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Vitamin K_2 and osteoporosis – facts and myths

Witamina K_2 i osteoporoza – fakty i mity

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S u m m a r y

The diagnostic-therapeutic algorithms, regarding osteoporosis, have over recent years demonstrated significant changes, as well as a number of medicinal products have been launched onto the market. It should be noted that a part of patients and their doctors take a cautious approach to these new developments. Taking the advantage of the fairly easy access to medical knowledge, patients are more and more aware of drug selection, while also reading with growing attention the leaflets, attached to medical products, sold at pharmacies and chemist's shops. There is also a certain group of patients, consciously giving up the proposed lines of therapy, the efficacy of which is confirmed by relevant scientific evidence. These patients replace doctor's therapy by natural methods, including diet supplementation. The market offers numerous agents which combine vitamins, microelements and various substances of the natural origin the composition of which is most often selected to support therapy of specific medical condition. Following the Pharmaceutical Law, the launching of the above-mentioned products onto the market does not require any separate studies and the medical properties of these products, assured in advertisements by their manufacturers, are not sufficiently supported by scientific evidence, however, it is not a rule in itself. This text has been set out to answer the question whether supplementation with vitamin K, including K_2, significantly influences the bone tissue, providing protection against osteoporosis.

S t r e s z c z e n i e

W ciągu ostatnich lat algorytmy diagnostyczno-lecznicze dotyczące osteoporozy uległy istotnym zmianom, pojawiło się na rynku również wiele leków, do których część pacjentów i lekarzy podchodzi z dużą ostrożnością. W związku z łatwym dostępem do wiedzy medycznej pacjenci częściej świadomie dokonują wyboru leków i bardziej wnikliwie czytają ulotki dołączone do zakupionych w aptece preparatów. Istnieje także pewna grupa chorych, świadomie rezygnująca z zaproponowanego, skutecznego w obliczu twardych dowodów naukowych leczenia na rzecz naturalnych metod postępowania, w tym również suplementów diety. Na rynku dostępne są liczne preparaty, stanowiące połączenia witamin, mikroelementów oraz substancji pochodzenia naturalnego, których skład najczęściej został specjalnie dobrany, aby wspomagać leczenie konkretnej jednostki chorobowej. Zgodnie z prawem farmaceutycznym wypuszczenie na rynek w/w produktów nie wymaga osobnych badań, a ich właściwości lecznicze, o których zapewnia producent, nie są wystarczająco poparte dowodami naukowymi, jednakże nie stanowi to reguły. Niniejszy tekst stanowi próbę odpowiedzi na pytanie, czy suplementacja witaminy K, w tym K_2, istotnie wpływa na układ kostny i chroni przed osteoporozą.

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INTRODUCTION

The term "Vitamin K" is referred to a group of compounds soluble in fats, called naphthoquinones. In its natural form, there are two types of vitamin K: K_1 (phylloquinone) and K_2 (menaquinone-n or MK-n). The particular forms of MK consist of 2-methyl-1,4-naphthoquinone, connected with a phytyl group (phylloquinone) and with a prenyl group of varying length (1).

Vitamin K_1 is of plant origin and is a dominating form of vitamin K in daily diet. Green vegetables and some fruits, e.g., kiwi fruit, green grapes and avocado. Vitamin K_2, i.e., n-menaquinone, is, in fact, a group of

compounds, marked with numbers, corresponding to the length of the lateral chain (difarnesyl group and other isoprene groups). Compounds from the vitamin K_2 group can, in the majority of cases, be synthesised by bacteria. Menatetrenone (MK-4) is an exception here. The type of menaquinone depends on the bacteria, participating in its synthesis. Vitamin K_2-containing foodstuffs include: liver, eggs, butter, milk, cheeses and some vegetables. Natto is among the richest sources of vitamin K2 (mainly menaquinone-7). It is a product from fermented soybeans, which contains 1100 μg of vit. K/100g (2). Other compounds from the vitamin K_2 group, such as, for example, MK-10 and MK-13, are produced by intestinal bacteria but their biological activity and digestibility are much lower. The supplements, available on the market, contain mainly phylloquinone, MK-4 or MK-7.

The reference dietary intake (RDI) is 65 μg/day for men and 55 μg/day for women (also pregnant and breast-feeding) (3). The above-mentioned RDI values are maintained within the range from 5 up to 65 μg/day, depending on gender and age and they apply only to phylloquinone (vitamin K_1). American recommendations propose a slightly higher supplementation of phylloquinone (4), i.e., 120 μg/day for men and 90 μg/day for women. Now, there are no data in the literature, concerning the maximal, safe doses of vitamin K and of RDI for vitamin K_2. In the majority of interventional studies, the applied daily supplementation considerably exceeded RDI (10 mg/day with vitamin K_1 and 45 mg/day with vitamin K_2-MK-4) and no serious adverse effects were noted. Therefore, it seems that the doses, used in the majority of available supplements, are safe (5-7).

The deficit of vitamin K is, as a rule, defined as bleeding, induced by the lack of activation of blood coagulation proteins, what is often assessed by undercarboxylated prothrombin concentration which increases proportionally to vitamin K deficit. The symptomatic deficit of vitamin K is rare and mostly associated with severe liver and pancreas disease, digestion and/or absorption disorders, alcoholism, cystic fibrosis or with chronic malnutrition (8). One should also remember about the drugs which may affect vitamin K absorption and metabolism, including phenytoin, cephalosporins, cholestyramine and high doses of vitamin E (9).

The subclinical deficit of vitamin K is more often observed in clinical practice than its clinically overt form and is most often biochemically defined as a low result of serum vitamin K concentration assay (the standard acc. to various sources: 0.5-2.5 nM; 0.2-3.2 ng/mL) or a high level of undercarboxylated osteocalcin) ($\geq$ 4.0 ng/mL) (10-12).

VITAMIN K EFFECTS ON THE OSSEOUS SYSTEM

Vitamin K plays the role of a co-factor for the gamma-glutamyl carboxylase (GGK) enzyme, localised at the endoplasmic reticulum. The proteins, which undergo vitamin K-dependent carboxylation, are called Gla proteins, demonstrate abilities to bind calcium ions and are present in the extracellular fluid, as well as in systemic fluids (13).

Vitamin K deficits result in reducing fraction of carboxylated Gla proteins, what translates into lower activity of the processes for which they are responsible; it may increase the risk of osteoporosis or enhance its course. It has been proven that vitamin K affects carboxylation of the following proteins present in the osseous tissue and in the cartilage: osteocalcin, matrix Gla protein (MGP) Gla-rich protein (GRP), S protein and gas 6 (11, 14). Osteocalcin is produced by osteoblasts in the course of bone mineralisation, being a local inhibitor for the process, thus protecting the tissue against excessive calcification. It has high affinity to hydroxyapatite calcium and its presence is thus most often confirmed in the extracellular matrix of the osseous tissue, while its much lower concentrations are found in blood serum (15). Osteocalcin concentration assays are used to evaluate the bone formation process intensity (as bone formation marker) but a hormonal role is also assigned to the above-mentioned protein (16-19). Therefore, vitamin K plays a significant role in the process of bone formation, especially in bone tissue mineralisation. Moreover, vitamin K_2 may also act via other, GGK-unrelated mechanisms (10). There is also some evidence that vitamin K_2-menaquinone (MK-7) may inhibit bone resorption, as well as osteoclastogenesis, while stimulating the bone formation process in result of induced osteoblastogenesis. It has also been demonstrated that menaquinone may play the role of a regulator in the transcription processes of genes responsible for bone metabolism (mainly bone formation), via the receptors for steroids and xenobiotics (20). It appears from other studies that OC may play some role also in the interactions between osteoclasts and osteoblasts and thus control the process of bone resorption (21, 22).

The presence of MGP is found in many systemic tissues and, similarly as in case of OC, its higher activity is observed in bones. MGP is responsible for calcium mobilisation in the osseous system. It also prevents precipitation of calcium ions in blood vessels, as well as exerts prophylactic effects against calcification of soft tissues (23). The role of the other mentioned Gla proteins has not yet been enough understood.

DOES VITAMIN K PROTECT AGAINST OSTEOPOROSIS?

As it has already been mentioned, there is a strong evidence for the beneficial role of vitamin K in bone metabolism control, what may also be associated with the prophylactics of osteoporosis. At present, the synergistic effects of many vitamins and minerals are analysed, many of which may improve the motor system, including, among others, magnesium, calcium, vitamin K and vitamin D (24-26). It has been demonstrated that a combined supplementation of vitamin K and vitamin D brings better therapeutic effects than a separate use of each of them, while their combination may stimulate the bone formation process.

VITAMIN K AND BONE MINERAL DENSITY

In clinical studies, evaluating bone mineral density (BMD), the beneficial therapeutic effects of the supplementation with vitamin K has often been demonstrated. However, data from observational studies are not entirely in line with one another, regarding the issue of the above-mentioned correlations (27-30). In two studies on the Japanese population, there was a significant relationship between the high intake of Natto, rich in vitamin K_1 and MK-7, and high BMD values (31, 32). In another study on an analogous population, the authors demonstrated a positive correlation between low concentrations of vitamin K_1 and K_2 in serum and low BMD (33).

In one of the metanalyses (5), based in their majority on randomised clinical studies, carried out on the population of healthy subjects and the population of patients with osteoporosis, the authors demonstrated a significant correlation between a high intake of vitamin K and BMD increase within the lumbar spine. In that case, the relationship between the administered therapy and hip BMD was insignificant. It should also be mentioned that, out of the 17 clinical studies, analysed by the above-mentioned group, vitamin K_2 was used in 10, while MK-7 only in 2. Moreover, in a group, receiving vitamin K_1 only, the described beneficial therapeutic effect was not found (5). In one of randomised, double-blinded clinical studies, carried out with participation of 244 Danish post-menopausal women (34), after 3 years of supplementation with 180 μg of MK-7, a statistically significant increase of BMD was observed in the femoral neck (34).

In the Postmenopausal Health Study II (PHSII), healthy female patients after menopause were enrolled to a one-year observation. All of them consumed milk and yoghurts, enriched with calcium, vitamin D and vitamin MK-7 (100 μg/day) and were educated in healthy life-style, what resulted in a significantly higher BMD increase in the lumbar spine vs. the control group (with no vitamin supplementation nor education) (35). In turn, in another study on the Norwegian population, the expected BMD increase within the proximal femur or in the lumbar spine was not demonstrated despite a relatively big dose of MK-7 supplement (360 μg/day), however, that observation had been carried out for merely 12 months (36).

Koitaya et al. (37) presented a protective effect of the annual use of low MK-4 vitamin dose (1.5 mg) on forearm BMD of healthy women after menopause. A daily intake of vitamin MK-7 in the dose of 180 μg may also prevent against osteoporosis after lung and heart transplantation, while the specific response to treatment may be highly individual (38). In another randomised clinical study, Sato et al. evaluated the effects of combined daily supplementation with 45 mg of MK-4, 1000 IU of vitamin D_2 and 600 mg of calcium on the osseous system of patients with Alzheimer's disease. That 2-year supplementation significantly improved metacarpal BMD (2.3%) vs. the control group (-5.2%), thus resulting in a significantly lower number of new fractures (2 vs. 22) (39). Vitamin MK-4, administered in same daily doses, seems also to prevent from BMD loss in the course of anorexia nervosa (40), Parkinson's disease (41), hepatic cirrhosis (42), chronic steroid therapy (43) or post-stroke hemiplegia (44).

In a meta-analysis, published in 2015 (45), the acquired data had come from 19 randomised clinical studies with participation of 6759 patients. In two studies, bisphosphonate was used for control, in seven studies, it was placebo, while in the remaining studies, the role of control was played by calcium, vitamin D or their combination. The data were analysed in two variants: an observation of medium duration (after approx. 6 months) and of long-term duration (after $\geq$ 12 months). Six of the studies evaluated lumbar spine BMD in observations of medium duration and ten studies in long-term observations. The evaluation of data from the subpopulation of female patients with osteoporosis revealed a significant increase in lumbar spine BMD, both in medium and long-term observations. Among the patients without osteoporosis, BMD changes were statistically insignificant (45).

VITAMIN K AND THE INCIDENCE OF FRACTURES

Already in the 80-ties of the previous century, it was found that patients with fracture history demonstrated low vitamin K concentrations in serum (46). A bit later, a correlation was demonstrated between the low concentrations of vitamin K_1, MK-7 and 8 and the increased incidence of vertebral and femoral fracture rates (47, 48). In a meta-analysis (49), involving 836 women of the Japanese population and 7 clinical studies, a beneficial effect of supplementation with vitamin K_2 was proven with regards to fracture risk. In result of a 2-year therapeutic intervention, the relative fracture risk significantly decreased to 0.23 for proximal femur fractures, 0.30 for vertebral fractures and only 0.19 for nonvertebral fractures. In the majority of published prospective studies (50, 51), evaluating the correlation between fracture risk and supplementation with vitamin K, phylloquinone or MK-4 was used, however, their results were optimistic. In the above-mentioned study on the population of Danish post-menopausal women (34), a lower number of vertebral fractures was observed in the group on a 3-year supplementation with vitamin MK-7, however, taking into account the rather small number of cases, the effect requires a reanalysis on a larger study population. On the other hand, some authors did not reveal any relationship between supplementation with vitamin K_2 and the risk of bone fractures (52).

In the above-mentioned meta-analysis of 19 clinical studies (45), an analysis of 7 studies, in which the researchers attempted to evaluate the fracture risk, did not, at first, demonstrate any significant drop in the fracture risk (RR = 0.63; p = 0.08) under the effect of the above-mentioned vitamin. However, having excluded one of the studies, which was characterised by high

heterogeneity of results, the relative fracture risk turned out significantly lower in the patients with vitamin K_2 supplementation (RR = 0.5; p = 0.0005) (45).

In another meta-analysis (53), the anti-fracture effect of vitamin MK-4 was evaluated in patients with neurological conditions. That meta-analysis comprised 3 randomised clinical studies, carried out in the following patient populations: patients after stroke (99 subjects in the mean age of 66 years) and with the following disease: Alzheimer's disease (178 subjects in the mean age of 78 years) and Parkinson's disease (110 subjects in the mean age of 72 years). The total relative risk of nonvertebral fracture risk (95% CI), assessed in patients supplemented with MK-4, was only 0.13 (0.05-0.35) and 0.14 for the relative hip fracture risk (0.05-0.43) in comparison with a non-supplemented group (53).

VITAMIN K AND BONE TURNOVER MARKERS

The observed changes in the concentration of studied bone markers may also announce beneficial therapeutic effects. Among others, a positive effect of the therapy with phylloquinone and vitamin K_2 (MK-4) was demonstrated with regards to reduced unOC, what may be an indirect proof of bone formation process stimulation (45, 50, 54, 55). However, in the above-mentioned studies, no significant changes were found in the concentrations of the bone specific alkaline phosphatase, thus it requires further studies and a thorough analysis of obtained results.

VITAMIN K AND COMBINED THERAPY

In one study, the subject of evaluation was the effect of a combined therapy with alendronate and vitamin K_2 (MK-4) (56). The authors of that study demonstrated higher increase of BMD in the femoral neck as a synergistic effects of the annual therapy (56). Sato et al. (57) demonstrated a significantly higher increase of the metacarpal BMD in patients, treated for 12 months with risedronate, combined with vitamin K_2 (MK-4) in comparison with a control group on risedronate only (5.7 vs. 2.1%) (57). In another clinical study (58), post-menopausal patients, treated for rheumatoid arthritis, with osteoporosis or osteopenia and with high concentrations of unOC (> 4.5 ng/mL), received a weekly alendronate dose of 35 mg and a daily MK-4 dose of 45 mg. A 12-month therapy resulted in a significant BMD increase, both in the hip and in the spine, while in the control group, receiving alendronate only, a significant BMD increase was noted only in the lumbar spine section. The obtained results may be regarded as an indirect proof of the combined therapy efficacy, however, the bias in group selection and the lack of randomisation raise certain doubts and questions (58).

Currently, another clinical study is underway, namely JOINT-03 (Japanese Osteoporosis Intervention Trial-03) (59), to which 1820 patients were qualified and divided into 2 equal groups. The first group receives risedronate (2.5 mg/day or 17.5 mg/week) and the other is on combined therapy with the above-mentioned bisphosphonate and 45 mg of MK-4 per day. After the planned 2 years of observation, an evaluation will, among others, include the prevalence rates of vertebral and nonvertebral fractures, BMD, possible height reductions and the quality of life of examined patients. The paper, published on 2014, informs that recruitment to the study was completed in February 2010, however, no results of the study have yet been published. It may therefore be assumed that the study is now in the follow-up phase (59).

DOES THE COST OF VITAMIN K APPLICATION TRANSLATE INTO ITS EFFICACY?

Attempts to answer the question are undertaken. In 2012, Gajic-Veljanoski et al. (60) published interesting results of a probabilistic analysis, using a microsimulation model to determine the cost-effectiveness of selected options of supplementations, used throughout the entire life to prevent fractures in 50 years old women after menopause and without diagnosed osteoporosis. The researchers also compared the following options: 1. Vitamin D_3 (800 IU/day) and 1200 mg of elementary calcium daily. 2. Option 1 + 45 mg of vitamin K_2. 3. Option 1 + 5 mg of vitamin K_1. 4. No supplementation. Following the authors' calculations, an additional supplementation with vitamin K_2 decreases the probability of fracture by 25% and increases by 0.7 the Quality-Adjusted Life Years (QUALYs) and also increases the cost-effectiveness index by 12,268 USD/QUALY. In turn, the application of vitamin K_1, instead of K_2, reduces the survival risk of fracture by 20%, increases QUALYs by 0.4 and also increases the cost-effectiveness index by 9,557 USD/QUALY (60). Despite promising reports, the issue of vitamin K_2 cost-effectiveness requires further studies.

IS VITAMIN K_2 BETTER THAN K_1?

It is difficult to provide an unequivocal answer to this question, as both vitamins act, in part, via the same mechanisms. However, the effects of vitamins from the K_2 group on the osseous system seem to be better documented. There are also data, indicating that the use of vitamin K_2 may exert pleiotropic effects (24). It has been demonstrated that vitamin K_2 has a longer half-life than K_1 (61). According to some authors, any comparison of the efficacy of the vitamins from the K group may turn out as serving no purpose for the possibility of systemic conversion of K_1 into K_2. Still, one should not forget that the intensity of the process in elderly subjects may be much lower than in healthy young people (62, 63). Moreover, the synthesis rate of vitamin K_2 drops down in elderly persons, most probably by smaller effectiveness of bacterial flora (64), while the absorption rate of vitamin K_1 remains unchanged regardless of ageing (65).

CONCLUSIONS

Vitamin K, especially K_2 and its MK-4 and MK-7 forms are currently the subject of research. Some

countries tend to put a huge amount of hope in the benefits from vitamin K. In 1995, vitamin MK-4 was registered in Japan as a second-line treatment of osteoporosis and for pain alleviation in the course of this disease (61). There are but very few results in the literature from large meta-analyses, comprising randomised, double-blinded clinical studies, carried out on large populations and evaluating the effects of vitamin K_2 on "hard" primary endpoints, e.g., the risk of fractures or mortality, and on specific clinical effects, e.g., BMD changes. However, as it appears from the presented data, the results of its supplementation are fairly promising and so, its additional supplementation, beside calcium and vitamin D, may improve BMD and even reduce the risk of fractures. However, further studies are needed for an objective evaluation of all the beneficial effects of vitamin K_2, especially in its low doses, with regards to osteoporosis prophylactics and therapy, as well as to optimise its dose in supplements and/or medicinal agents. One should also remember the data, indicating that vitamin K_2 may prevent from malignancy conditions, chronic inflammations, osteoarthrosis or vascular calcifications (24). Thus perhaps, vitamin K_2 should be considered as a substance of pleiotropic character, the multiyear supplementation of which may bring about additional, still unrecognised benefits.

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