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VITAMIN K2 IN OSTEOPOROSIS TREATMENT

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Abstract: *Osteoporosis is represented by loss of bone mass with consequent bone fragility and increased risk of fractures. Current treatment options include several classes of drugs and adjuvant use of vitamin D and calcium. The aim of this review is to study whether vitamin K2 could be of use to the actual treatment schemes as it is directly implicated in the normal metabolism of bone tissue. After consulting the current literature, we have found that vitamin K2 is able to reduce the risk of fracture in osteoporotic patients, increase osteocalcin and diminish levels of undercarboxylated osteocalcin. In conclusion, vitamin K2 has the capability of improving the outcome and evolution of osteoporosis with minimal to no adverse effects and possibly achieving higher treatment compliance.*

INTRODUCTION

Osteoporosis (OP) is defined as a systemic skeletal disease due to loss of bone mineral density (BMD). Microarchitecture of the bone is also affected, leading to higher fragility and consequently increased risk of fractures.(1) In Europe, actual treatment options for OP include selective estrogen receptor modulators, bisphosphonates, peptides of the parathyroid hormone family and denosumab (monoclonal antibody against RANKL). Hormonal replacement therapy after the onset of menopause and vitamin D with calcium are also used to alleviate consequences of OP.(2)

A possible treatment option could be represented by vitamin K2 (VK) because of its several roles in bone metabolism. It works by stimulating osteoblastogenesis and inhibiting the formation of osteoclasts. In presence of VK, osteocalcin (OC) is undergoing gamma carboxylation followed by a reduction of undercarboxylated osteocalcin(ucOC) level, thus improving bone calcification and alleviating healing of fractures. VK insufficiency is considered a risk factor for OP and OP fractures.(3,4)

Synthesis of OC is highly dependent on vitamin D3 (calcitriol), but OC can bind to hydroxyapatite in the bone tissue only in the carboxilated form. Therefore, vitamin K promotes mineralization of the bone.(5,6)

AIM

The aim of this review is to present the effects of VK alone or in combination with other accepted treatments of OP on BMD, risk of fractures (RF) and its way of action on OC levels.

MATERIALS AND METHODS

Data Sources and Study Selection

We performed a MEDLINE search using the following terms: "osteoporosis treatment", "osteoporosis vitamin K", "osteoporosis menatetrenone" having applied the following filters: Clinical Study, Clinical Trial, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial.

Articles ranging from 1995 till 2020 were found, but only thosde published in English were taken into consideration. A possible limitation of the search process might include using only one website (PubMed) for article selection.

Inclusion and exclusion criteria

All the articles found were manually reviewed and selected based on the presence of the osteoporosis diagnosis of the patients and inclusion of VK in the treatments studied. A total of 10 articles were chosen to be presented. In all the sorted studies VK was administered in form of menatetrenone, 45mg/day.

RESULTS

Numerous studies have compared the efficacy of VK in increasing BMD and reducing the risk of fractures. A randomized open label study assessed the impact of daily administration of VK on BMD and incidence of OP fractures, over a period of 24 months. BMD declined with -0.5%±1.0% (0.735±0.016% g/cm^2), showing a better outcome then the control group (which received no treatment). Declined RF was observed despite the lowered BMD, also serum levels of OC were significantly raised by VK with 42.4 ± 6.9% compared to baseline values.(7) Further studies have confirmed these findings. Iwamoto at al. have tested VK against etidronate (first generation bisphosphonate) and calcium over a period of 2 years. BMD was efficiently increased only by etidronate. RF has been proved to be lowered by VK with 65.2%, also by etidronate. VK did not register a better outcome than etidronate, only than calcium.(8)

In relation with other types of treatments, Ishida et al. published a study in 2004 in which they compared VK to hormonal therapy, bisphosphonates, calcitonin, vitamin D and a control group, for a period of 2 years. VK registered a decrease of -1.9% in BMD, which in comparison to the control group (-3.3%) showed significance at delaying loss of density (P=0.03). Relative risk of new vertebral fractures, in the VK group compared to control, was 0.44 (95% CI: 0.20 to 0.99) which

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reached significance. Even with this data, VK did not achieve better results than the other treatments, except for raising serum levels of OC.(9)

Third generation bisphosphonates (risedronate or minodronate) were also tested in monotherapy versus in combination with VK. Results found no significant changes in incidence of fractures or BMD between the 2 groups. The only difference noted was the decrease in the serum levels of ucOC and maintenance of higher OC levels in the VK groups, fact that was pointed in most studies.(4,10,11) VK alone can decrease serum ucOC in short periods of time (less than 6 months). It was also remarked to provoke an increase in levels of OC containing gamma-carboxylated glutamic acid, intact levels of OC and urinary excretion of N-telopeptide of type 1 collagen (a marker of bone resorbtion).(12,13)

A finding that could be of interest is the significant decrease of the FR in a subgroup of patients with severe OP (at least 5 OP fractures at the time of study enrolment) that underwent treatment of VK and calcium (oral calcium L-aspartate 1.2 g/day or dibasic calcium phosphate 3 g/day).(14)

This discovery could be expected in part because patients with severe OP and history of OP fractures tend to have a higher level of ucOC, thus by administering VK levels decrease leading to a lower risk.(11)

Another therapeutic scheme to be taken into consideration is combining VK with VD3. Menatretenone 45mg/day with 1α hydroxyvitamin D3, 0.75µg/day have been proved to increase BMD of the lumbar spine more than monotherapy of VK, VD or calcium.(6) A summarization of the studies presented can be found in table no. 1.

DISCUSSIONS

Based on the results found, VK (menatetrenone) could be prescribed in osteoporotic patients for decreasing RF. Patient's therapeutic scheme should be consulted before, as VK is contraindicated in co-administration with warfarin. Adverse effects of VK were not reported in any significant manner, in comparison with the other pharmaceutical drug classes used for OP. This could be of major advantage, as introducing VK into the therapeutic scheme may be able to reduce the dose of other drugs and consequently limit the adverse effects. The outcome may result in better treatment compliance and an increase in quality of life.

Another potential use of VK could be together with VD3 and calcium for patients who are not under treatment with other classes of drugs. This combination might also be effective in preventing or delaying the onset of OP in women with multiple risk factors.

CONCLUSIONS

The mechanism of reducing RF, but not improving BMD is not understood and further research should be performed in this direction. As far as data shows, VK has the ability to improve the evolution of OP and diminish additional risks as OP fractures.

Table no. 1. Summarization of the studies presented and their findings

Study (year)	Groups of patients (based on treatment)	BMD	Risk of fracture
Iwamoto et al. (2000) (6)	VD3 VK VD3+VK Calcium 24 months period	VD3+VK registered the best outcome P<0.01 vs VK P<0.05 vs VD3 P<0.0001 vs calcium	-
Shiraki et al. (2000) (7)	Control (no treatment) VK 24 months period	Not improved by VK. Control performed worse. Difference between groups at 24 months P=0.0339	Significantly lower in the VK group P=0.0273
Iwamoto et al. (2001) (8)	Control (calcium) Etidronate VK 24 months period	Etidronate had the best outcome P<0.0001 vs calcium P<0.01 versus VK	No difference between VK and Etidronate. Both overcame calcium
Ishida et al. (2004) (9)	Control (no treatment) Hormone replacement therapy Etidronate Calcitonin VD VK 24 months period	VK was overcome by the other treatments, except control	VK did not perform better than the other groups
Inoue et al. (2009) (14)	Calcium Calcium+ VK 36 months period	-	Significance not obtained.
Kasukawa et al. (2014) (10)	Risedronate Risedronate +VK 12 months period	No difference between groups	No difference between groups
Ebina et al. (2016) (4)	Minodronate Minodronate+VK Minodronate+VD 12 months period	Minodronate+VD surpassed the other groups P=0.0002 vs monotherapy P=0.03 vs +VK *lumbar spine	-
Tanaka et al. (2017) (11)	Risedronate Risedronate+VK 24 months period	No difference between groups P=0.62	No difference between groups P=0.21

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