calcification of the arteries, 41 percent less likely to develop heart disease, and 57 percent less likely to die from it (6). However, intake of vitamin K1 had no effect on cardiovascular disease outcomes. In a subsequent study called the Prospect study, 16,000 people were followed for 10 years. Researchers found that each additional 10 mcg of vitamin K2 in the diet resulted in nine percent fewer cardiac events. Animal studies show that vitamin K2 not only prevents hardening of the arteries but can actually reverse calcification of highly calcified arteries by activating MGP. That arterial calcification is an actively regulated process. Healthy arterial tissues have been shown to contain 100 times more vitamin K2 than calcified arteries – meaning that one can actively protect their cardiovascular system by obtaining adequate vitamin K2.

Vitamin K and vitamin D work together to increase Matrix GLA Protein (or MGP), the protein responsible for protecting your blood vessels from calcification. In healthy arteries, MGP congregates around the elastic fibers of your tunica media (arterial lining), guarding them against calcium crystal formation.

MGP is the most potent inhibitor of vascular calcification presently known. Fortunately, animal research showed that vascular calcification might not only be prevented, but even reversed by increasing the daily intake of vitamin K_2 (6). The strongly protective effect of K_2 and not vitamin K_1 on cardiovascular health was confirmed by, among others, Geleijnse et al. in the Rotterdam Study (6) performed on a group of 4,800 subjects. Results of more than 10 years of follow-up were verified, also by Gast et al., who demonstrated that among K vitamins, the long-chain types of K_2 (MK-7 through MK-9) are the most important for efficiently preventing excessive calcium accumulation in the arteries (23). MGP is so important that it can be used as a laboratory measure of your vascular and cardiac status.

Vitamin D itself has been found to protect the heart. A study in the Netherlands provides compelling evidence that a high vitamin D status is associated with improved survival in heart failure patients. Vitamin D concentration was assessed in plasma samples from 548 heart failure patients. According to the researchers, patients with lower concentrations had a higher risk of death or required re-hospitalization, whereas patients with higher concentrations had lower survival risks for these endpoints. The study was noted to provide evidence that a high vitamin D status is associated with improved survival in heart failure patients.

The study was designed to compare the effect of oral administration of vitamin K2 (MK-7) plus vitamin D, or vitamin D alone, on the progression of coronary artery calcification score and carotid intima media thickness, which are hallmarks of potentially heart disease and stroke. The data revealed a slower progression of calcification in those taking both vitamin K2 and vitamin D compared to those taking vitamin D alone (24).

Further, a 2012 double-blind, randomized, clinical trial evaluated the results of a 3-year regular intake of a 180 mcg daily dose of vitamin K2 menaquinone-7 (MK-7) by a group of 244 healthy post-menopausal Dutch women, randomly assigned to receive daily either vitamin K2 or placebo capsules. The trial showed substantial benefits in preventing age-related stiffening of arteries resulting in increase of the PWV (pulse wave velocity) in the placebo group, but not in the vitamin K2 group. Most remarkably, the vitamin K2 group showed it not only prevented stiffening, it also resulted in an unprecedented statistically significant improvement of vascular elasticity both measured with ultrasound techniques and PWV (25).

Food sources and Deficiency

Many high calcium foods also contain high amounts of vitamin K2. Nature cleverly gives us these two nutrients in combination, so they work optimally. Common food sources of K2 are: Grass-fed organic animal products (i.e. eggs, butter, dairy), Certain fermented foods such as natto, or vegetables fermented using a starter culture of vitamin K2-producing bacteria, Goose liver pâté, Certain cheeses e.g. Brie and Gouda (these two are particularly high in K2, containing about 75 mcg per ounce).

In Europe and the USA 60%, or more, of total vitamin K_1 intake comes from vegetables; the majority in green leafy vegetables. National surveys reveal that K_1 intakes vary widely. Intakes determined by weighed-dietary Intakes are similar in UK to the USA with average daily intakes of around 70–80 μg, which is a less than adequate intake for vitamin K. Apart

from animal livers, the richest dietary source of long-chain menaquinones are fermented foods (from bacteria not moulds or yeasts) typically represented by cheeses (MK-8, MK-9) in Western diets and natto (MK-7) in Japan.

In 2012, Canadian health writer Kate Rhéaume-Bleue suggested the Recommended Daily Allowance (RDA) for K vitamins (range of 80-120 µg) might be too low (1).

Vitamin K_2 is preferred by the extra-hepatic tissues (bone, cartilage, vasculature) and is of bacterial origin. Scientific discussions are ongoing as to what extent K2 produced by our intestinal bacteria contributes to our daily vitamin K_2 needs. If, however, intestinal bacterial supply was enough to supplement all tissues needing K2, we would not find high fractions of undercarboxylated Gla-proteins in human studies. Carboxylation of vitamin K-dependent proteins, known as Gla-proteins, is important and serves as a recycling pathway to recover vitamin K from its epoxide metabolite (KO) for reuse in carboxylation (26,27).

Recent scientific data show that the amount of vitamin K is not as abundant in the diet as once thought. Mean dietary intake of vitamin K is currently significantly lower than it was 50 years ago, while the daily consumption of vitamin K has gradually decreased since 1950 (28). Dietary patterns have also changed over decades. For example, children in 1950 derived around 15% of their vitamin K intake from fats and oil sources and 55% from vegetables (excluding potatoes). In the 1990s, 35% came from fats and oils, and just 30% from vegetables.

Natto contains the highest concentration of K2 of any food measured; nearly all of it is present as MK-7, which research has shown to be a highly effective form. A recent study demonstrated that MK-7 increased the percentage of osteocalcin in humans three times more powerfully than did vitamin K1 (29).

Vitamin K deficiency results in undercarboxylation of MGP. Vascular calcification was shown to appear in warfarin-treated experimental animals within two weeks (30). Also in humans on OAC treatment, two-fold more arterial calcification was found as compared to patients not receiving vitamin K antagonists (31,32).

Unlike the other fat-soluble vitamins, vitamin K is not stored in any significant quantity in the liver; therefore toxic level is not a described problem. All data available at this time demonstrate that vitamin K has no adverse effects in healthy subjects.

Dosage

"The most recent clinical trials used around those amounts of K2,"Rheaume-Bleue says. "The average person is getting a lot less than that. That's for sure. In the North American diet, you can see as little as maybe 10 percent of that or less. Certainly, not near enough to be able to optimize bone density and improve heart health."

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Children have much higher bone metabolism than adults, so they need K vitamins in significantly larger quantities. During childhood and adolescence, bones are highly active

and osteocalcin levels are 8 to 10 times higher compared to adult bones – therefore, children require much higher levels of vitamin K2 (33).

Conclusions

Scientific evidence supports unquestionably the multiple benefits of Vitamin D on human physiology. The surge of people now taking mega doses of Vitamin D3 should be met with some caution in view of the potential for calcium deposition outside of the bones, most notably, the risk of increased risk of arteriosclerosis and subsequent heart disease in the presence of excessive circulating calcium. We have learnt over the years that it is rare for molecules to act in unison and they are almost invariably paired; magnesium with calcium, oestrogen with progesterone, copper wit zinc etc. So it would seem that vitamin D3 needs a partner especially for its role in calcium management and evidence would suggest that this partner is Vitamin K2 (especially in the MK7 form). Vitamin K2 not only keeps the arteries clear of calcium but evidence is presented here indicates that it may even reverse calcium deposits already present in the arteries. Almost certainly, in vitamin K2, we have another natural molecule that is an under-estimated ally.

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