The MOSS NUTRITION REPORT

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Product Review

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NEW MK-7 SELECT™ INTRODUCTION

As we have all known for several years now, the presence of optimal amounts of vitamin D is essential for maintaining optimal bone health and bone calcification, as noted by Dahlquist et al (Dahlquist DT et al, Plausible ergogenic effects of vitamin D on athletic performance and recovery, *J Int Soc Sports Nutr,* Vol. 12, No. 33, 2015):

"…low vitamin D levels are linked to increased bone turnover, increasing the risk of stress fractures."

Furthermore, significant doses of vitamin D are often necessary to function optimally in terms of bone health. Again, Dahlquist et al state:

"It has been shown that it takes roughly 2000 to 5000 IU/day of vitamin D from all available sources in order to optimize bone health…"

Unfortunately, it has also been suggested that higher doses of vitamin D may have several adverse consequences, most especially calcification of soft tissues such as arterial walls. Price et al (Price PA et al. The amino bisphosphonate Ibandronate prevents vitamin D toxicity and inhibits vitamin D-induced calcification of arteries, cartilage, lungs and kidneys in rats, *J Nutr*, Vol. 131, pp. 2910-2915, 2001) point out:

"We speculate that the demonstrated ability of toxic doses of vitamin D to strongly stimulate bone resorption accounts for the calcification of the diverse set of soft tissues observed in the present studies, and that bone resorption, therefore, is linked to the calcification of a wide variety of tissues in vitamin D-treated rats."

However, more current research suggests that the risk of soft tissue calcification with significant doses of vitamin D may not be so much an issue of too much vitamin D but an issue of vitamin K deficiency. The relationship between vitamin D and vitamin K was discussed in the above mentioned paper by Dahlquist et al:

"Any discussion of vitamin D toxicity merits mention of vitamin K. As with calcium, vitamin K works synergistically with vitamin D to regulate bone resorption, activation and distribution. Vitamin K carboxylates the newly-formed osteocalcin proteins that are produced in mature bone cells and are tightly regulated by vitamin D. Once the protein is carboxylated, it interacts with calcium ions in bone tissue and has a significant effect on bone mineralization, formation, the prevention of bone loss, and potentially the stoppage of fractures in women. However, when levels of vitamin K are inadequate, the osteocalcin production is not suppressed. This situation facilitates a build-up of uncarboxylated (inactive) osteocalcin proteins in bone, leading to a potential increase in calcium release from bone and the deposition of calcium into soft tissues (causing arterial calcification). Thus, vitamin D_3 toxicity might occur only in the absence of sufficient vitamin K stores."

Therefore, as noted in the above quote, while vitamin D is important for promoting delivery of calcium to bone, the calcium will not stay in the bone without optimal amounts of vitamin K. Instead, without optimal vitamin K levels, calcium will travel to soft tissue sites such as arterial walls.

Because of the above, it was only a matter of time until the greatly increased interest in vitamin D supplementation was accompanied by a well-deserved interest in vitamin K

supplementation. Unfortunately, discussions about clinical approaches to vitamin K supplementation have led to some considerable confusion about how practitioners should proceed due to the fact that several forms of supplemental vitamin K exist in the marketplace.

Because of the confusion about the different forms of supplemental vitamin K, this newsletter will be devoted to a review of the paper "Vitamin K-containing dietary supplements: comparison of synthetic vitamin K_1 and natto-derived menaquinone-7" by Schurgers et al (Schurgers LJ et al. *Hemostasis, Thrombosis, and Vascular Biology*, Vol. 109, No. 8, pp. 3279-3283, April 2007), which provides not only an excellent explanation of the most popular forms of supplemental vitamin K but a rationale as to why our new vitamin K product, **MK-7 Select™**, employs the MK-7 form of vitamin K.

VITAMIN K: BASIC BIOCHEMISTRY AND PHYSIOLOGY

Schurgers et al begin their paper by discussing basic vitamin K biochemistry and physiology:

"Vitamin K is a group name for a number of structurally related compounds including phylloquinone (vitamin K_1) and menaquinones (K_2 vitamins). Menaquinones are classified according to the length of their aliphatic side chain and are designated as MK-n, where n stands for the number of isoprenoid residues in that chain."

As will be discussed in more detail, the commercially available forms of vitamin K_2 menaquinones are MK-4 and MK-7. As will also be discussed, there are distinct benefits to the MK-7 form that is found in **MK-7 Select™.** The authors continue with their discussion of vitamin K biochemistry and physiology:

"The function of all forms of vitamin K is that they serve as a cofactor for the posttranslational carboxylation of certain protein-bound glutamate residues, which are converted into gamma-carboxy glutamate (Gla). These Gla residues from calcium-binding sites that are essential for the activity of the proteins in which they are found."

What does this mean in plain English? There are certain glutamate residues that are important for directing calcium where it is needed the most. These glutamate residues, though, cannot perform their functions unless a carboxyl group is added to them. Vitamin K facilitates addition of the carboxyl group to the glutamate residues so these residues can do their job in terms of calcium metabolism.

The next important clinical point made by Schurgers et al relates to the metabolic fate of vitamin K:

"During gamma-glutamate carboxylation, vitamin K is oxidized into its epoxide form (KO), which is reconverted to vitamin K quinone (K) by the enzyme vitamin K epoxide reductase (VKOR)."

What does this mean in plain English? During the process of donating the carboxyl group, vitamin K is oxidized to an inactive form. The enzyme VKOR converts oxidized vitamin K back to an active vitamin K form, thus conserving vitamin K. Why is it important clinically to know this? Blood-thinners such as warfarin inhibit VKOR, thus preventing oxidized vitamin K from being recycled:

"Derivatives of 4-hydroxycoumarin (including warfarin and acenocoumarol) specifically inhibit VKOR, thus preventing the recycling of vitamin K."

In what organ systems do Gla-containing proteins play a role in terms of facilitating optimal calcium metabolism? One important area, as we know, is blood clotting:

"Well-known Gla-containing proteins are the blood coagulation factors II, VII, IX, and X, which are all synthesized in the liver."

However, still other Gla-containing proteins facilitate optimal calcium metabolism in tissues outside of the liver:

"Gla-proteins not related with blood clotting are osteocalcin (synthesized in bone) and

matrix Gla protein (primarily synthesized in cartilage and in the vessel wall."

Thus, as the above quote suggests, Gla proteins that need vitamin K for proper formation also essential for proper calcium metabolism in bone, cartilage, blood vessel walls.

FOOD SOURCES OF VITAMIN K

Schurgers et al state the following about food sources of the various forms of vitamin K:

"In food, the most important K vitamins are K_1 (notably found in green vegetables and some plant oils) and the long-chain menaquinones MK-7, MK-8, and MK-9 present in fermented foods, notably cheese and natto."

Before continuing, please note that the most well-known source of vitamin K, green vegetables, only provides vitamin K_1. Green vegetables are not a source of vitamin K_2. The clinical importance of this distinction will be discussed later in this monograph.

The next quote from the Schurgers et al paper discusses supplemental forms of vitamin K:

"In food supplements, 3 forms of vitamin K may be found: MK-4 (prepared by organic synthesis and almost exclusively used in Japan), K_1 (also synthetic and the predominant form used in the rest of the world), and MK-7 (a natural form prepared by extraction of natto food)."

Interestingly, the structures of K_1 and MK-4 are very similar:

Since the molecular structures of K_1 and MK-4 are comparable…, their physico-chemical characteristics are closely similar."

In contrast, MK-7 is unique:

"The higher menaquinones including MK-7 are much more hydrophobic, however, and in vivo they are handled very differently: they have longer half-life times, and in the circulation they are incorporated into low-density lipoproteins."

Of course, K_1 is the most well-known of the three, having been available for years.

However, MK-7 is continuing to attract increasing interest:

"K_1 is by far the most common form of vitamin K in commercially available supplements, but because of the health claims for the regular consumption of natto that are repeatedly made in the scientific literature, MK-7 in the form of a natto extract is rapidly gaining interest."

WHY SUPPLEMENT WITH MK-7 RATHER THAN TRADITIONAL COMMERCIAL VITAMIN K FORM, K_1?

The remainder of the Shurgers et al paper discusses research that compares clinical benefit of MK-7 versus K_1. Probably the biggest clinical benefit, as noted in the quote below, is that MK-7 performs much better than K_1 in terms of promoting bone health. However, as you will also see, it is more effective in promoting clot factors in the liver making it more effective in reducing the effectiveness of coumarin anticoagulants:

"In this paper we have compared the in vivo properties of 2 forms of vitamin K: MK-7 and K_1. We demonstrate that after oral ingestion, MK-7 is more effective in both catalyzing osteocalcin carboxylation in bone and counteracting coumarin anticoagulants in the liver. The mechanism underlying this observation may be MK-7's much longer half-life time in the circulation and its reported 6-fold higher cofactor activity in vitro."

However, before continuing, as will be reported shortly, the adverse impact of MK-7 on efficacy of coumarin anticoagulants is dose-dependent.

The next quote discusses more reasons why MK-7 performed better than K_1. As you will see, the main reason is what was mentioned above – MK-7, unlike K_1, can be taken up and circulated via low-density lipoproteins:

"The difference between the 2 vitamins may be related to the fact that following intestinal absorption, both are taken up in the triglyceride fraction from which they are rapidly cleared by the liver but that only

higher menaquinones are redistributed via low-density lipoproteins. A consequence of the long half-life time of MK-7 is that it is available longer than K_1 for uptake by extrahepatic tissues. If expressed as area under the curve (AUC) over 24 hours, the availability of MK-7 is 2.5-fold better than that of K_1; if expressed as AUC over 96 hours, it is even 6-fold better."

What does this mean in terms of dosing? The authors comment:

"This means that if taken in single daily doses of 100 µg, only MK-7 is effectively present in the circulation and available for absorption by various tissues during the 24 hours following intake."

The authors continue:

"…if taken on a regular basis, there is no accumulation of K_1, whereas MK-7 accumulates…during the first 2 weeks, after which a steady-state level is reached. At comparable intakes, the final level of MK-7 was 7- to 8-fold higher than that of K_1, suggesting that if taken on a daily basis, 25 µg/d of MK-7 is more efficacious than 100 µg/d of K_1."

WHAT ARE THE CLINICAL IMPLICATIONS OF THE COMPARATIVELY BETTER BIOAVAILABILITY OF MK-7?

On the positive side, it appears that because, in many adults, there exists a fair amount of undercarboxylated osteocalcin (ucOC), which will not be optimally effective in promoting bone, MK-7 will be much more effective in repleting what appears to be a very common state of vitamin K deficiency in bone:

"In the healthy adult population, about 30% of the circulating osteocalcin occurs in its undercarboxylated form, and increased vitamin K intake results in rapid decline of ucOC, suggesting a state of subclinical vitamin K deficiency in healthy bone tissue. In a study designed to compare the efficacy of equimolar amounts of K_1 and MK-7, we measured the degree of osteocalcin carboxylation after a 6-week period of vitamin K intake. A small increase of osteocalcin carboxylation was visible for both forms of vitamin K at day 3, but whereas the effect of K_1 remained constant after that time, that of MK-7 inclined during the entire 6 weeks of treatment. At the end of the study, the change in the carboxylated OC/undercarboxylated OC ratio was 3 times higher for MK-7 than for K_1, suggesting that the higher serum levels of MK-7 reflect higher tissue levels and better utilization of MK-7."

Of course, on the negative side, this increased tissue utilization of MK-7 can pose problems for patients using coumarin anticoagulants. One reason is that, unlike osteocalcin in bone, in the average healthy population clotting factors in the liver are fully carboxylated:

"The vitamin K-dependent clotting factors are all produced in the liver and, in contrast to osteocalcin, they are all fully carboxylated in the healthy population."

What does this mean clinically in terms of anticoagulant medication? The authors state:

"It turned out that if expressed on a molar basis, MK-7 is a 3 to 4 times more potent antidote for oral anticoagulation than is K_1. If expressed per weight, the efficacy of MK-7 in the liver is still 2.5 times higher than that of K_1."

What does this mean in terms of a dose of vitamin K that will not interfere with coumarin activity?

"In a previous paper we demonstrated that vitamin K_1 supplements containing no more than 100 µg/d are not likely to result in clinically relevant disturbances of oral anticoagulant therapy. Extrapolating these figures, it may be concluded that MK-7 supplements containing more than 50 µg/d may interfere with oral anticoagulant treatment, whereas doses of at least 50 µg are not likely to affect INR value in a relevant way."

CONCLUDING STATEMENTS FROM THE SHURGERS ET AL PAPER

The first statement is a summary of the different properties of K_1 versus MK-7 and why MK-7 would be a preferable supplement:

"Taken together, these data demonstrate considerable differences between MK-7 and K_1: higher and more stable serum levels are reached with MK-7, and MK-7 has a higher efficacy in both hepatic and extrahepatic protein carboxylation. During recent years many studies have demonstrated that the extrahepatic vitamin K requirement exceeds the recommended daily allowance (100-120 µg/d) for vitamin K_1. For the food industry, an alternative to increasing the recommended dose would be introducing on a larger scale the more potent MK-7 instead of K_1 in functional foods and multivitamin supplements."

Of course, as was mentioned, the downside of MK-7 supplementation relates to its impact on anticoagulant therapy:

"Hematologists, on the other hand, need to be aware that relatively low doses of MK-7 may have a larger impact on the stability of oral anticoagulation than vitamin K_1."

With the above in mind, Shurgers et al make the following recommendation:

"…we propose to use an upper safety limit for intake of 50 µg/d for long-chain menaquinones (including MK-7) in patients on oral anticoagulant treatment. This dose is comparable with the menaquinone content of 75 to 100 g of cheese;…such an amount would lead to a disturbance of the INR value of no more than 10% which may be regarded as tolerable in the management of oral anticoagulant therapy."

Shurgers et al end their paper on a positive note in relation with the use of MK-7 with patients on anticoagulant medication:

"…its long half-life time suggests that regular intake of MK-7 in combination with properly adapted coumarin doses may result in more stable INR values."

SOME FINAL COMMENTS ON MK-7 SELECT™

MK-7 Select™ from Moss Nutrition contains 160 µg of MK-7 per capsule. Therefore, for those patients who demonstrate a need for increased bone calcification and/or are at risk for calcification of soft tissues such as arteries, and are not using coumarin-type anticoagulants, it is suggested that whenever vitamin D is supplemented, also supplement with 1-2 caps per day of **MK-7 Select™.** For those patients using coumarin-type anticoagulants, based on the research discussed above, **MK-7 Select™** can be used safely and successfully at a dose of 1-2 caps per week. However, we at Moss Nutrition do recommend that, even with the above discussed research in mind, patients using coumarin-type anticoagulants should talk with their physicians before using **MK-7 Select™** in any amount. Also, it should be noted that this concern does not apply to the newer generation of anticoagulants such as Plavix, which function in a way that does not involve vitamin K metabolism. Finally, please note that for patients who require long-term, preventive use of vitamin D and K for ongoing bone calcification support and avoidance of soft tissue calcification, a cost-effective approach to supplementation would be our many **Vitamin D+K** products that also contain MK-7 as well as our general bone support product that contains MK-7, **OsteoSelect™**, listed below**:**

MK-7 Select™ 160 mg 60 VC

Vitamin D+K 2000 120 VC & 240 VC

Vitamin D+K 5000 60 VC & 180 VC

OsteoSelect™ 120 T & 240 T