Patient Safety & Quality Improvement Journal
http://psj.mums.ac.ir
PSQI

Effect of Vitamin K and Alendronate Combination Treatment on Bone Mineral Density of Postmenopausal Osteoporosis Patients: A Pilot Study

Mohammad Hassan Jokar[1]* (MD); Zahra Mirfeizi[1] (MD); Habib Allah Esmaili[2] (PhD); Mohsen Khamoshi[3] (MD)

1. Department of Internal Medicine, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Health Sciences Research Center, Department of Biostatistics and Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

ARTICLEINFO

Article type:
Original Article

Article history:
Received: 19- Sep-2015
Accepted: 11-Oct-2015

Keywords:
Alendronate
Osteoporosis
Vitamin K

ABSTRACT

Introduction: Osteoporosis is a common problem in postmenopausal women. Numerous studies investigated the effects of vitamin K on bone health, which yielded conflicting results. In this study, we aimed to compare the effect of vitamin K and alendronate combination with alendronate alone on Bone Mineral Density (BMD) of women with postmenopausal osteoporosis.

Materials and Methods: This study was performed in Imam Reza Hospital of Mashhad, Iran, during 14 months (January 1, 2014-February 29, 2015). Our patients (n=28) were randomly divided into two groups of receiving calcium, vitamin D, and alendronate (n=13) and receiving the same combination + vitamin K1 supplement (10 mg daily) (n=15). BMD was measured pre- and post-intervention by the same bone scanner.

Results: The baseline characteristics of the two groups did not differ significantly. The mean variation in femoral neck BMD of the alendronate and alendronate + vitamin K groups were -4.20±11.91% and 0.39±11.80%, respectively. There was no significant difference between the two groups in terms of mean change in femoral neck BMD (P=0.32). The mean variations in lumbar spine BMD of the alendronate and alendronate + vitamin K groups were 0.71±0.06% and 0.76±0.11%, respectively. There was no significant difference between the two groups in terms of mean change in lumbar spine BMD (P=0.24).

Conclusion: It was found that combined treatment with vitamin K and alendronate was not more effective than alendronate alone in increasing BMD of postmenopausal osteoporosis patients.

***Please cite this paper as*:**
Jokar MH, Mirfeizi Z, Esmaili HA, Khamoshi M. Effect of Vitamin K and Alendronate Combination Treatment on Bone Mineral Density of Postmenopausal Osteoporosis Patients: A Pilot Study. Patient Saf Qual Improv. 2016; 4(1):320-323.

Introduction

Osteoporosis is a bone disorder in which reduced strength and density of the bones increase the risk of fracture. Osteoporosis is a silent progressive disease, which remains asymptomatic until the incidence of the first fracture. Although osteoporosis is often preventable and treatable, its inaccurate and delayed diagnosis can result in substantial physical, psychosocial, and economic consequences (1, 2).

Alendronate is one of the best bisphosphonates in the treatment of osteoporosis (3).

Vitamin K has a pivotal role in coagulation, synthesis of osteocalcin, and bone health; moreover, its deficiency in women significantly increases the risk of osteoporosis (4). Few studies have investigated the effects of combination therapy with bisphosphonates and vitamin K on postmenopausal osteoporosis using etidronate or risedronate (5). However, there is a paucity of studies on vitamin K and alendronate combination for osteoporosis treatment. In this study, therefore, we aimed to compare the effect of vitamin K and alendronate combination treatment with alendronate alone on Bone Mineral Density (BMD) of postmenopausal osteoporosis patients.

Materials and Methods

This randomized, open-label study was carried out

***Corresponding Author:** Mohammad Hassan Jokar, Department of Internal Medicine, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Email: Jokarmh@mums.ac.ir

on 28 patients with postmenopausal osteoporosis. The patients were referred to the department of Rheumatology of Imam Reza Hospital, Mashhad, Iran. The inclusion criteria were: 1) postmenopausal women, 2) T-score≤-2.5 in bone densitometry, and 3) aged 45-65 years.

The exclusion criteria were: 1) having secondary osteoporosis, 2) taking anticoagulants, 3) sustaining digestive and renal problems, 4) having previous history of bisphosphonate therapy side effects, 5) having any contraindication to the use of calcium or vitamin D supplementation, 6) taking other anti-osteoporotic drugs, and 7) requiring vitamin K supplementation (for the alendronate group).

The patients were allocated to alendronate and alendronate + vitamin K groups through permuted-block randomization. The alendronate group received 70 mg alendronate orally (Alenate®, Abidi Company, Iran) once a week. The alendronate + vitamin K group received oral alendronate once a week besides 10 mg of vitamin K (Minoo Company, Iran), which was taken orally on a daily basis. All the patients received calcium and vitamin D (two doses a day, each dose contained 500 mg of calcium carbonate and 200 IU of vitamin D) (calcium-D, Jalinus Company, Iran). The treatment continued for one year, and the patients were examined every two months for adverse side effects of the drugs. At the beginning and end of the study, BMD was measured in all the patients using the same scanner.

We registered our study in the Iranian Registry of Clinical Trials (available at www.irct.ir; registration No.: IRCT201504141479N3). The Ethics Committee of Imam Reza Hospital, Mashhad, Iran, approved the study protocol, and informed consent was obtained from all the patients.

Intention-to-treat analysis was not performed in this study. The data are presented in frequency tables and indices. Student's T-test and paired T-test were performed, using SPSS statistical software (Version $_{21}$). P-value less than 0.05 was considered statistically significant.

Results

A total of 60 patients referred to our clinic, 47 of whom were eligible for the study. The samples (n=47) were randomly assigned to alendronate and alendronate + vitamin K groups (Figure 1).

The baseline characteristics of the patients are exhibited in Table 1.

Table1: Baseline characteristics of the samples

Variable	Alendronate group (n=13)	Alendronate+ vitamin K group (n=15)	
Age (year)	59.0±6.3	59.0±6.3	t=0.46 P=0.64
Height (cm)	1.53±5.6	1.53±5.6	t=0.02 P=0.98
Weight (kg)	59.3±7.0	59.3±7.0	t=0.23 P=0.95
BMI*	25.1±3.2	25.1±3.2	t=0.11 P=0.92

* Body mass index

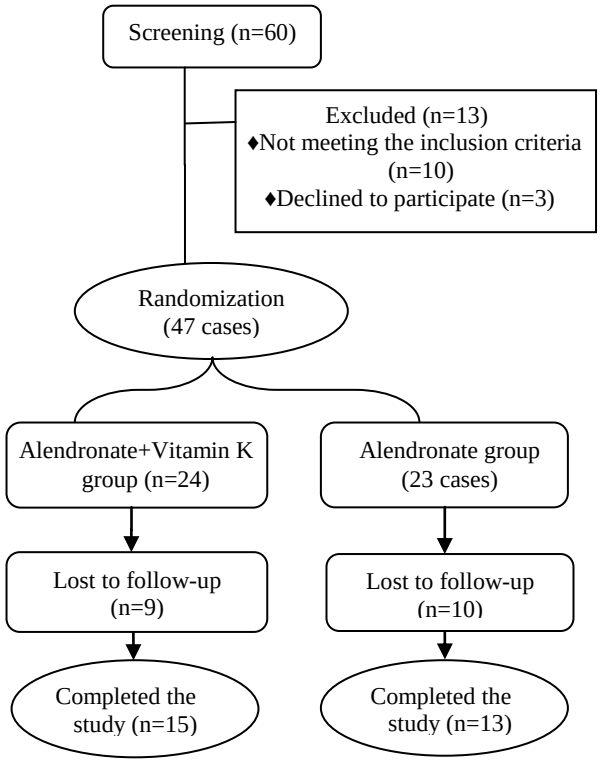

Figure1: Flowchart demonstrating the process of assigning patients in the trial arms.

There was no significant difference in the baseline characteristics between the two groups. The mean femoral neck BMDs in the alendronate group before and after the treatment were 0.61±0.09 g/cm^2 and 0.58±0.09 g/cm^2, respectively (P=0.20). In the alendronate + vitamin K group, the mean femoral neck BMDs before and after the intervention were 0.56±0.08 g/cm^2 and 0.56±0.08 g/cm^2 (P=0.93).

There was no significant difference between the two groups regarding the mean femoral neck BMD change (P=0.32) (Table 2).

Table2: The mean femoral neck bone mineral density (g/cm^2) before and after the intervention in the two groups

	Alendronate group (n=13)	Alendronate+ vitamin K group (n=15)	Independent T-test
Before the intervention	0.61±0.09	0.56±0.08	t=1.47 P=0.15
After the intervention	0.58±0.09	0.56±0.08	t=0.63 P=0.50
Difference	-0.02±0.07	*-0.001±0.06*	t=0.97 P=0.33
Change (%)	-4.20±11.91	0.39±11.80	t=1.02 P=0.32
Paired T-test	t=1.32 P=0.20	t=0.08 P=0.93	

In the alendronate group, the mean lumbar spine BMDs before and after the intervention, were 0.71±0.06 g/cm^2 and 0.76±0.04 g/cm^2, respectively (P=0.009). In the alendronate + vitamin K group, the mean lumbar spine BMDs before and after the

intervention were 0.76±0.11 g/cm^2 and 0.79±0.12 g/cm^2, respectively. Likewise, there was no significant difference between the two groups in terms of the mean change in lumbar spine BMD (P=0.24) (Table 3). In these two groups, no osteoporotic fracture was reported.

Table3: The mean bone mineral density (g/cm^2) of the lumbar spine before and after the intervention in the two groups

	Alendronate group (n=13)	Alendronate+ vitamin K group (n=15)	Independent T-test
Before the intervention	0.71±0.06	0.76±0.11	t=1.39 P=0.17
After the intervention	0.76±0.04	0.79±0.12	t=0.80 P=0.43
Difference	0.04±0.05	0.02±0.06	t=0.97 P=0.34
Change (%)	0.71±0.06	0.76±0.11	t=1.18 P=0.24
Paired T-test	t=3.11 P=0.009	t=1.57 P=0.13	

Discussion

Given the scarcity of studies on the effect of combined treatment with vitamin K and alendronate on osteoporosis, this study aimed to investigate the effect of vitamin K supplement on the treatment of postmenopausal osteoporosis.

In a study by Booth and colleagues (2003), the effect of dietary vitamin K intake on BMD of 553 female and 335 male samples was investigated. In their study, although no association between vitamin K intake and bone density was found, an indirect correlation between the number of bone fractures and amount of vitamin K intake was demonstrated (6). A 10-year prospective study, performed on 72,327 healthy female nurses, showed that dietary vitamin K intake of less than 109 µg (per day) had a direct correlation with hip fracture (7). In a review of the literature (2006), Cockayne and colleagues found that vitamin K supplement diminished bone loss (8).

In a controlled clinical trial (2008), vitamin K was administered to 440 postmenopausal osteopenic patients for 2-4 years. In the mentioned study, although no change in BMD was observed, bone fractures were fewer in vitamin K group (9). In another study (2008), vitamin K supplementation (500 µg per day) was given to male and female samples, aged 60-80 years, for three years. This study showed that bone density did not differ between vitamin K and control groups (10).

Ishida and colleagues (2004) conducted a study in Japan to investigate the effects of hormone replacement therapy (HRT), calcitonin, etidronate, alfacalcidol, and vitamin K on BMD of 396 postmenopausal osteoporosis patients (11). HRT, etidronate, calcitonin, alfacalcidol, and vitamin K caused 2.0%, -0.5%, 1.6%, -3.6%, and -1.9% variations in BMD after two years of treatment, while a mean change of -3.3% was reported in control group. Moreover, 26% of the patients in the control group developed new vertebral fractures. In comparison with the control group, the relative risks of spinal fracture were 0.35 for HRT, 0.40 for etidronate, 0.41 for calcitonin, 0.56 for alfacalcidol, and 0.44 for vitamin K.

A study by Miki and colleagues (2003), performed in Japan, evaluated the impact of vitamin K_2 on reducing serum level of undercarboxylated osteocalcin (a biomarker of vitamin K deficiency). For this purpose, 20 elderly osteoporosis women with vertebral fracture were divided into two groups of calcium and calcium + vitamin K_2. The results showed that vitamin K_2 significantly reduced the serum level of undercarboxylated osteocalcin (12).

In a study by Hidaka and colleagues (2002) (13), which aimed to evaluate the effectiveness of HRT and vitamin K in 94 postmenopausal osteoporosis patients who were treated with HRT, a decrease in BMD was observed. The results indicated that co-administration of vitamin K_2 and HRT significantly increased BMD (P=0.03). A review (2009) on the effect of vitamin K on postmenopausal women concluded that despite the lack of change in BMD, high-doses of vitamin K could promote bone strength and lower the risk of femoral neck fracture (14).

Only few studies have investigated the effects of combination therapy with bisphosphonates and vitamin K on postmenopausal osteoporosis patients (5). Sasaki and colleagues (15) studied the effects alendronate and vitamin K_2 combination therapy on BMD and bone strength of ovariectomized mice. They concluded that both treatment regimens (alendronate alone and combined treatment with alendronate and vitamin K_2) could significantly increase BMD, but the combination therapy was more effective than alendronate alone in improving bone density.

A recent randomized, open-label study, conducted on 98 postmenopausal osteoporosis patients, demonstrated significantly decreased fracture rates in 23 patients (2 out of 23) taking vitamin K_2 (45mg/ day) and 25 patients (2 out of 25) taking etidronate (200 mg/day for two weeks every three months), compared to 24 patients (6 out of 24) taking calcium lactate (2 g/day). The fracture rate in 26 samples (1out of 26) taking vitamin K_2 and etidronate decreased more than the others (5). The above-mentioned studies have shown conflicting results on the efficacy of vitamin K for the treatment of osteoporosis. Although it is possible that vitamin K alone cannot increase BMD, it seems that vitamin K improves bone quality and attenuates bone fracture risk. The results of the present study showed that combined treatment with vitamin K and alendronate was not more effective than alendronate alone in increasing BMD of postmenopausal osteoporosis patients. Our study was the first attempt to investigate the effects of this regimen on osteoporosis. The limitations of our study include: 1) the small sample size, 2) short study duration, and 3) high rate of dropout.

Conclusion

In our study, combined treatment with vitamin K and alendronate was not more effective than alendronate alone in increasing BMD of postmenopausal osteoporosis patients. It is recommended to conduct prospective long-term studies with larger sample sizes to investigate this issue.

Acknowledgement

This study was supported by a research grant from the Vice Chancellor for Research, Mashhad University of Medical Sciences.

References

1- Kanis JA, Melton Lr, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9(8):1137-41.
2- Drake MT, Clarke BL, Lewiecki EM. The pathophysiology and treatment of osteoporosis. Clinical therapeutics. 2015;37(8):1837-50.
3- Lin JT, Lane JM. Bisphosphonates. The Journal of the American Academy of Orthopaedic Surgeons. 2003 Jan-Feb;11(1):1-4.
4- Hamidi MS, Cheung AM. Vitamin K and musculoskeletal health in postmenopausal women. Molecular nutrition & food research. 2014 Aug;58(8):1647-57.
5- Iwamoto J, Sato Y, Takeda T, Matsumoto H. High-dose vitamin K supplementation reduces fracture incidence in postmenopausal women: a review of the literature. Nutrition research (New York, NY). 2009 Apr;29(4):221-8.
6- Booth SL, Broe KE, Gagnon DR, Tucker KL, Hannan MT, McLean RR, et al. Vitamin K intake and bone mineral density in women and men. The American journal of clinical nutrition. 2003 Feb;77(2):512-6.
7- Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. The American journal of clinical nutrition. 1999 Jan;69(1):74-9.
8- Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. Archives of internal medicine. 2006 Jun 26;166(12):1256-61.
9- Cheung AM, Tile L, Lee Y, Tomlinson G, Hawker G, Scher J, et al. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. PLoS medicine. 2008 Oct 14;5(10):e196.
10- Booth SL, Dallal G, Shea MK, Gundberg C, Peterson JW, Dawson-Hughes B. Effect of vitamin K supplementation on bone loss in elderly men and women. The Journal of clinical endocrinology and metabolism. 2008 Apr;93(4):1217-23.
11- Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. The American journal of medicine. 2004 Oct 15;117(8):549-55.
12- Miki T, Nakatsuka K, Naka H, Kitatani K, Saito S, Masaki H, et al. Vitamin K2 (menaquinone 4) reduces serum undercarboxylated osteocalcin level as early as 2 weeks in elderly women with established osteoporosis. Journal of bone and mineral metabolism. 2003;21(3):161-5.
13- Hidaka T, Hasegawa T, Fujimura M, Sakai M, Saito S. Treatment for patients with postmenopausal osteoporosis who have been placed on HRT and show a decrease in bone mineral density: effects of concomitant administration of vitamin K(2). J Bone Miner Metab. 2002;20(4):235-9.
14- Iwamoto J, Takeda T, Ichimura S. Combined treatment with vitamin k2 and bisphosphonate in postmenopausal women with osteoporosis. Yonsei medical journal. 2003 Oct 30;44(5):751-6.
15- Sasaki H, Miyakoshi N, Kasukawa Y, Maekawa S, Noguchi H, Kamo K, et al. Effects of combination treatment with alendronate and vitamin K(2) on bone mineral density and strength in ovariectomized mice. J Bone Miner Metab. 2010 Jul;28(4):403-9.