Efficacy of Vitamin K as a supplement in Osteoporosis

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Abstract
Osteoporosis is characterized by decreased bone strength, weak skeletal microarchitecture and low BMD. It manifests as pain in weight bearing bones with increased incidence of fractures. Measurement of BMD and serum osteocalcin are 2 of the various methods to diagnose osteoporosis. Various treatment options for osteoporosis have their own side effect profile or failure rate. Certain studies have demonstrated supplementation of vitamin K to enhance effect of anti-osteoporotic treatment. Vitamin K is a fat soluble vitamin involved in Blood coagulation. Blood coagulation is carried out by gamma carboxylation of factors II, VII, IX and X. In the similar manner vitamin K causes Gamma carboxylation of osteocalcin. Osteocalcin is a protein which binds to hydroxyapatite in bone matrix and promotes bone formation. Various studies have been compiled in this article that have demonstrated the beneficial effect of vitamin K in various types of osteoporosis – post menopausal, disuse induced, drug induced.

Keywords: Osteoporosis vitamin K Osteocalcin BMD Post-Menopausal

1. Introduction
Osteoporosis is a condition where bone strength is decreased. It is seen in both men and women having conditions associated with bone demineralization. Osteoporosis is seen in > 10 million population in the USA and close to 25 million in India. Histologically osteoporosis manifests as defective bone mineralization leading to weak skeletal microarchitecture. Clinically, osteoporosis manifests as pain in weight bearing bones with increased incidence of fractures. Measurement of Bone Mineral Density (BMD) is a crucial investigation for diagnosis of osteoporosis. Several biochemical markers related to bone formation or bone resorption provide an index to overall rate of bone remodeling. These markers are usually used to assess treatment response. For example, serum osteocalcin is one of the markers for bone formation [1]. Treatment options for osteoporosis include calcium and vitamin D supplementation, estrogen replacement therapy, anabolic steroids, etc [2]. Certain studies have demonstrated supplementation of vitamin K to enhance effect of anti-osteoporotic treatment.

2. Vitamin K
Vitamin K is a fat soluble vitamin which comprises of structurally similar fat soluble molecules – Phylloquinone (K₁), Menaquinone (K₂) and Menadione (K₃). Phylloquinone (K₁) also called as phytonadione is obtained from plant sources such as green leafy vegetables. Vitamin K₁ content in green leafy vegetables is about 2000-8000 ng/g; while that in Cheese and curd is about 20-100 ng/g [3]. Menaquinone (K₂) is of bacterial origin [4]. Menadione (K₃) is a synthetic molecule [5] recommended daily allowance of vitamin K is 90 – 120 mcg/day [6].

2.1 Functions of Vitamin K
Blood coagulation is the major function of vitamin K. Blood coagulation by vitamin K is carried out by gamma carboxylation of coagulation proteins such as factors II, VII, IX and X. In this reaction, reduced vitamin K acts via gamma glutamyl carboxylase enzyme to deprotonate glutamate residue of target proteins. This deprotonation leads to oxidation of vitamin K (KO) which is recycled to reduced vitamin K (KH) by the enzyme – vitamin K epoxide.
Among all the isoforms of Vitamin K, Menaquinone (K₂) has most potent carboxylation activity [7].

2.2 Role of Vitamin K in bone formation

Some bone forming proteins such as osteocalcin require gamma carboxylation in order to get into their active form. Gamma carboxylation of osteocalcin occurs in the same way as blood clotting factors. Osteocalcin is synthesized by osteoblasts. Its function is to bind to hydroxyapatite in bone matrix in order to promote bone formation [8]. Osteocalcin cannot bind to hydroxyapatite without itself undergoing gamma carboxylation [9]. This fact is supported by the evidence that serum undercarboxylated osteocalcin is raised in vitamin K deficient individuals [10]. However unlike blood clotting factors which require low blood levels of vitamin K, osteocalcin requires higher levels of vitamin K for gamma carboxylation [11]. This fact has been proved by Binkley NC et al., where they studied 219 healthy adult Americans eating daily routine diet. Insufficient vitamin K levels for gamma carboxylation of osteocalcin but sufficient enough to maintain normal prothrombin time were observed in these volunteers [12].

2.3 Concern about hypercoagulation due to high doses of Vitamin K

Asakura et al., administered 15 mg vitamin K₂ three times a day to 29 geriatric patients of osteoporosis for 12 weeks. All hemostatic markers were found to be within normal range after 12 weeks [13]. Ushiyoyama et al., studied the effect of combination of vitamin K₂ and vitamin D₃ on BMD in female volunteers of post-menopausal age group. Coagulation factors increased but the effect was counterbalanced by increase in fibrinolysis [14]. Likewise, many such clinical trials have failed to demonstrate hypercoagulability with high dose of vitamin K even up to 40 mg/day [15, 16].

2.4 Effect of Vitamin K in Osteoporosis

Comparison with placebo

Orimo et al., recruited 80 osteoporosis patients and grouped them into 2 groups. First group received placebo and second group received vitamin K in dose of 90 mcg/day for 24 weeks. BMD of second metacarpal was recorded before and after treatment. Vitamin K group had shown increase in BMD by 2.20±2.48 % while placebo group had shown decrease in BMD by 7.31±3.65 % [16].

2.5 Effect of Vitamin K supplementation with calcium

Shiraki et al., recruited 241 female osteoporosis patients and grouped them into calcium group and calcium + vitamin K group. Dose of calcium used was 150 mg/day and that of vitamin K was 45 mg/day. Treatment was given for 24 months. After 24 months, calcium + vitamin K group had demonstrated lower fracture incidence of 10% compared calcium group which was 30% [17].

2.6 Effect of Vitamin K and Vitamin D₃ co-supplementation

Ushiyoyama et al., studied 172 female osteoporosis patients having BMD < 0.98 g/cm². These women were assigned randomly to one of the 4 groups – Vitamin D₃, Vitamin K₂ Vitamin D₃ + K₂ and Placebo. The above treatments were given for 24 months. Vertebral BMD of these patients were recorded at 6 monthly intervals from start of treatment. It was found that vitamin K group increased BMD from 18th month and this effect was comparable to vitamin D₃ alone. However, the combination group had shown highly significant improvement in BMD when compared to its baseline and with other groups (p<0.001). This statistically significant change was observed from 6th month itself [18].
2.7 Effect of Vitamin K supplementation with Bisphosphonates

Iwamoto et al., studied 98 post-menopausal women suffering from osteoporosis. They assigned these patients randomly into 4 groups – Calcium, Etidronate, Vitamin K, and combination of Etidronate + Vitamin K. Dose of Calcium used was 150 mg/day for 3 months and that of Vitamin K was 45 mg/day for 3 months. Etidronate was given in dose of 200 mg/day for 2 weeks/month for 3 months. It was found that incidence of fracture was significantly less in vitamin K (2 of 23 => 8.70 %) and Etidronate (2 of 25 => 8%) compared to calcium group (6 of 24 => 25 %) while fracture incidence was further decreased in combination group (1 of 26 => 3.85 %) [19].

2.8 Role of Vitamin K in Osteopenia due to immobility

Immobility is commonly seen in stroke patients whose BMD is lost significantly on the affected side compared to unaffected side. This bone loss occurs due to immobilization induced hypercalcemia and hypovitaminosis D [20]. Sato studied 108 patients of hemiplegic stroke. 54 patients were administered vitamin K for 12 months and 54 patients served as controls. BMD of second metacarpal on hemiplegic side increased by 4.3% in vitamin K treated patients whereas BMD decreased by 4.7% in controls [21].

2.9 Role of Vitamin K in Leuprolide induced Osteoporosis

Gonadotropin releasing hormone antagonists like leuprolide are commonly used for endometriosis, leiomyoma and prostate cancer. Reduction in BMD is one side effect seen in GnRH antagonist treated patients [22, 23]. Somekawa et al., studied 110 patients receiving Leuprolide. These patients were grouped as – Leuprolide only group, Vitamin K group, Vitamin D3 group, and Vitamin K + Vitamin D group. Leuprolide was not withheld for any of the above group. Dose of vitamin K was 45 mg/day and that of vitamin D was 0.5 mcg/day. These patients were followed for 6 months. Lumbar spine BMD was noted before and after the treatments. It was observed that vitamin K prevented bone loss compared to leuprolide only group. This beneficial effect of vitamin K was enhanced significantly when given in combination with vitamin D [24].

2.10 Role of Vitamin K in Osteoporosis associated with Anorexia

Anorexia is an eating disorder in which the individual restricts food intake to a large extent in order to lose weight. This leads to malnutrition. Malnutrition further leads to different sets of health problems. 1% of anorexic females suffer from osteoporosis [25].

Iketani et al., studied 21 patients diagnosed with anorexia for 11 months, during which 10 patients were prescribed vitamin K in dose of 45mg/day 11 patients did not consent for vitamin
K so they were recruited as controls. It was observed that loss of BMD was less in vitamin K treated group (-2.8%) compared to control group (-6.9%).

Graph 7

2.11 Biochemical marker for activity of Vitamin K in Osteoporosis

It would be desirable to have a serum marker for vitamin K in order to check for requirement, activity, and side effects of vitamin K. Serum Osteocalcin serves as a sensitive indicator for vitamin K activity [26]. Osteocalcin is naturally secreted by osteoblasts. It is involved in mineralization and calcium homeostasis. Osteocalcin is a vitamin K dependent calcium binding protein. Certain molecules like 1,25-dihydroxy-vitamin D, estrogen, glucocorticoids, etc. regulate transcription of osteocalcin gene. Post translational modification of osteocalcin occurs through vitamin K just like that of blood clotting factors. Vitamin K and vice versa. High levels of ucOC have been observed in elderly women [28, 29].

3. Conclusion

Vitamin K plays an important role in bone formation apart from its role in blood coagulation. Vitamin K causes Gamma carboxylation of osteocalcin – a bone forming protein, in the same way as that of blood clotting factors. Role of vitamin K in osteoporosis is supported by the fact that undercarboxylated osteocalcin is elevated in osteoporosis patients having physiological or subphysiological vitamin K levels. Supraphysiological doses are required for carboxylation of osteocalcin in osteoporosis. High doses of vitamin K are safe and do not effect prothrombin time. Various studies have proved effectiveness of vitamin K in osteoporosis as a supplement with calcium, vitamin D and bisphosphonates. Effectiveness of vitamin K has been proved in different types of osteoporosis – post menopausal, GnRH antagonists induced, anorexia associated, immobility associated, etc. Serum undercarboxylated osteocalcin can be utilized as a serum marker for activity of vitamin K.

In present scenario, if vitamin K supplementation cannot be considered due to some reason, consuming vitamin K enriched foods – Green vegetables, cheese, curd, fish, meat; could also be beneficial for osteoporosis patients.

4. References