



## Menatetrenone: The Right K for Bone, Heart, and More!

Vitamin K may be the most misunderstood vitamin in the world.

In 1929, the Danish nutritional scientist Dr. Henrik Dam found that feeding chicks a totally fat-free diet caused uncontrolled bleeding under their skin. Dr. Dam quickly discovered the reason for this disturbing effect: the diet was missing a previously unknown fat-soluble nutrient, which he appropriately named “*koagulationsvitamin*” – literally, the “clotting vitamin.” The English name for the new vitamin was taken from Dr. Dam’s Danish: “K,” for “Koagulation.”

And for over fifty years, nearly everyone thought that the vitamin K story began and ended with blood clotting. If doctors paid attention to it at all, it was only to make sure that it didn’t interfere with the blood-thinning drug warfarin (Coumadin®). But even as nutrition textbooks and mainstream medicine continued to think of vitamin K as a one-act show, a paradigm shift had been forced onto researchers in the late 1970s, when new vitamin K-dependent proteins associated with bone-building **osteoblast** cells were discovered.

Yet as late as 1990, a Canadian government report was still trotting out the old “‘K’ for ‘koagulation’” view of vitamin K. While noting that “a number of non-clotting proteins” w h i c h needed vitamin K for their activation “have been found in bone, skin, kidney, atherosclerotic plaque, lung, spleen, placenta, and reproductive organs,” the nutrition panel

quickly shoved this evidence into a corner with the off-hand comment that the “physiological significance and biochemical functions of these non-clotting proteins have yet to be determined.”<sup>1</sup>

Another anomaly mentioned in passing in the report was the fact that – except in the liver – humans don’t use much

of the vitamin K in our diet “as is.” Instead, we *biochemically convert* the common plant form of the vitamin (**phylloquinone, or vitamin K<sub>1</sub>**) into a *different* vitamin K molecule: **Menatetrenone, or MK-4** (see **Figure 1**). **Menatetrenone** is a member of a distinct family of vitamin K molecules called the **menaquinones, or vitamin K<sub>2</sub>**. There are many K<sub>2</sub> vitamins made by bacteria, but **humans and other animals specifically make Menatetrenone in our tissues**, using K<sub>1</sub> as a raw material.

You’d think that these facts would rouse Health Canada’s committee from its slumber and cause them to ask some obvious questions. Why does the body need all of those mysterious vitamin K-dependent proteins? Why are they found scattered in such a wide range of tissues – tissues which have such disparate functions? And above all, *why does the body convert so much of its phylloquinone into Menatetrenone*, when plain old phylloquinone does a much *better* job of maintaining normal blood clotting?<sup>2,3</sup>



But instead of grappling with these enigmas, these government nutrition “experts” chose instead to ignore them. The rest of their discussion of vitamin K is devoted to prothrombin times, blood-thinning drugs, and the risks of hemorrhagic disease in newborns. The report contains no call for answers to the **Menatetrenone** mystery.

In the ten years since Health Canada promulgated its curiously un-curious report, research into vitamin K – and especially **Menatetrenone** – has been accelerating, as revolutionary discoveries surrounding the vitamin’s critical role in protecting you from **osteoporosis, arteriosclerosis**, and perhaps **Alzheimer’s disease** have been made. Science has suddenly moved **Menatetrenone** from being an obscure form of a boring “blood-clotting factor” to being an orthomolecule of crucial importance to your health and well-being.

So why have you never heard of it?

## Boning Up on Menatetrenone

Well, the odds are that you *have* heard some of the most important news about **Menatetrenone**. You just haven't recognized what you were seeing. If you've caught any recent magazine articles or books on the role of nutrition in bone health, you may remember reading that the Japanese are now using "vitamin K," not just to *prevent* osteoporosis, but as an officially-approved *treatment* for the disease. But what the people writing these articles don't seem to realize is that **the "vitamin K" that's prescribed as an osteoporosis-fighting "drug" in Japan is not phylloquinone, but Menatetrenone**. To understand why the Japanese are using **Menatetrenone** – and not the common, cheaper K<sub>1</sub> form of the vitamin – to shield the bones of women and men at risk of crippling fractures, we'll have to look at a little history.

The "vitamin K" that's prescribed as an osteoporosis-fighting "drug" in Japan is not phylloquinone, but Menatetrenone.

And what nutritional factor is needed for the gamma-carboxylation of BGP and other proteins? You guessed it: vitamin K. And in fact, gamma-carboxylation of another protein (**prothrombin**) also explained the biochemical basis for vitamin K's involvement in blood clotting. Once this role was discovered, however, the scientific community again put artificial limits on the scope of vitamin K's activity in the body: it came to be believed that vitamin K's biochemical actions could be explained *entirely* through its role in gamma-carboxylation of proteins.

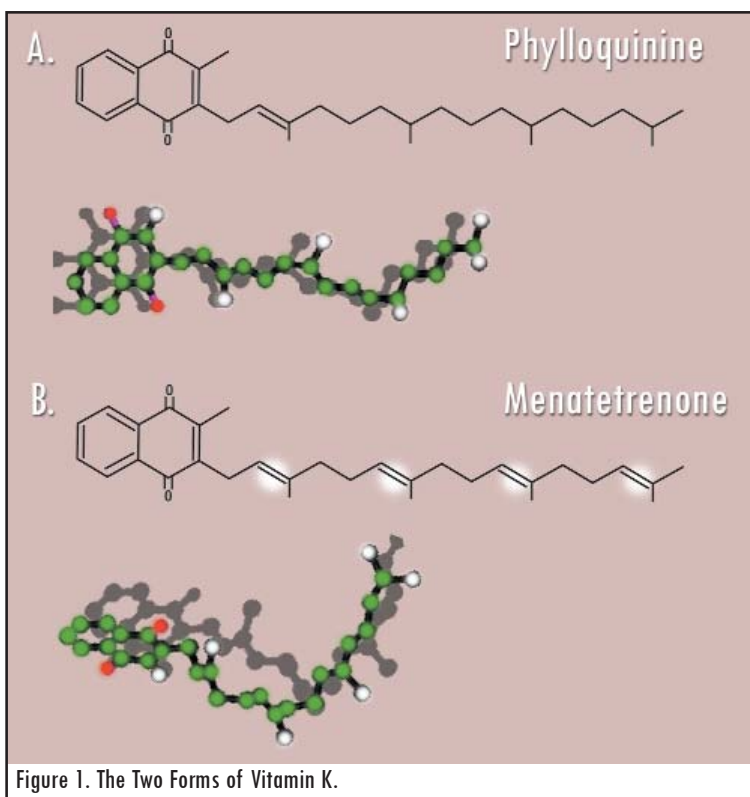
All of this got researchers thinking. Without vitamin K, there would be no "activation" of BGP. Without "activation," BGP would not be able to do its bone-mineralizing job. So might decades of low vitamin K intake lead to suboptimal mineralization, weak bones, and osteoporosis?

Scientists went looking for a link. And they found one. You'll probably have heard about the studies showing that women who get more phylloquinone in their diets have a lower risk of suffering a fracture.<sup>4,5</sup> Likewise, in an early study,<sup>6</sup> levels of vitamin K<sub>1</sub> were found to be significantly lower in the serum of women with osteoporosis than in women who were free of the disease. A role for vitamin K in bone health seemed to be clear.

But some of the science didn't seem to mesh with the vitamin K/bone health connection. For instance, if "activation" of BGP through gamma-carboxylation were so vital to bone health, then you'd expect that taking warfarin (Coumadin®) – a "blood-thinning" drug that works by blocking gamma-carboxylation – would increase your risk of breaking a bone. But when this idea was put to the test, the results were murky. One study found that the use of these drugs increased the risk of a spine or rib fracture – but not the risk of a fractured hip, or of any other kind of fracture.<sup>7</sup> And another study found that women taking such drugs were at no greater risk than women not taking them.<sup>8</sup> In fact, when growing animals are given warfarin at doses so ridiculously high that *all* BGP became under"activated," there were *no* resulting changes in bone mineral density, bone strength, or markers of bone metabolism.<sup>9</sup>

Women with fractures have only half as much K<sub>2</sub> – yet levels of K<sub>1</sub> were the same.

Another sticking point: if the "activation" of BGP gave bone-protective powers to vitamin K, then you'd expect that the body would use both forms of vitamin K equally, since



The 1975 discovery of **Bone Gla Protein (BGP** – or "osteocalcin" as it's sometimes called) marked a dramatic twist in the plot of the vitamin K story. While it wasn't clear *exactly* what the new protein's function was, it was clear from the get-go that BGP was *somehow* involved in the mineralization of bone. But it was quickly discovered that BGP can only do its job after it's been "*activated*" through a biochemical reaction called **gamma-carboxylation**. Through gamma-carboxylation, the residues of the amino acid **glutamine** in BGP are modified in a way that allows them to bind calcium. Without this calcium-binding capacity, BGP is inactive.



K<sub>2</sub> is actually *inferior* to K<sub>1</sub> at gamma-carboxylation of proteins (see **Figure 4**).<sup>2,10,11</sup> But instead, **the body selectively concentrates Menatetrenone in bone tissue.** In fact, even when the diet contains *no* K<sub>2</sub>, but is adequate in K<sub>1</sub>, bone tissue contains over *twice* as much menatetrenone as phylloquinone – despite the fact that there is nearly *fifteen times* as much K<sub>1</sub> as K<sub>2</sub> circulating in the serum under these conditions!<sup>12</sup> And when animals are actually fed **Menatetrenone itself**, it quickly begins to accumulate *specifically* in bone tissue – and **the highest concentrations of Menatetrenone are found in areas which are being actively remodeled.**<sup>13</sup>

It's just these kinds of anomalies that forced researchers to ask a more fundamental question – the question that the Canadian government's 1990 nutrition panel was unwilling to pose and unable to answer. If gamma-carboxylation is the only use for vitamin K in the body, then *why do our bodies go to the trouble of converting phylloquinone into Menatetrenone in the first place?* The situation is especially puzzling in the heart: when you first re-feed phylloquinone to a mammal after depriving it of vitamin K for long enough to create dangerous bleeding problems, **Menatetrenone is immediately synthesized, and accumulates more quickly in the heart than anywhere else in the body**<sup>14</sup> – despite the fact that the heart has *no* gamma-carboxylase activity!<sup>2,15-17</sup>

Acting on hints that **Menatetrenone** might be the preferred form of vitamin K in mammals, researchers decided to find out if there were any differences in the amounts of K<sub>1</sub> and K<sub>2</sub> in the plasma of men and women with spinal and hip fractures.<sup>18</sup> As you might expect, levels of K<sub>1</sub> and K<sub>2</sub> were both lower in the people with fractures than in fracture-free folk. But what was really revealing about this study was the fact that **the fracture victims' levels of K<sub>2</sub> were found to be over three times more depressed than their levels of K<sub>1</sub>.**

**Where women ate more K<sub>2</sub>, there were fewer fractures.**

In a similar study conducted in Japan,<sup>19</sup> **women with spinal fractures were found to have only half as much K<sub>2</sub> in their serums as women without fractures – yet the two groups' levels of K<sub>1</sub> were the same.**

### Look to the East

Several other studies confirmed that people with low serum levels of vitamin K<sub>2</sub> have lower bone mass<sup>20,21</sup> and are more likely to have fractured bones<sup>22,23</sup> than people with higher levels. But if **Menatetrenone** has a special place in bone health, then you'd also expect to see the same connections with the amount of K<sub>2</sub> in a person's *diet*. Unfortunately, it's hard to test this idea in the West, because our diets contain so *little Menatetrenone*. Ounce-for-ounce, the best sources are goose liver, butter, egg yolks, and fatter Emmental cheeses.<sup>24</sup> And even *these* foods provide only tiny quantities of this crucial orthomolecule, especially granted how little of them we eat at a time. A 100 gram serving of cooked broccoli, for instance, contains 113 micrograms of K<sub>1</sub> – but even if you slather it with a full tablespoon of butter, you're only getting 2.1 micrograms of K<sub>2</sub>.

The result is that almost no one in the West gets a diet that's very high in **Menatetrenone**, making it hard to compare the impact on bone health provided by high- versus low-**Menatetrenone** diets. But the situation is different in Japan. By an accident of cultural history, people in *eastern* regions of Japan typically get a *lot* more of one kind of K<sub>2</sub> (menaquinone-7) in their diets than do people in Japan's

more *western* areas – and the Japanese as a whole tend to eat diets richer in K<sub>2</sub> than do Westerners. That's because, along with rice, pickles, seaweed, and grilled fish, a traditional eastern Japanese meal will

often contain a fermented soy condiment called *natto* – the richest known food source of this form of the vitamin.<sup>24</sup> So Japan is the perfect place to look for connections between K<sub>2</sub> in the diet and bone health.

When scientists compared the average consumption of *natto* in different prefectures (provinces) of Japan with the fracture rates in those prefectures, they found that **the hip fracture rates among women living in areas where more K<sub>2</sub>-rich natto is consumed were consistently lower** than were the rates among women living in areas where *natto* consumption is lower.<sup>23</sup> And when researchers reanalyzed the data from two previous national dietary studies,<sup>25,26</sup> they confirmed the same association: **where women ate more K<sub>2</sub> (in natto), there were fewer fractures.**

But the investigators weren't satisfied with this. How could they be sure that it was the K<sub>2</sub> that was providing the fracture-fighting advantage? Might not some other

component of natto – say, the estrogen-like **isoflavones** – be responsible for the protective effect?

Fortunately, there was an easy way to settle the issue. Natto is, after all, just fermented soy beans. And the Japanese eat many other soy foods, such as tofu, *miso*, fried bean curd, and even soy sauce – soy foods with negligible K<sub>2</sub> content. If something in natto other than vitamin K<sub>2</sub> were the key to its association with low fracture risk, then the consumption of these other soy foods would be expected to provide the same fracture-fighting benefit that natto does. But when the investigators tested this idea, they found that consumption of other soy foods was not significantly related to the regional differences in fracture risk. **K<sub>2</sub>-rich natto was the only soy food whose consumption was associated with a low risk of fracture.**<sup>23</sup>

The scientists then took the final step: they directly tested the levels of different K vitamins in the serum of women in Tokyo (where fracture incidence is low) and in Hiroshima (where fractures are more common). And now the results seemed indisputable. As a group, **women from low-fracture-incidence Tokyo had higher serum levels of K<sub>2</sub> than did women from high-risk Hiroshima.** And just as revealingly, *there was no significant difference in their levels of K<sub>1</sub>.*<sup>23</sup>

In fact, the same pattern seems to hold internationally. While serum K<sub>1</sub> levels vary only slightly between women from the Japan and the UK, Japanese women's levels of K<sub>2</sub> are many times higher than those of their British counterparts.<sup>23</sup> That may explain why Japanese women, taken as a whole, have much lower rates of osteoporosis than Western women, despite their lower intake of such important bone-building nutrients as calcium and vitamin D.

### What's the Diff'?

All of this evidence suggests that K<sub>2</sub> plays some unique role in maintaining bone health – a role not shared by K<sub>1</sub>. And indeed, Japanese scientists have spent the last two decades comparing the effects of the two forms of the vitamin on bone metabolism, and have found that **Menatetrenone has multiple bone-protective mechanisms that phylloquinone simply lacks.**

One of the first such discoveries was the fact that **Menatetrenone can prevent the loss of calcium from bone tissue caused by prostaglandin E2 (PGE2),** an inflammatory **eicosanoid** (local cellular messenger-molecule) known to cause the resorption (breakdown) of bone.<sup>27,28</sup> Yet **the same concentration of K<sub>1</sub> provides no**

**protection.**<sup>28</sup> In another study,<sup>29</sup> scientists were able to show that K<sub>2</sub>'s ability to defend bone tissue against PGE2 is even stronger: in addition to blocking the negative impact of the eicosanoid *once it has been formed*, **Menatetrenone also cuts down on the bone cells' formation of PGE2 in the first place.**

Scientists have also compared K<sub>1</sub> and K<sub>2</sub> for their effects on **osteoclasts** (the cells that tear down bone). Osteoclasts, like other cell types, begin their lives as **stem cells**: early, simple cells which have the potential to grow up into many different kinds of cells, depending on the growth factors and other signals to which they are exposed. These researchers have found that **Menatetrenone is able to reduce the creation of osteoclasts from these early, simple cell types** – but again, **phylloquinone has no such power.**<sup>28</sup>

In another study, researchers again confirmed the ability of K<sub>2</sub> – *but not K<sub>1</sub>* – to prevent osteoclast formation, this time using a different type of forerunner cell.<sup>30</sup> In the process, they also showed that **a specific gene ([ODF]/RANK) which encourages these cells to develop into osteoclasts is turned off by K<sub>2</sub>.**<sup>30</sup> And in further research,<sup>31</sup> scientists demonstrated that **Menatetrenone, but not phylloquinone, actually increases the programmed cell death (“apoptosis”) of existing osteoclasts.**

These effects aren't just test-tube results: they happen in living, breathing mammals given extra **Menatetrenone**. When animals are injected with the growth factor **macrophage colony-stimulating factor (M-CSF)**, osteoclast formation skyrockets, reaching a bone-ravaging peak about five days after the injection and then slowly returning to numbers which are closer to normal: by 20 days after the injection, the animals “only” have about a third as many excess osteoclasts as they did at the five day maximum. But if, one day before the growth factor is injected, these animals are given high-dose K<sub>2</sub>, **Menatetrenone prevents 85% of the excess osteoclast formation** – and there are *no* excess osteoclasts remaining by day 20.<sup>32</sup> The study demonstrates that K<sub>2</sub> both prevents most of the excess osteoclasts from being formed, and accelerates their programmed demise.

In addition to protecting the body against an excess number and activity of osteoclasts, studies also show that **Menatetrenone strengthens the bone-building legions of the osteoblasts.** Menatetrenone cranks up levels of a chemical marker of osteoblast maturation,<sup>30</sup> protects osteoblasts from being pushed into cellular suicide by substances that trigger it,<sup>33</sup> and reduces the expression of

## Menatetrenone has multiple bone-protective mechanisms that phylloquinone simply lacks.

genes involved in the cellular suicide process.<sup>33</sup> On top of this, K<sub>2</sub> increases levels of DNA in osteoblasts, suggesting that it may stimulate the creation of *new* osteoblast cells.<sup>34</sup>

Beyond its ability to support higher *numbers* of osteoblast cells, **Menatetrenone** also enhances *each* osteoblast's bone-building *activity*. For instance, it has been found that, in addition to “activating” the mineralizing protein BGP, K<sub>2</sub> also increases the *amount* of this protein in the osteoblast matrix.<sup>34,35</sup> K<sub>2</sub> also boosts levels of **alkaline phosphatase** (a marker of osteoblastic metabolism and bone formation) and of new protein.<sup>35</sup> Interestingly, drugs which block the cell's ability to make new protein also interfere with some of these effects,<sup>35</sup> suggesting that part of K<sub>2</sub>'s unique support for bone health may lie in stimulating the synthesis of key proteins.

While **Menatetrenone's** effects on osteoblasts are only mild compared to those recently found hidden in the mineral **Strontium** (see “Strontium: The First Bone Builder” in this special issue of *Advances*), this research suggests that supporting the health of bone-building cells is at least part of the reason for **Menatetrenone's** protective effects on bone.

For more on the molecular basis for the superior bone-building potency of **Menatetrenone** compared with phylloquinone, see the sidebar, “**For Biochemistry Geeks Only.**”

### “K” is for “Klinical”

By now you have a pretty good idea of what first got Japanese scientists thinking about using **Menatetrenone** – and not phylloquinone – as a treatment for osteoporosis. Before performing clinical trials in humans, however, they first wanted to test the effects of **Menatetrenone** on animal models of osteoporosis. The results have been very encouraging: these studies have consistently found that **K<sub>2</sub> can increase the strength, improve the structure, and boost the mineral content of bone** in animal models of menopausal osteoporosis,<sup>41–47</sup> as well as protecting their bone health against the effects of calcium deficiency<sup>48</sup> and of bone-wasting drugs like cortisol<sup>49</sup> and phenytoin.<sup>50</sup>



## For Biochemistry Geeks ONLY!

What underlies the superior support for bone health provided by **Menatetrenone** as compared with phylloquinone? The answer must ultimately lie in the different structures of the molecules themselves. The “head” of the vitamin K molecule – the **naphthaquinone group** – is the same in both forms of this nutrient (see **Figure 1**). It's this naphthaquinone “head” that's largely responsible for the gamma-carboxylation activity that they share – the ability to “activate” a variety of proteins in the body, allowing them to bond to calcium. Since the “head” of the molecule is identical, it's no surprise that both forms of vitamin K are active in gamma-carboxylating proteins.

But since phylloquinone does a *better* job of gamma-carboxylation than does **Menatetrenone** (see **Figure 4**),<sup>2,10,11</sup> the “activation” of vitamin K-dependent proteins cannot explain the *greater* bone-building powers of **Menatetrenone**. And indeed, by using warfarin (Coumadin®) – a drug that inhibits the gamma-carboxylation of proteins by vitamin K – researchers have shown that **key bone-saving effects of K<sub>2</sub> still occur when gamma-carboxylation is blocked.**<sup>28</sup>

The difference, at the molecular level, between **Menatetrenone** and K<sub>1</sub> is in the “tail” of the molecule. Where phylloquinone's tail is a **phytyl group**, whose carbon bonds are all “saturated” with hydrogen, **Menatetrenone** has a tail with several “unsaturated” carbon bonds, forming a **geranylgeranyl group**. Scientists have found that the geranylgeranyl group *alone* has many of the unique effects of **Menatetrenone**, including suppressing the maturation of osteoclasts<sup>28,36,37</sup> and helping osteoblasts to mature.<sup>36</sup>

Our ability to explain **Menatetrenone's** unique effects has recently taken a leap forward, with the discovery that **there is a specific binding protein for vitamin K<sub>2</sub> in the nucleus of osteoblasts**, where the DNA code is housed.<sup>38</sup> This would suggest that **Menatetrenone** has specific, direct effects on gene expression in these bone-building cells, which dovetails with the finding that K<sub>2</sub> increases the level of DNA and protein in these bone-building cells<sup>35</sup> and might go a long way toward explaining how **Menatetrenone** protects bones in ways *unrelated* to gamma-carboxylation.

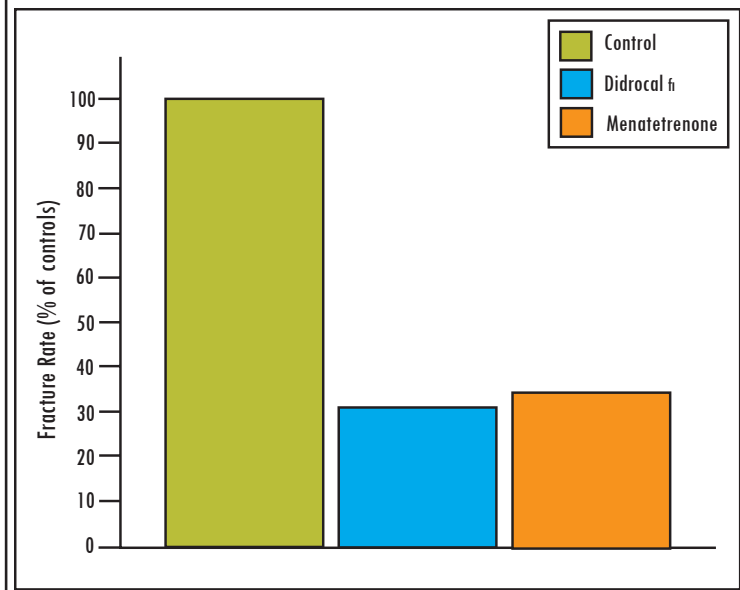
These facts help us understand why women taking warfarin don't seem to consistently suffer a greater risk of fracture than women who don't,<sup>7,8</sup> and why the drug doesn't prevent the skeletal development of growing animals,<sup>9</sup> despite the fact that the drug *does* interfere with the gamma-carboxylation of Bone Gla Protein – even at very low doses.<sup>39,40</sup> Simply put, the important effects of vitamin k on bone health come from **Menatetrenone**, not phylloquinone – and they are independent of the nutrient's effects on gamma-carboxylation.

All of this is good science – but none of it is the “gold standard” of the randomized, double-blind, controlled clinical trial. Fortunately, Japanese researchers have moved on from preliminary research to this higher level. Over the course of the last decade, at least sixteen clinical trials have been performed using **Menatetrenone**, and every single one has found that **K<sub>2</sub> supplements protect bone health**.<sup>51-66</sup> **Menatetrenone not only slows, halts, or even reverses loss of bone mass: it dramatically reduces your risk of suffering a fracture.**

The bone-building power of **Menatetrenone** has been proven in women suffering with menopausal osteoporosis,<sup>52,55,56,58,61,62,65,66</sup> and also in the similar case of younger women taking **leuprolide**,<sup>60</sup> a drug used to treat disorders like endometriosis which are triggered by excess estrogen, and which works by blocking the release of sex hormones (and thereby mimicking menopause’s negative effects on the bones). Additionally, however, **Menatetrenone** has proven its ability to protect against bone loss caused by cirrhosis of the liver,<sup>51,54</sup> immobility (such as long-term confinement to bed or a wheelchair),<sup>59,63,64</sup> and cortisol drugs.<sup>53,57</sup> And although it wasn’t a true controlled clinical trial, there’s even a case report of **Menatetrenone** (combined with vitamin D) fighting the osteoporosis that followed graft-versus-host disease resulting from a bone marrow transplant.<sup>67</sup>

For instance, in a recent double-blind, placebo-controlled trial,<sup>62</sup> eighty women with osteoporosis took either a megadose **Menatetrenone** supplement (90 milligrams – twice the dose used in most clinical trials), or a lookalike pill with no effect on bone health, for 24 weeks. At the end of the study, **women who took the Menatetrenone supplement increased their bone mineral density by an impressive 2.2%, even as the women taking the dummy pill lost 7.31% of their bone density.**

Figure 2: Menatetrenone protects against fractures. Drawn from data in (52).



Even more exciting results came from a later trial in which the power of **Menatetrenone** was put to the test in a direct comparison against both the bisphosphonate drug etidronate (Didrocal®) and a plain calcium supplement.<sup>52</sup> A

### **K<sub>2</sub> can increase the strength, improve the structure, and boost the mineral content of bone.**

group of 75 menopausal, osteoporotic women were first given help to improve their diets, ensuring that they got at least 800 milligrams of calcium and 400 IU of vitamin D a day from food sources. (This amount of calcium would not be enough for most Westerners, but it meets the needs of Japanese women, because of their shorter stature and lower body mass: the average woman in this study weighed just 100 pounds).

Then the women were divided into three groups. One group took a 45 milligram **Menatetrenone** supplement every day; a second group took the drug, following the on again/off again cycle that is standard with bisphosphonates; and a third group of women took a daily low-dose (260 milligram) calcium supplement.

Despite an adequate calcium and vitamin D intake, the women receiving only the calcium supplement lost 1.7% of their bone mineral density (BMD) over the course of the two-year trial. In the group taking etidronate, by contrast, BMD *increased* by 2.1%. Meanwhile, the women in the **Menatetrenone** group held steady: over the course of two years, no significant change in BMD occurred.

Now we come to another surprise – a new twist in the vitamin K research. If all you had to go by was the bone mineral density numbers, you’d *think* that **Menatetrenone** would provide less anti-fracture protection than the drug. But instead, **Menatetrenone proved to be just as effective at reducing fractures as etidronate, slashing women’s odds of breaking a bone by about two thirds** as compared to women taking the calcium supplement! See **Figure 2**. These results closely parallel the findings of a third trial involving 241 osteoporotic women,<sup>58</sup> in which **women taking Menatetrenone supplements sustained nearly no bone loss** over two years (a reduction of 0.5% in bone mineral density, versus a 3.3% reduction in the control group), **while cutting fracture risk by 64%** as compared with non-supplementing women. In an extension of this trial,<sup>68</sup> women have continued to benefit from this dramatic bone-shielding effect through an additional year of testing.

Once again, **Menatetrenone** presented researchers with a mystery – a paradox. How can **Menatetrenone** cut fracture risk as effectively as drugs whose effects on bone mineral density are much more marked? Answers have not been long in coming. As it turns out, **the most important**

**bone-shielding power of Menatetrenone is not its capacity to preserve the quantity of bone, but its ability to improve bone quality.**

### Quantity vs. Quality

Bone mineral density (BMD) is a measure of the *amount* of calcium and other minerals in a given amount of bone, and it tells you something about the *quantity* and *rigidity* of bone tissue. But when it comes to predicting your risk of *actually suffering a fracture*, **bone mineral density doesn't tell you the whole story.** That's because **the ability of bone to resist breakage is also strongly determined by bone quality:**<sup>71</sup> the structural soundness of the living tissue.

We tend to think of bone as being a solid mass, like steel girders or stone columns. But bone is actually a complex honeycomb, composed of an interpenetrating network of plates woven together by rods of tissue (see **Figure 3a**).



This is especially true of **trabecular bone**, the mineralized, regularly-ordered bone type found at the end of long bones. The integrity of this network – its “**connectivity**” – is a major contributor to the overall architecture of bone, and to the bone's ability to withstand fracture. So even if you have a high bone mineral density, your bones can still be

easily broken if weak *structure* – poor bone *quality* – makes them *brittle*.

Along with loss of bone mineral density, osteoporosis causes the deterioration of bone connectivity – especially in trabecular bone (see **Figure 3b**). In fact, loss of bone connectivity is the most dangerous part of the disease process, and is also the most difficult to restore.<sup>72</sup> Simply increasing BMD does nothing to re-establish the architectural integrity of the bone. As a result, the National Institutes of Health and other scientific bodies now define osteoporosis in terms of the *overall fragility* of the bone – whether this fragility is due to lower bone mineral density, or lower bone quality, or both. A recent consensus conference therefore defined osteoporosis as “a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk”<sup>73</sup> – a definition now used in standard osteoporosis textbooks<sup>74</sup> and by the Merck manual.

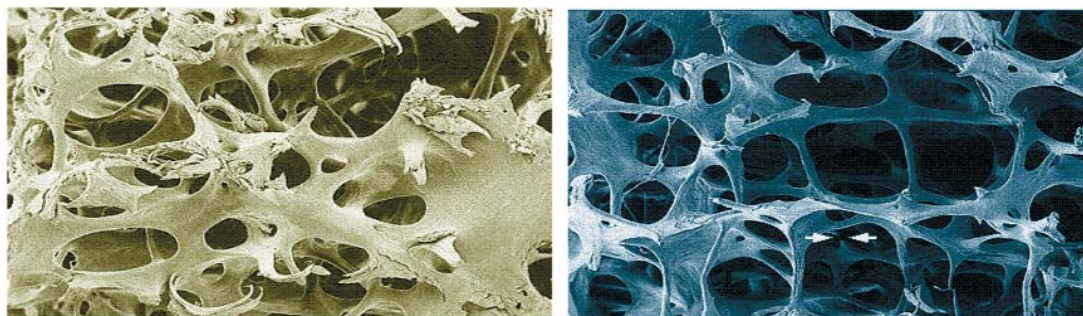
The problem is that **restoring BMD doesn't necessarily restore bone quality.** The most extreme example of this is the effects of **fluoride** on the skeletal system. It's long been known that fluoride drugs can increase the mineral content in bone, because fluoride is absorbed into the bone structure in basically the same way that calcium is. But **while fluoride can increase bone mineral density, it can actually degrade the quality of bone**<sup>75,76</sup> because the incorporation of fluoride into the bone mineral crystals warps their structure. As a result, fluoride drugs don't

**Menatetrenone dramatically reduces your risk of suffering a fracture.**

actually reduce a woman's risk of broken bones.<sup>77</sup> In fact, some trials have even found that **a woman who takes fluoride drugs actually increases her fracture risk,**<sup>78,79</sup> especially if she hasn't *already* suffered a broken bone before she starts taking the drug! Some scientists believe that newer fluoride drugs may limit these problems, but whether

these revised versions are either effective or safe is still an unresolved question<sup>80</sup> – and the quality-versus-quantity tradeoff will continue to be a concern. To this day, no fluoride drug has ever been approved for use in the United States, although Canada allows the sale of the fluoride drug Fluoic.<sup>8</sup>

Figure 3



a. Healthy bone with intact connectivity.

b. Osteoporotic bone with loss of connectivity. With permission<sup>74a</sup>).

Even the widely-hailed **bisphosphonate drugs** like alendronate (Fosamax®), etidronate (Didrocal®) and risedronate (Actonel®) appear to increase BMD at the cost

Women taking Menatetrenone supplements sustained nearly no bone loss while cutting fracture risk by 64%.

of bone quality, because they reduce the activity of **osteoclasts** (the cells that tear down old bone), without having any effect on **osteoblasts** (the cells that build up new bone). Because old bone is not torn down as quickly, but the bone-building osteoblasts continues, the *total mass of bone* slowly increases. But by allowing old bone tissue to hang around longer without speeding its replacement, bisphosphonate use results in bone tissue that is, on average, *older* – and thus, of poorer quality. Because this older bone tends to be more brittle, the overall architectural quality of the bone is decreased.<sup>71,81,82</sup>

For women whose bone mineral density is very low, and whose bone connectivity has *already* decayed, bisphosphonates clearly reduce the odds of a fracture. For these women, a slight decrease in *quality* is a small price to pay for a considerable increase in bone *quantity*. But recent clinical trials suggest that the same can't be said for women who have **osteopenia** – that is, who have lost significant (but not extreme) amounts of bone mineral density, but who haven't yet suffered a fracture. Such women's bone *structure* is usually still intact, and the decay of this quality appears to neutralize the benefits of an increased BMD numbers.

**There was no clear anti-fracture benefit from taking Fosamax®** in a trial involving such women.<sup>83</sup> Their rate of hip fractures was *apparently* reduced by 21%, but their risk of suffering a wrist fracture risk actually appeared to *increase* by 19% – and *neither* result was strong enough to rule out a statistical fluke. As was emphasized in an editorial in the *Journal of the American Medical Association*, “the antifracture benefit of bisphosphonates in women with low bone mass but without prevalent fracture must be judged to be small.”<sup>84</sup>

Unfortunately, *all* of the mainstream drug treatments for osteoporosis – including **hormone replacement therapy**, **selective estrogen receptor modulators (SERMs)**, such as **raloxifene (Evista®)**, or **calcitonin (Calcimar® or Miacalcin®)** and even calcium and vitamin D<sup>85</sup> – share this problem to one extent or another: they slow down the resorption of bone, but don't support the formation of *new* bone mass.<sup>86</sup> Fluoride is a pseudo-exception: it directly increases the formation of new bone mineral crystals – but

## “But Won't My Blood Curdle??”

Because vitamin K's involvement in blood clotting is the one function that *everyone* knows about, many people understandably worry that taking high doses of **Menatetrenone** will cause excessive or abnormal blood clotting.

Fortunately, it turns out that there is no cause for concern, except in people taking “blood-thinning” (anticoagulant) drugs such as warfarin (Coumadin®). In the many clinical trials which have been conducted using megadose **Menatetrenone**, abnormal blood clotting has never been reported, even though nearly all of the studies have carefully watched for signs of such changes. For instance, in one trial women took either 90 milligrams of **Menatetrenone** (which is twice the amount used in most other trials) or a lookalike capsule with no active ingredients. The women's clotting patterns (as measured by **prothrombin times**) did not change; nor were they any different from the clotting pattern of the women taking the dummy pills.<sup>62</sup>

More recently, a twelve-week study looked in painstaking detail at the issue of possible overactivation of the body's blood-clotting machinery by a standard therapeutic dose of 45 milligrams of **Menatetrenone** per day.<sup>69</sup> These researchers used every test they could think of to root out abnormalities in blood clotting, including not just the usual **prothrombin times**, but also such exotic tests as **Automated Partial Thromboplastin Time, thrombin-antithrombin III complex, fibrinogen, prothrombin levels, prothrombin fragment 1+2, proteins S and C, antithrombin activity, and factor VII**. As you'd expect, **Menatetrenone** corrected the abnormally “thin” blood in people with frank vitamin K deficiency; but no changes in these parameters were seen in people not suffering deficiency, and **there was absolutely no hint of any hyperactivation of the clotting system as a result of Menatetrenone**.

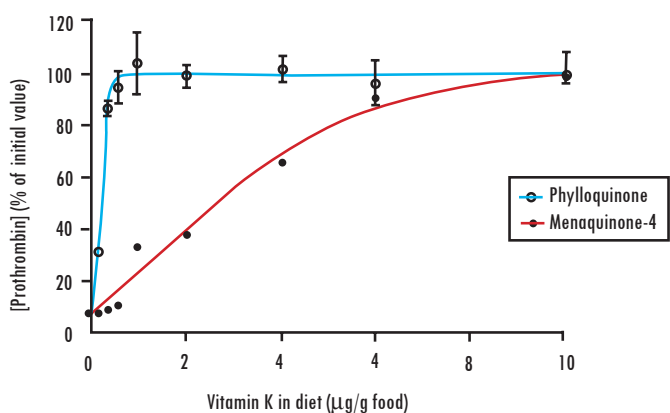
This may seem a little strange, but it makes sense when you think about the role played by vitamin K in clotting. Vitamin K “activates” the clotting protein **prothrombin** through the biochemical process of gamma-carboxylation. When prothrombin is not “activated,” it doesn't do its job. But once prothrombin *has been* “activated,” it can't be *further* “activated” by more vitamin K. It's like an on/off switch: prothrombin is either “activated,” or it's not. Once all available prothrombin has been gamma-carboxylated (which will be the case with anyone not suffering with vitamin K deficiency or taking “blood-thinning” drugs), there is nothing more that vitamin K can do to influence the protein (see **Figure 4**).

On the other hand, **high-dose vitamin K can definitely interfere with the effects of the “blood thinning” drug**

**warfarin** (Coumadin®). That's because this works precisely by interfering with the gamma-carboxylation of prothrombin. This is why some doctors tell their patients to avoid vitamin K-rich foods like broccoli, kale, and even lettuce. At doses higher than the new DRI of 100 *micrograms* (one-tenth of a *milligram*), there is a clear interference with the drug's activity, and higher doses result in higher interference.<sup>70</sup> So while your physician can work with you to adjust your warfarin dose to counter the interference produced by an extra daily helping of vitamin K-rich food (so long as such food is eaten consistently), it's impossible to do the same thing with a true megadose of vitamin K.

As compared with K<sub>1</sub>, an equal dose of K<sub>2</sub> causes less interference with the effects of warfarin, but a single dose exerts a longer-lasting effect.<sup>70</sup> The point is moot at the kind of megadoses of **Menatetrenone** used in clinical trials: **you absolutely cannot combine high-dose Menatetrenone supplements with these drugs.** On the other hand, there are some drugs and supplements which can fight excessive thrombosis *without* interacting with "activation" of prothrombin by vitamin K: you might talk with your physician about such options, including **Nattokinase**, which works by enhancing **fibrinolysis** (the body's ability to break up blood clots).

Actually, the situation is a little more interesting, because of vitamin K's effects on some other proteins, research suggests that it may actually *prevent* the abnormal clotting on blood vessel walls (**thrombosis**) that contributes to heart disease and can trigger a heart attack, even as it is necessary to normal coagulation. We'll explore this, and other heart-protective effects of **Menatetrenone**, in a future issue of *Advances*.



**Figure 4:** Prothrombin levels quickly plateau as vitamin K intake increases. Note the lower capacity of Menatetrenone for protein "activation". Redrawn from (2).

those crystals are of inferior quality. So the integrity of the architecture of your skeleton continues to degrade.

A "fantasy molecule" for bone health, then, would be a safe, natural substance which would address *both* sides of the osteoporosis coin: quantity *and* quality. It would

### Restoring BMD doesn't necessarily restore bone quality.

maintain or increase bone *mass*, but would also improve the *structural* integrity of the bone tissue itself.

It turns out that this molecule isn't a fantasy at all. It manifests in reality as **Menatetrenone**.

#### 'K' is for 'Kwality'

We've already seen that K<sub>2</sub> stops – or even *reverses* – bone mineral loss in clinical trials. Its effects on BMD are not as strong as those of bisphosphonates (or of the newly-rediscovered bone-building powerhouse mineral, **strontium** (see "Strontium: The First Bone *Builder*" in this special issue of *Advances*)), and yet **clinical trials prove that Menatetrenone slashes fracture risk by much more than you'd expect from a glance at the BMD numbers.** This "extra" protection would make sense if it could be shown that **Menatetrenone** improves bone *quality* as well as *quantity*. Looking into this possibility, scientists recently demonstrated that, indeed, **Menatetrenone improves the quality, architecture, and "connectivity" of bone** in animal models of menopausal osteoporosis.<sup>41,42,43</sup>

In one study,<sup>43</sup> four groups of experimental animals were compared. Two groups underwent surgery to prevent estrogen production (thereby mimicking the hormonal environment of menopause). One of these "menopausal" groups was given no treatment, while another group was given **Menatetrenone** supplements. At the same time, a third group was kept in its natural, youthful hormonal condition as a control group, and a fourth group was kept non-"menopausal" but consumed **Menatetrenone** supplements anyway.

Eight weeks of this extreme "menopause" caused the first group to suffer the loss of 20.4% of their BMD, 77% of the volume in their trabecular bone – and 78% of *their bone connectivity*, as compared with the control group. But giving the "menopausal" animals **Menatetrenone supplements kept their bone mineral density at a level which was not significantly different from the level of the controls, protected against 51% of the loss in trabecular bone volume, and prevented 74.5% of the loss of bone connectivity!**<sup>43</sup>

Just as excitingly, when the animals that were *not* placed in

the menopausal hormonal milieu were given **Menatetrenone**-fortified diets, **Menatetrenone supplements actually increased BMD and bone connectivity, to levels which were above those of the control group!**<sup>43</sup>

So where can you get more of this remarkable nutrient?

### Little K2 in Food

As we mentioned earlier, the richest Western food sources for **Menatetrenone**, per gram, are goose liver, butter, egg yolks, and fattier Emmental cheeses.<sup>24</sup> The problem is that the *amounts* of K<sub>2</sub> even in these “high-**Menatetrenone**” foods is pretty minimal, especially compared to the dosages proven to be effective in clinical trials. Goose liver paté appears to be the best dietary source of K<sub>2</sub> in the West, and its **Menatetrenone** content is just 48 *micrograms* per serving – not much more than a *thousandth* of the 45 *milligrams* (45 000 *micrograms*) proven to protect against fracture. And it hardly makes good health sense to start eating a few dozen egg yolks every day in hopes of increasing your **Menatetrenone** intake!

On the other hand, if you have a more adventuresome palate, you might see if you enjoy natto, the stringy Japanese condiment. For a food source, natto is very rich in the *bacterial* forms of K<sub>2</sub> (longer-chain **menaquinones**, such as MK-7): one tablespoon serving contains 193 *micrograms* of these forms of the nutrient. This is still well below the kinds of megadoses used to treat women with existing osteoporosis: even natto can’t give you the standard dose of 45 *milligrams* of K<sub>2</sub> used in clinical trials, which is what’s needed to get your tissue levels high enough to manifest the full range of **Menatetrenone**’s powerful effects at the cellular level. Also, it isn’t certain that the *bacterial* forms of K<sub>2</sub> (such as MK-7) will give the full benefits of **Menatetrenone** (MK-4), the form of K<sub>2</sub> made specifically by *mammals* (including people) for their use. But as the dietary studies in Japan show,<sup>23,25,26</sup> years of such lower-dose K<sub>2</sub> intake (as MK-7), beginning in your youth and continuing as a lifelong habit, clearly provides some bone-healthy benefits.

## Menatetrenone improves the quality, architecture, and “connectivity” of bone.

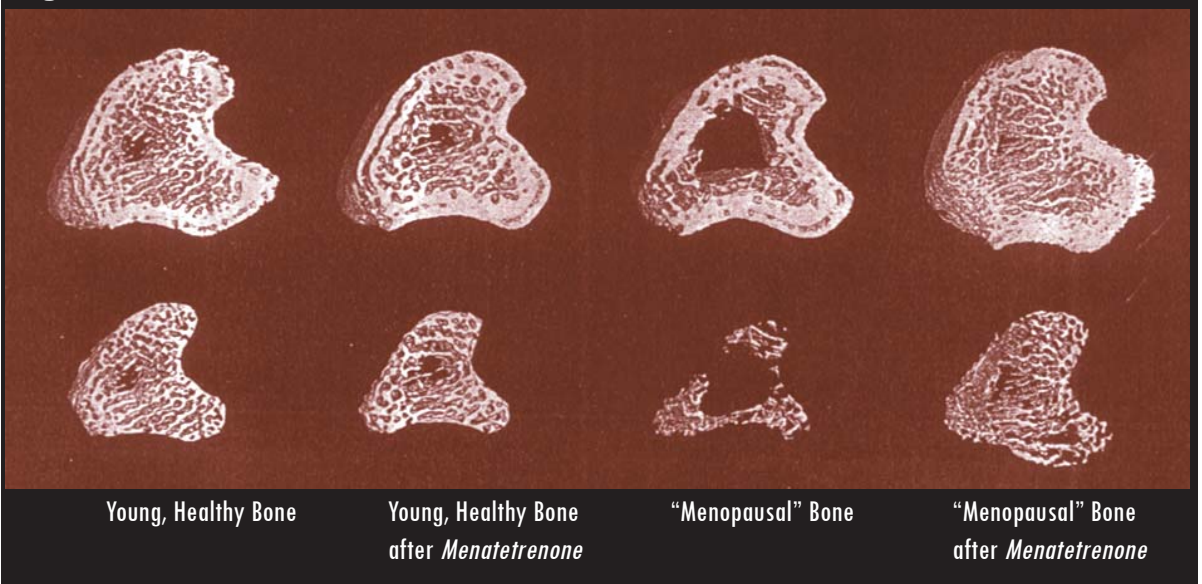
One important heads-up on natto: you’ll want to make sure that you’re getting authentic, traditional natto, which is fermented using the *Bacillus subtilis* bacterium (the specific strain is sometimes called “*Bacillus subtilis* (natto)” or even “*Bacillus natto*”). Because of excessive concern about this bacterium “contaminating” other foods, some North American food companies are selling a product labeled “natto,” which looks and tastes much like the real thing but is actually fermented using *Lactobacillus* species. Also, some supplement companies offer fermented soy supplements as a rich source of highly-bioavailable soy isoflavones. But neither of these fermented soy products contain any appreciable amount of K<sub>2</sub>.

### The Myth of the Probiotic K2 Source

“But,” you may ask, “isn’t K<sub>2</sub> made in abundance by the friendly bacteria in the colon?” Yes, it is – but unfortunately, you can’t *absorb* this K<sub>2</sub>.

It first came to be believed that the vitamin K made by probiotic bacteria in the gastrointestinal tract was a significant source of the nutrient when it was observed that rodents fed vitamin K-free lab chow did not develop severe deficiency of the vitamin. It turned out, however, that these rodents were staving off bleeding disorders through a cunning (if repulsive) act of desperation: they were consuming their own K<sub>2</sub>-containing feces.<sup>87</sup> When this tactic was blocked by using barriers which keep the rats from accessing their stool, dangerous deficiency states quickly set in.<sup>12,88</sup> Stronger evidence was provided by studies in which the colon was directly flooded with different K vitamins: virtually no vitamin K was absorbed, even when very high concentrations of vitamin K were used.<sup>88,89</sup>

**Figure 5:** Menatetrenone protects against loss of bone quality. With Permission. 43



## Menatetrenone: The Bottom Line

Vitamin K is an essential nutrient, best known for its role in blood clotting. Plants make one form of vitamin K (**phylloquinone**, or **vitamin K<sub>1</sub>**) for their use. But your body doesn't use all of the K<sub>1</sub> in your diet "as is." Instead, the body converts some of this *plant* form of the vitamin into a *different* vitamin K molecule: **Menatetrenone**, or **MK-4**, a form of vitamin K<sub>2</sub>. Tissues vary in their vitamin K needs, and it's become clear that some tissues have a *specific need* for **Menatetrenone** which is not met by phylloquinone. For some purposes (like blood clotting), phylloquinone works fine; but extensive evidence shows that **Menatetrenone** has unique effects on bone health not shared by phylloquinone.

- Fracture victims' levels of **Menatetrenone** are more depressed than are their levels of phylloquinone.
- Areas where more K<sub>2</sub> is consumed in the diet have lower fracture rates.
- Menatetrenone** inhibits the resorption (teardown) of bone caused by the local cellular messenger **prostaglandin E2 (PGE2)**. The same concentration of phylloquinone has no effect. **Menatetrenone** also cuts down on the bone cells' *formation* of PGE2 *in the first place*.
- Menatetrenone** is able to reduce the creation of **osteoclasts** (cells involved in the teardown of bone tissue) out of early cell types – but again, phylloquinone has no such power.
- Menatetrenone**, but not phylloquinone, actually increases the programmed cell death ("apoptosis") of *existing* osteoclasts.
- Menatetrenone** strengthens the bone-building legions of the **osteoblasts** (cells involved in the manufacture of new bone), mildly increasing both their numbers and their activity.

Over the course of the last decade, at least sixteen clinical trials have been performed using **Menatetrenone**, and every single one has found that **K<sub>2</sub> supplements protect bone health. Menatetrenone not only slows, halts, or even reverses loss of bone mass: it dramatically reduces your risk of suffering a fracture.**

- In one trial, women who took an ultra-high dose **Menatetrenone** supplement for 24 weeks increased their bone mineral density by an impressive 2.2%, even as the women taking a placebo (dummy pill) *lost* 7.31% of their bone density.
- In another trial, **Menatetrenone** was put to the test in a direct comparison against the bisphosphonate drug etidronate (Didrocal®). **Menatetrenone** preserved bone mass, and also slashed fracture risk by roughly *two thirds* over the course of two years.
- In a third trial, osteoporotic women taking **Menatetrenone** supplements sustained nearly no bone loss over two years, while cutting fracture risk by 64% as compared with non-supplementing women.

The ability of bones to withstand fractures is not just determined by the *quantity* of bone (as measured by **Bone Mineral Density (BMD)**), but also by the *quality* of bone – bone "microarchitecture," including especially "trabecular connectivity." Evidence suggests that **Menatetrenone's most important effects are on bone quality, not bone quantity.**

- Clinical trials have found that **Menatetrenone** provides as much protection against fracture as drugs that have much more powerful effects on BMD. Clearly, **Menatetrenone's** bone-protective effects extend to aspects of bone health beyond the BMD numbers.
- Menatetrenone** provides powerful protection against the loss of trabecular connectivity in laboratory animal models of menopausal osteoporosis.
- Menatetrenone** supplements *increase* bone quality in young, healthy animals.

To get the amount of **Menatetrenone** used to produce these effects in clinical trials and experimental studies requires a specific **Menatetrenone** supplement.

- Existing science shows that phylloquinone does not provide the same benefits as **Menatetrenone**. No clinical trials using phylloquinone supplements have been performed to show reduced fracture risk.
- The body's ability to convert phylloquinone into **Menatetrenone** is limited, flattening out at levels far below what's used in clinical trials. This ability is further reduced with aging.
- Very little vitamin K<sub>2</sub> exists in the diet, even in the richest food sources.
- While the body's friendly bacteria produce some K<sub>2</sub>, little or none of this K<sub>2</sub> is absorbed.

**Menatetrenone's** health benefits extend well beyond the skeletal system. Emerging science is now documenting the role of vitamin K – and *specifically of Menatetrenone* – in protecting our cardiovascular health, and the health of that all-important organ, the brain.

Another reason that it was once believed that the K<sub>2</sub> from colonic probiotics was absorbed was the fact that people on antibiotics often develop a vitamin K deficiency. By killing off a person's probiotic bacteria, the theory went, the antibiotics eliminated a major source of vitamin K, and deficiency set in. But it's now known that these deficiency states are not caused by the effects of the antibiotics on colonic bacteria, but by the fact that some kinds of antibiotics prevent the body from recycling "used" vitamin K into the form which is active in gamma-carboxylation.<sup>90,91</sup>

Why can't you absorb the K<sub>2</sub> supply created by your probiotics? Partly, it's because those friendly bacteria don't release the K<sub>2</sub> that they make: it's tightly bound into their cell walls.<sup>92</sup> But it also has to do with the way that the body absorbs *all* fat-soluble nutrients, such as CoQ<sub>10</sub>, lycopene, or vitamin k. Simply put, oil and water don't mix. To be absorbed, **Menatetrenone** and other K vitamins must first be dissolved in fat, and then incorporated into **micelles**, which are tiny transport globules (not unlike a simple cell membrane) formed in the small intestines from bile salts. Micelles must then be moved through the small intestine wall by special transport proteins before they can be released into the lymphatic system and, from there, work their way into the bloodstream.

Low down in the intestinal tract where probiotic bacteria live, there is little fat available into which K<sub>2</sub> can be dissolved, no bile salts available for micelle formation, and no transport proteins to move any micelles that might be formed into the lymph. As a result, little or none of the K<sub>2</sub> made by these bacteria is absorbed. In fact, the need for active transport is so strong that little or no K<sub>2</sub> is absorbed into the lymphatic system even if unbound K<sub>2</sub> and bile are specially injected into the colon.<sup>89</sup>

Bottom line: for protection against the risk of a broken hip, you'll want to consider a supplement.

**K<sub>1</sub> Won't Get You There**

We've seen the reasons to choose **Menatetrenone** over phylloquinone as the vitamin K for bone health – and, in future issues, we'll explore the similar evidence for K<sub>2</sub>'s ability to protect heart health and the brain. But some will wonder: *if the body converts K<sub>1</sub> into Menatetrenone, won't an extra-large dose of phylloquinone do just as well?*

Unfortunately, this strategy won't work, because in addition to phylloquinone's lower bioavailability<sup>24,93,94</sup> as compared with **Menatetrenone**, careful animal feeding experiments have shown that **the body's ability to make Menatetrenone from K<sub>1</sub> is limited**, and the *percentage* conversion in vital tissues like bone and heart gets lower and lower as intake of phylloquinone increases. As a result, **total**

**Little or none of the K<sub>2</sub> made by these bacteria is absorbed.**

**Table 1:** Conversion of K<sub>1</sub> to **Menatetrenone** is limited. Data taken from (2).

Menatetrenone (ng/g tissue)				
	Testis	Pancreas	Bone	Heart
<u>Baseline</u>	107	239	2.2	0.9
<u>Extra Phylloquinone</u>				
"RDA"	91	339	3.7	1.9
10 × "RDA"	70	570	8.2	1.3
1000 × "RDA"	85	1471	12	1.3
5000 × "RDA"	343	938	9.6	1.3
<u>Extra Menatetrenone</u>				
"RDA"	230	810	2.9	5.1
10 × "RDA"	409	3490	15	1447
100 × "RDA"	467	5212	121	4217
<u>500 × "RDA"</u>	<u>734</u>	<u>10648</u>	<u>355</u>	<u>12931</u>

\* "RDA" = the amount of vitamin K required to reach peak prothrombin levels.

**levels of K<sub>2</sub> formed from K<sub>1</sub> grind to a halt well before megadose levels are reached<sup>2</sup> (see Table 1).**

On top of this, **the body's ability to upgrade phylloquinone into menatetrenone falls with age**, plummeting during the first half of life and then continuing to slowly peter out as old age advances.<sup>95</sup> The result is that tissue levels of K<sub>2</sub> get lower the older you get,<sup>96</sup> even if you continue to get the same amount of K<sub>1</sub> in your diet and supplements (see **Table 2**).<sup>95</sup> By contrast, when megadoses of **Menatetrenone** itself are provided (as in clinical trials), the extra K<sub>2</sub> is eagerly absorbed and incorporated into these organs (**Table 1**). Clearly, getting the equivalent of the megadose levels of **Menatetrenone** used in clinical trials from phylloquinone just isn't feasible.

Finally, it's important to note that **no clinical trial has ever**



been performed to show that K<sub>1</sub> supplements actually increase bone mass or protect women from fractures.<sup>97</sup>

No clinical trial has ever been performed to show that K<sub>1</sub> supplements actually increase bone mass or protect women from fractures.

Since it's now clear (as we've seen) that K<sub>2</sub> protects bone mass through several mechanisms which do *not* involve gamma-carboxylation or boosting bone mineralization, and that these mechanisms are *not* shared with phylloquinone, the two cannot be considered equivalent.

**Table 2:** Conversion of K<sub>1</sub> to Menatetrenone goes down with age. Data taken from (95).

Tissue	Menatetrenone (pmol/g tissue)		
	Young	Middle-Aged	Old
Heart	13.1	8.0	8.2
Cerebral cortex	35.6	27.2	32.8
Cerebellum	36.6	29.4	27.8
Kidney	27.0	16.5	12.9
Testis/Ovary	76.3	86.2	80.0

In other words: to experience the results seen in the clinical trials, do what the women in the clinical trials did. At the end of the day, **the only thing equivalent to Menatetrenone is Menatetrenone itself** – the clinically-proven supplement, at the clinically-proven dose.

### And if Protecting Your Bones Weren't Enough ...

For many people, **Menatetrenone's** potent support of bone health – its undeniable ability to not only preserve (or even increase) bone mass, but to improve bone *quality* and reduce the risk of suffering a fracture – will be reason enough to supplement with this powerful orthomolecule. And that one facet of **Menatetrenone's** role in health has been the only aspect for which we've had the room to explore in this article.

But **Menatetrenone's** health benefits extend well beyond the skeletal system. Emerging science is now documenting the role of vitamin k – and *specifically of Menatetrenone* – in protecting our cardiovascular health, and the health of that all-important organ, the brain. And while it won't mean much to most people, evidence has recently come to light that **Menatetrenone** (and not phylloquinone) can help restore normal blood cell development in people suffering with **myelodysplastic syndrome (MDS)** – a rare disorder caused by damage to blood stem cells, leading to low levels of many blood cell types and (too often) to leukemia.

We'll get into these other powers in an upcoming issue of *Advances*.



Until then, know that, when you choose to support the health of your bones using **Menatetrenone**, you'll also be giving much-needed support to the health of your heart, and also of your brain – the biological home of your identity.

Flesh and blood.

Body and soul.

## References

- 1 "Vitamin K." In: Scientific Review Committee. Nutrition recommendations: report of the Scientific Review Committee. Ottawa, ON: Minister of National Health & Welfare Canada. 1990; H49-42/1990E: 97-8.
- 2 Rondan JE, Thijssen HH, Vermeer C. Tissue distribution of K-vitamins under different nutritional regimens in the rat. *Biochim Biophys Acta*. 1998 Jan 8;1379(1):16-22.
- 3 Groenen-van Dooren MM, Soute BA, Jie KS, Thijssen HH, Vermeer C. The relative effects of phylloquinone and menaquinone-4 on the blood coagulation factor synthesis in vitamin K-deficient rats. *Biochem Pharmacol*. 1993 Aug 3;46(3):433-7.
- 4 Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, Wilson PW, Ordovas J, Schaefer EJ, Dawson-Hughes B, Kiel DP. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr*. 2000 May;71(5):1201-8.
- 5 Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr*. 1999 Jan;69(1):74-9.
- 6 Hart JP, Shearer MJ, Klenerman L, Catterall A, Reeve J, Sambrook PN, Dodds RA, Bitensky L, Chayen J. Electrochemical detection of depressed circulating levels of vitamin K1 in osteoporosis. *J Clin Endocrinol Metab*. 1985 Jun;60(6):1268-9.
- 7 Caraballo PJ, Heit JA, Atkinson EJ, Silverstein MD, O'Fallon WM, Castro MR, Melton LJ 3rd. Long-term use of oral anticoagulants and the risk of fracture. *Arch Intern Med*. 1999 Aug 9;159(15):1750-6.
- 8 Jamal SA, Browner WS, Bauer DC, Cummings SR. Warfarin use and risk for osteoporosis in elderly women. Study of Osteoporotic Fractures Research Group. *Ann Intern Med*. 1998 May 15;128(10):829-32.
- 9 Haffa A, Krueger D, Bruner J, Engelke J, Gundberg C, Akhter M, Binkley N. Diet- or warfarin-induced vitamin K insufficiency elevates circulating undercarboxylated osteocalcin without altering skeletal status in growing female rats. *J Bone Miner Res*. 2000 May;15(5):872-8.
- 10 Craciun AM, Groenen-van Dooren MM, Thijssen HH, Vermeer C. Induction of prothrombin synthesis by K-vitamins compared in vitamin K-deficient and in brodifacoum-treated rats. *Biochim Biophys Acta*. 1998 Mar 12;1380(1):75-81.
- 11 Groenen-van Dooren MM, Soute BA, Jie KS, Thijssen HH, Vermeer C. The relative effects of phylloquinone and menaquinone-4 on the blood coagulation factor synthesis in vitamin K-deficient rats. *Biochem Pharmacol*. 1993 Aug 3;46(3):433-7.

- 12 Sato T, Ohtani Y, Yamada Y, Saitoh S, Harada H. Difference in the metabolism of vitamin K between liver and bone in vitamin K-deficient rats. *Br J Nutr*. 2002 Apr;87(4):307-14.
- 13 Sano Y, Tadano K, Kaneko K, Kikuchi K, Yuzuriha T. Distribution of menaquinone-4, a therapeutic agent for osteoporosis, in bone and other tissues of rats. *J Nutr Sci Vitaminol (Tokyo)*. 1995 Oct;41(5):499-514.
- 14 Thijssen HH, Drittij-Reijnders MJ, Fischer MA. Phylloquinone and menaquinone-4 distribution in rats: synthesis rather than uptake determines menaquinone-4 organ concentrations. *J Nutr*. 1996 Feb;126(2):537-43.
- 15 Thijssen HH, Baars LG. Tissue distribution of selective warfarin binding sites in the rat. *Biochem Pharmacol*. 1991 Nov 6;42(11):2181-6.
- 16 Vermeer C, Hendrix H, Daemen M. Vitamin K-dependent carboxylases from non-hepatic tissues. *FEBS Lett*. 1982 Nov 8;148(2):317-20.
- 17 Friedman PA, Smith MW. A survey of rat tissues for phylloquinone epoxidase activity. *Biochem Pharmacol*. 1977 Apr 15;26(8):804-5.
- 18 Hodges SJ, Pilkington MJ, Stamp TC, Catterall A, Shearer MJ, Bitensky L, Chayen J. Depressed levels of circulating menaquinones in patients with osteoporotic fractures of the spine and femoral neck. *Bone*. 1991;12(6):387-9.
- 19 Kaneki M, Mizuno Y, Hosoi T, Inoue S, Hoshino S, Akishita M, Akedo Y, Horiki K, Nakamura T, Shiraki M, et al. Serum concentration of vitamin K in elderly women with involutional osteoporosis. *Nippon Ronen Igakkai Zasshi*. 1995 Mar;32(3):195-200.
- 20 Kanai T, Takagi T, Masuhiro K, Nakamura M, Iwata M, Saji F. Serum vitamin K level and bone mineral density in post-menopausal women. *Int J Gynaecol Obstet*. 1997 Jan;56(1):25-30.
- 21 Tamatani M, Morimoto S, Nakajima M, Fukuo K, Onishi T, Kitano S, Niinobu T, Ogihara T. Decreased circulating levels of vitamin K and 25-hydroxyvitamin D in osteopenic elderly men. *Metabolism*. 1998 Feb;47(2):195-9.
- 22 Hodges SJ, Akesson K, Vergnaud P, Obrant K, Delmas PD. Circulating levels of vitamins K1 and K2 decreased in elderly women with hip fracture. *J Bone Miner Res* 1993 Oct;8(10):1241-5.
- 23 Kaneki M, Hodges SJ, Hosoi T, Fujiwara S, Lyons A, Crean SJ, Ishida N, et al. Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K2: possible implications for hip-fracture risk. *Nutrition*. 2001 Apr;17(4):315-21.
- 24 Schurgers LJ, Vermeer C. Determination of phylloquinone and menaquinones in food. Effect of food matrix on circulating vitamin K concentrations. *Haemostasis*. 2000 Nov-Dec;30(6):298-307.
- 25 Orimo H, Hosoda Y, Fujiwara S, Mizuno S, Hashimoto T, Tamaki T, Nose T, Yamamoto K, Sasaki R. Fracture incidence in Japan. *J Bone Miner Metab*. 1991 Aug;9(Suppl):89-93. Cited in (23).
- 26 Orimo H, Hashimoto T, Shiraki M, et al. Nation-wide survey of hip fracture incidence in Japan. *Jpn Med J*. 1995;3707:27. Cited in (23).
- 27 Hara K, Akiyama Y, Tajima T, Shiraki M. Menatetrenone inhibits bone resorption partly through inhibition of PGE2 synthesis in vitro. *J Bone Miner Res*. 1993 May;8(5):535-42.
- 28 Hara K, Akiyama Y, Nakamura T, Murota S, Morita I. The inhibitory effect of vitamin K2 (menatetrenone) on bone resorption may be related to its side chain. *Bone*. 1995 Feb;16(2):179-84.
- 29 Koshihara Y, Hoshi K, Shiraki M. Vitamin K2 (menatetrenone) inhibits prostaglandin synthesis in cultured human osteoblast-like periosteal cells by inhibiting prostaglandin H synthase activity. *Biochem Pharmacol*. 1993 Oct 19;46(8):1355-62.
- 30 Takeuchi Y, Suzawa M, Fukumoto S, Fujita T. Vitamin K(2) inhibits adipogenesis, osteoclastogenesis, and ODF/RANK ligand expression in murine bone marrow cell cultures. *Bone*. 2000 Dec;27(6):769-76.
- 31 Kameda T, Miyazawa K, Mori Y, Yuasa T, Shiohara M, Nakamaru Y, Mano H, Hakeda Y, Kameda A, Kumegawa M. Vitamin K2 inhibits osteoclastic bone resorption by inducing osteoclast apoptosis. *Biochem Biophys Res Commun*. 1996 Mar 27;220(3):515-9.
- 32 Kawata T, Zernik JH, Fujita T, Tokimasa C, Tanne K. Mechanism in inhibitory effects of vitamin K2 on osteoclastic bone resorption: in vivo study in osteopetrotic (op/op) mice. *J Nutr Sci Vitaminol (Tokyo)*. 1999 Aug;45(4):501-7.
- 33 Urayama S, Kawakami A, Nakashima T, Tsuboi M, Yamasaki S, Hida A, Ichinose Y, Nakamura H, Ejima E, Aoyagi T, Nakamura T, Migita K, Kawabe Y, Eguchi K. Effect of vitamin K2 on osteoblast apoptosis: vitamin K2 inhibits apoptotic cell death of human osteoblasts induced by Fas, proteasome inhibitor, etoposide, and staurosporine. *J Lab Clin Med*. 2000 Sep;136(3):181-93.
- 34 Koshihara Y, Hoshi K. Vitamin K2 enhances osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. *J Bone Miner Res*. 1997 Mar;12(3):431-8.
- 35 Yamaguchi M, Sugimoto E, Hachiya S. Stimulatory effect of menaquinone-7 (vitamin K2) on osteoblastic bone formation in vitro. *Mol Cell Biochem*. 2001 Jul;223(1-2):131-7.
- 36 Wang X, Wu J, Shidoji Y, Muto Y, Ohishi N, Yagi K, Ikegami S, Shinki T, Udagawa N, Suda T, Ishimi Y. Effects of geranylgeronic acid in bone: induction of osteoblast differentiation and inhibition of osteoclast formation. *J Bone Miner Res*. 2002 Jan;17(1):91-100.
- 37 Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, Wesolowski G, Russell RG, Rodan GA, Reszka AA. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. *PNAS*. 1999 Jan 5;96(1):133-8.
- 38 Hoshi K, Nomura K, Sano Y, Koshihara Y. Nuclear vitamin K2 binding protein in human osteoblasts: homologue to glyceraldehyde-3-phosphate dehydrogenase. *Biochem Pharmacol*. 1999 Nov 15;58(10):1631-8.
- 39 Bach AU, Anderson SA, Foley AL, Williams EC, Suttie JW. Assessment of vitamin K status in human subjects administered "minidose" warfarin. *Am J Clin Nutr*. 1996 Dec;64(6):894-902.
- 40 Sokoll LJ, O'Brien ME, Camilo ME, Sadowski JA. Undercarboxylated osteocalcin and development of a method to determine vitamin K status. *Clin Chem*. 1995 Aug;41(8 Pt 1):1121-8.
- 41 Mawatari T, Miura H, Moro-oka T, Kawano T, Higaki H, Karamura H, Iwamoto Y. Effect of delayed therapeutic intervention with vitamin K2 after trabecular connectivity was lost in ovariectomized rats. *J Bone Miner Res*. 2000 Sep;15(Suppl 1):S308(AbsSA401).
- 42 Xin F, Takemitsu M, Atsuta Y. Effect of vitamin K(2) on lumbar vertebral bone: histomorphometric analyses in experimental osteoporotic rats. *J Orthop Sci*. 2001;6(6):535-9.
- 43 Mawatari T, Miura H, Higaki H, Moro-Oka T, Kurata K, Murakami T, Iwamoto Y. Effect of vitamin K2 on three-dimensional trabecular microarchitecture in ovariectomized rats. *J Bone Miner Res*. 2000 Sep;15(9):1810-7.
- 44 Yamaguchi M, Kakuda H, Gao YH, Tsukamoto Y. Prolonged intake of fermented soybean (natto) diets containing vitamin K2 (menaquinone-7) prevents bone loss in ovariectomized rats. *J Bone Miner Metab*. 2000;18(2):71-6.
- 45 Akiyama Y, Hara K, Kobayashi M, Tomiura T, Nakamura T. Inhibitory effect of vitamin K2 (menatetrenone) on bone resorption in ovariectomized rats: a histomorphometric and dual energy X-ray absorptiometric study. *Jpn J Pharmacol*. 1999 May;80(1):67-74.
- 46 Yamaguchi M, Taguchi H, Gao YH, Igarashi A, Tsukamoto Y. Effect of vitamin K2 (menaquinone-7) in fermented soybean (natto) on bone loss in ovariectomized rats. *J Bone Miner Metab*. 1999;17(1):23-9.
- 47 Akiyama Y, Hara K, Ohkawa I, Tajima T. Effects of menatetrenone on bone loss induced by ovariectomy in rats. *Jpn J Pharmacol*. 1993 Jun;62(2):145-53.
- 48 Tomiura T, Akiyama Y, Kobayashi M, Hara K, Kawashima H. Vitamin K2 (menatetrenone) treatment increased bone strength in rats given low-calcium diets. *Nippon Yakurigaku Zasshi*. 1999 Nov;114(5):303-13.
- 49 Hara K, Akiyama Y, Ohkawa I, Tajima T. Effects of menatetrenone on prednisolone-induced bone loss in rats. *Bone*. 1993 Nov-Dec;14(6):813-8.
- 50 Onodera K, Takahashi A, Sakurada S, Okano Y. Effects of phenytoin and/or vitamin K2 (menatetrenone) on bone mineral density in the tibiae of growing rats. *Life Sci*. 2002 Feb 15;70(13):1533-42.
- 51 Shiomi S, Nishiguchi S, Kubo S, Tamori A, Habu D, Takeda T, Ochi H. Vitamin K2 (menatetrenone) for bone loss in patients with cirrhosis of the liver. *Am J Gastroenterol*. 2002 Apr;97(4):978-81.
- 52 Iwamoto J, Takeda T, Ichimura S. Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. *J Orthop Sci*. 2001;6(6):487-92.
- 53 Inoue T, Sugiyama T, Matsubara T, Kawai S, Furukawa S. Inverse correlation between the changes of lumbar bone mineral density and serum undercarboxylated osteocalcin after vitamin K2 (menatetrenone) treatment in children treated with glucocorticoid and alfacalcidol. *Endocr J*. 2001 Feb;48(1):11-8.
- 54 Nishiguchi S, Shimoi S, Kurooka H, Tamori A, Habu D, Takeda T, Kubo S. Randomized pilot trial of vitamin K2 for bone loss in patients with primary biliary cirrhosis. *J Hepatol*. 2001 Oct;35(4):543-5.
- 55 Bunyaratavej N, Penkitti P, Kittimanon N, Boonsangsom P, Bonjongsat A, Yunoi S. Efficacy and safety of menatetrenone-4 postmenopausal Thai women. *J Med Assoc Thai*. 2001 Oct;84 Suppl 2:S553-9.
- 56 Iwamoto J, Takeda T, Ichimura S. Effect of combined administration of vitamin D3 and vitamin K2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis. *J Orthop Sci*. 2000;5(6):546-51.
- 57 Yonemura K, Kimura M, Miyaji T, Hishida A. Short-term effect of vitamin K administration on prednisolone-induced loss of bone mineral density in patients with chronic glomerulonephritis. *Calcif Tissue Int*. 2000 Feb;66(2):123-8.
- 58 Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res*. 2000 Mar;15(3):515-21.
- 59 Sugiyama T, Saito Y, Kaichi I, Sugi M, Tanaka H, Kawai S. Menatetrenone plus alfacalcidol treatment for bone problems in eight children with skeletal unloading. *J Bone Miner Metab*. 2000;18(1):41-4.
- 60 Somekawa Y, Chiguchi M, Harada M, Ishibashi T. Use of vitamin K2 (menatetrenone) and 1,25-dihydroxyvitamin D3 in the prevention of bone loss induced by leuprolide. *J Clin Endocrinol Metab*. 1999 Aug;84(8):2700-4.
- 61 Iwamoto I, Kosha S, Noguchi S, Murakami M, Fujino T, Douchi T, Nagata Y. A longitudinal study of the effect of vitamin K2 on bone mineral density in postmenopausal women: a comparative study with vitamin D3 and estrogen-progesterone therapy. *Maturitas* 1999 Jan;31(2):161-4.
- 62 Orimo H, Shiraki M, Tomita A, Morii H, Fujita T, Ohata M. Effects of menatetrenone on the bone and mineral metabolism in osteoporosis: a double-blind placebo-controlled trial. *J Bone Miner Metab*. 1998;16(2):106-12.
- 63 Tsuji H, Honke K, Hasui M. Effects of a vitamin K2 preparation in severely handicapped patients complicated by osteopenia. *No To Hattatsu*. 1998 Nov;30(6):477-82.
- 64 Sato Y, Honda Y, Kuno H, Oizumi K. Menatetrenone ameliorates osteopenia in disuse-affected limbs of vitamin D- and K-deficient stroke patients. *Bone*. 1998 Sep;23(3):291-6.
- 65 Orimo H, Fujita T, Onomura T, Inoue T, Kishida K, Shiraki M. Clinical evaluation of Ea-0167 (menatetrenone) in the treatment of osteoporosis. Phase III double-blind multicenter comparative study with alfacalcidol. *Clin Eval*. 1992;20(1):45-100.
- 66 Orimo H, Shiraki M, Fujita T, Onomura T, Inoue T, Kishida K. Clinical evaluation of menatetrenone in the treatment of involutional osteoporosis - a double-blind multicenter comparative study with 1-alpha-hydroxy vitamin D3. *J Bone Miner Res*. 1992 Aug;7(Suppl1):S122(118).
- 67 Hattori M, Morita N, Tsujino Y, Yamamoto M, Tanizawa T. Vitamins D and K in the treatment of osteoporosis secondary to graft-versus-host disease following bone-marrow transplantation. *J Int Med Res*. 2001 Jul-Aug;29(4):381-4.
- 68 Shiraki M. Vitamin K2 effects on the risk of fractures and on lumbar bone mineral density in osteoporosis - a randomized prospective 3-year study. *Osteoporos Int*. 2002 Apr;13(Suppl 1):S160 (Abs SY29).
- 69 Asakura H, Myou S, Ontachi Y, Mizutani T, Kato M, Saito M, Morishita E, Yamazaki M, Nakao S. Vitamin K administration to elderly patients with osteoporosis induces no hemostatic activation, even in those with suspected vitamin K deficiency. *Osteoporos Int*. 2001 Dec;12(12):996-1000.
- 70 Schurgers LJ, Shearer MJ, Hamulyak K, Vermeer C. Effect of dietary vitamin K on stability of oral anticoagulant therapy: dose-response relationships in healthy subjects. *Thromb Haemost*. 2001 Jul;85(Suppl):P769.
- 71 Turner CH. Biomechanics of bone: determinants of skeletal fragility and bone quality. *Osteoporos Int*. 2002;13(2):97-104.
- 72 Parfitt AM. Trabecular bone architecture in the pathogenesis and prevention of fracture. *Am J Med*. 1987 Jan 26;82(1B):68-72.
- 73 Consensus development conference. Diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med*. 1993 Jun;94(6):646-50.
- 74 Marcus R, Majumder S. The nature of osteoporosis. In: Marcus R, Feldman D, Kelsey J (eds). *Osteoporosis*. Second Edition. 2001; New York, NY: Academic Press, Vol 2, pp 3-17.

74a World Health Organization. Study Group on Assessment of Fracture Risk and Its Application to Screening and Postmenopausal Osteoporosis. Report of a WHO Study Group. Technical Report Series Number 84. 1994;Geneva: WHO.

75 Marcelli C, Meunier PJ. Fluoride therapy. Influence on the microarchitecture and biomechanical properties of bone. *Presse Med.* 1994 Oct 1;23(29):1344-8.

76 Sogaard CH, Mosekilde L, Richards A, Mosekilde L. Marked decrease in trabecular bone quality after five years of sodium fluoride therapy – assessed by biomechanical testing of iliac crest bone biopsies in osteoporotic patients. *Bone.* 1994 Jul-Aug;15(4):393-9.

77 Hagenauer D, Welch V, Shea B, Tugwell P, Adachi JD, Wells G. Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis *Osteoporos Int* 2000;11(9):727-38.

78 Riggs BL, Hodgson SF, O'Fallon WM, Chao EY, Wahner HW, Muhs JM, Cedel SL, Melton LJ 3rd. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med.* 1990 Mar 22;322(12):802-9.

79 Hedlund LR, Gallagher JC. Increased incidence of hip fracture in osteoporotic women treated with sodium fluoride. *J Bone Miner Res.* 1989 Apr;4(2):223-5.

80 Rosen CJ, Bilezikian JP. Clinical review 123: Anabolic therapy for osteoporosis. *J Clin Endocrinol Metab.* 2001 Mar;86(3):957-64.

81 Meunier PJ, Boivin G. Bone mineral density reflects bone mass but also the degree of mineralization of bone: therapeutic implications. *Bone.* 1997 Nov;21(5):373-7.

82 Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res.* 2000 Apr;15(4):613-20.

83 Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA.* 1998 Dec 23-30;280(24):2077-82.

84 Heaney RP. Bone mass, bone fragility, and the decision to treat. *JAMA.* 1998 Dec 23-30;280(24):2119-20.

85 Netelenbos C. Osteoporosis: intervention options. *Maturitas.* 1998 Nov 16;30(3):235-9.

86 Wimalawansa SJ. Prevention and treatment of osteoporosis: efficacy of combination of hormone replacement therapy with other antiresorptive agents. *J Clin Densitom.* 2000 Summer;3(2):187-201.

87 Vermeer C, Jie KS, Knapen MH. Role of vitamin K in bone metabolism. *Annu Rev Nutr.* 1995;15:1-22.

88 Groenen-van Dooren MM, Ronden JE, Soute BA, Vermeer C. Bioavailability of phyloquinone and menaquinones after oral and colorectal administration in vitamin K-deficient rats. *Biochem Pharmacol.* 1995 Sep 7;50(6):797-801.

89 Ichihashi T, Takagishi Y, Uchida K, Yamada H. Colonic absorption of menaquinone-4 and menaquinone-9 in rats. *J Nutr.* 1992 Mar;122(3):506-12.

90 Suttie JW. The importance of menaquinones in human nutrition. *Annu Rev Nutr.* 1995;15:399-417.

91 Igarashi O. Vitamin K. *Nippon Rinsho.* 1993 Apr;51(4):910-8.

92 Shearer MJ. Vitamin K. *Lancet.* 1995 Jan 28;345(8944):229-34.

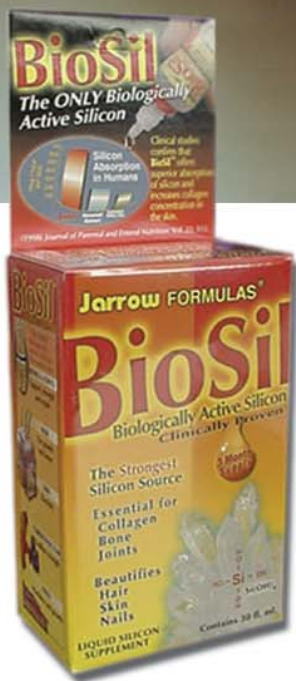
93 Koivu-Tikkanen TJ, Schurgers LJ, Thijssen HH, Vermeer C. Intestinal, hepatic, and circulating vitamin K levels at low and high intakes of vitamin K in rats. *Br J Nutr* 2000 Feb;83(2):185-90.

94 Gijbbers BL, Jie KS, Vermeer C. Effect of food composition on vitamin K absorption in human volunteers. *Br J Nutr.* 1996 Aug;76(2):223-9.

95 Huber AM, Davidson KW, O'Brien-Morse ME, Sadowski JA. Tissue phyloquinone and menaquinones in rats are affected by age and gender. *J Nutr.* 1999 May;129(5):1039-44.

96 Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet.* 2002 Jun 8;359(9322):2018-26.

97 Zittermann A. Effects of vitamin K on calcium and bone metabolism. *Curr Opin Clin Nutr Metab Care.* 2001 Nov;4(6):483-7.



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