ALTERNATIVE TREATMENTS FOR OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN - A

SYSTEMATIC REVIEW

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ABSTRACT:

Introduction: Many postmenopausal women desire non-pharmaceutical alternatives to bisphosphonates for the treatment of osteoporosis and prevention strategies against osteoporosis. Although highly effective in the treatment of osteoporosis, bisphosphonates have a serious side effect profile. These side effects limit the use and duration of bisphosphonates for the treatment of osteoporosis, thus revealing the need for alternative therapies for osteoporosis.

Methods: The systematic review was conducted by searching the electronic database of PubMed/MEDLINE using the MeSH terms "postmenopausal osteoporosis" and "vitamins" from January 1961 to April 2019. The review included randomized controlled trials that studied the effects of vitamin supplementation on bone turnover markers and bone mineral density in postmenopausal women with or without osteoporosis. The articles selected for use in this review were assessed for quality using an assessing instrument developed by Jadad et al (1).

Results: Twelve articles were included in the final systematic review. These studies showed that vitamin supplements, soy isoflavones, or probiotics decreased the measured markers of bone turnover in studies with a treatment period ranging from 84 days to 48 months.

Discussion: Supplementation with probiotic supplements, folic acid, vitamin K, calcium, and phytochemicals with vitamins D and K are shown to be beneficial to bone health with evidence that bone turnover markers are decreased in these treatment groups, although these findings demonstrate that vitamin or probiotic supplementation are not effective in increasing bone mineral density.

<u>INTRODUCTION:</u>

Osteoporosis-related fractures pose a significant burden to postmenopausal women in regards to morbidity, mortality, and cost to society. The age-related decline of bone health is apparent as the body becomes less responsive to the hormones that control calcium homeostasis, less efficient at extracting necessary vitamins and minerals from the diet, and more sensitive to any deficiencies that were present earlier in life. Because the skeletal stores of calcium are designed to take on the imbalances that result from less-than-optimal diet, sun exposure, weight-bearing activities, and moderate hormone imbalances, the pathology that results from these deficiencies may not appear until much later in life. The overall theme of the pathology is bone loss leading to weak, porous bones and eventually, fractures.

The risk for osteoporosis increases with age and is more common in women than in men. Osteoporosis is a concern because of the types of fractures that can result, including but not limited to Colles' fracture of the distal forearm, vertebral fractures, and most notably, hip fractures. To diagnose osteoporosis, the bone mineral density of the hip and spine is assessed using a central dual-energy x-ray absorptiometry (central DXA test). The bone mineral density (BMD) is then compared to the average value in a healthy young adult. A BMD value is considered normal if it is within 1 standard deviation (SD) of the young adult average value, osteopenic if it lies between 1 – 2.5 SD below the average value, and osteoporotic if it is below 2.5 SD (2). The diagnostic criteria that has been laid out by the Osteoporosis Diagnostic Criteria Review Committee categorizes the different causes of osteoporosis into primary and secondary osteoporosis, and targets patients who have symptoms like dorsolumbar pain (3).

The diagnostic criteria for osteoporosis, the accuracy of the BMD-determining methods, the process of bone remodeling, the complex physiology of calcium homeostasis, and the effect of diet, sun exposure, and weight-bearing exercises are important to understand as a whole in order to face the intricate and weighty problem of osteoporosis that affects postmenopausal women.

Estrogen, progesterone, prolactin, and testosterone are also recognized as calcium-regulating hormones, and the effects of these hormones on calcium levels is often seen as the hormone levels decrease in aging patients. Estrogen and progesterone work in concert to decrease the rate of resorption of bone in women (4), prolactin has been shown to work with calcitriol to increase intestinal calcium absorption (5), and testosterone levels are correlated with bone mineral content in men (6).

Vitamins and minerals absorbed through the gut or the skin have an impactful effect on calcium metabolism and bone health based on diet and lifestyle. Vitamin D in the form of calcitriol has already been established as a major factor in bone health, and the importance of its synthesis and regulation need to be recognized. Vitamin K is an unlikely contributor to bone health in women, and studies are emerging that relate vitamin K intake with bone mineral density. Clinical trials have also shown that vitamin C, zinc, copper, and manganese are essential to preserving bone mass by decreasing osteoclast resorption. Finally, research has shown that dietary protein intake affects intestinal calcium absorption. There are many dietary factors that contribute to the changing state of bone and the balance of calcium levels.

In the human body, the skin contains 7-dehydrocholesterol (provitamin D[3]), which can be converted to cholesterol in the cholesterol biosynthetic pathway, or to previtamin D[3] upon exposure to sunlight (specifically UVB rays). Previtamin D[3] then rapidly isomerizes into vitamin D[3], the circulating, but inactive, form (7). Plasma vitamin D binding protein transports the inactive vitamin D[3] to the liver and kidney for a two-step activation process and then to the target cells. In the liver, vitamin D[3] is converted to 25-hydroxyvitamin D[3], and in the kidney, 25-hydroxyvitamin D[3] is converted into 1,25-dihydroxyvitamin D[3], or calcitriol, the hormonally active metabolite (8). From there, the plasma vitamin D binding protein will transport calcitriol to its target cells. As previously mentioned, vitamin D can be absorbed through the gut. The adequate intake (AI) needed to maintain a healthy level of vitamin D in a population that has uncertain UVB exposure is 200 mg/day for those younger than 50 years, 400 mg/day for those between 51–70 years, and 600 mg/day for those older than 70 years (9). Appropriate vitamin D intake and UVB exposure is essential in maintaining bone health and preventing bone loss leading to fractures.

Many postmenopausal women desire non-pharmaceutical alternatives to bisphosphonates for the treatment of osteoporosis and prevention strategies against osteoporosis. Although highly effective in the treatment of osteoporosis, bisphosphonates have a serious side effect profile including, but is not limited to, osteonecrosis of the jaw, musculoskeletal pain, ocular inflammation, and upper gastrointestinal effects. These side effects limit the use and duration of bisphosphonates for the treatment of osteoporosis, thus revealing the need for alternative therapies for osteoporosis.

METHODS:

The systematic review was conducted by searching the electronic database of PubMed/MEDLINE using the MeSH terms "postmenopausal osteoporosis" and "vitamins" from January 1961 to April 2019. The review included randomized controlled trials that studied the effects of vitamin supplementation on bone turnover markers and bone mineral density in postmenopausal women with or without osteoporosis. Studies that were written in another language other than English, or studies that did not have a published English translation, were excluded from this review. Observational studies, case reports, and review articles were also excluded from this review.

The articles selected for use in this review were assessed for quality using an assessing instrument developed by Jadad et al (1). The guidelines for assessment included the randomization, double blinding, and statement of withdrawals or dropouts from the study. Articles with a score of three or above were included in the final review.

The following data were extracted from the randomized controlled trials: the number of participants, the intervention and study design, the duration of treatment, and outcomes, including differences in bone turnover markers, and bone mineral density of the lumbar spine, total hip, and femoral neck before and after the proposed treatment.

<u>RESULTS:</u>

A search of electronic databases for articles used in this review resulted in a total of 77 full-text

articles from the PubMed database using the MeSH terms described in the 'Methods' section.

Randomized controlled trials were selected from the 77 articles, resulting in 17 full-text articles.

Each article was assessed for adequate randomization of study participants, mention of

withdrawn participants, and presence of double blinding, with each article receiving a score of 3

or higher. Following thorough examination of study design and outcomes measured, 12 articles

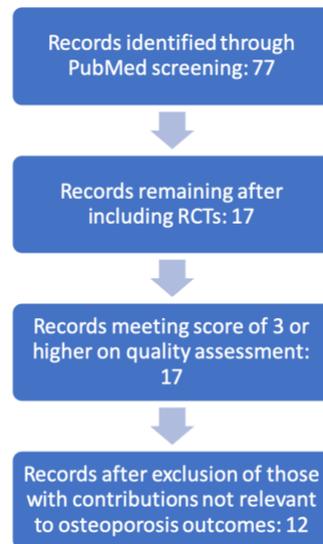remained that were relevant to the systematic review (see Figure 1).

Figure 1. Flowcharts of records included in systematic review.

The results of the studies related to alternative interventions and their effects of bone turnover

markers, lumbar spine bone mineral density, total hip bone mineral density, and femoral neck

bone mineral density are summarized in Table 1. In the study conducted by Barnuevo, et al.,

the effectiveness of intake of various dairy products were studied, and resultant biochemical

markers were evaluated in 210 women (10). This study discovered no significant difference with

supplementation with calcium and vitamin D, calcium and vitamins D and K, and calcium alone

on osteocalcin, a bone turnover marker in the 18 months that were studied. The comparative analysis of the dairy products that varied in concentrations of calcium, vitamin D, and vitamin K ultimately showed that each product had the same effectiveness on preventing or reducing bone loss. Although not statistically significant, the intake of CALNAT48 resulted in a decrease in total hip BMD of 1% and a decrease in femoral neck BMD of 1.1%. However, it also resulted in an non-statistically significant increase in lumbar spine BMD of 1.2%. In all, there were no statistically significant differences from baseline for the study participants who took in the fortified dairy products (10).

In a different study design involving a placebo-controlled trial, a study of a probiotic supplement on bone health of osteopenic postmenopausal women showed no statistically significant difference between the treatment and control groups for bone mineral density at the spine and total hip after 6 months of treatment. (11). However, this study did reveal a statistically significant decrease in bone turnover markers, namely bone alkaline phosphatase and collagen type 1 cross-linked C-telopeptide compared to the placebo group. Similarly, three studies analyzing the effect of vitamin K supplementation, folic acid, and a combination of phytochemicals and vitamins D and K, respectively, each showed a statistically significant decrease in various bone turnover markers (13) (16) (20). A randomized controlled trial assessing the effects of a calcium supplement in the form of chicken eggshell powder also showed a significant decrease in bone turnover markers such as bone-specific alkaline phosphatase, deoxypyridinoline, and calcitonin as compared to placebo (21). However, this study differed from others in this review in that it also showed an increase in femoral neck bone mineral density, as all other studies except for one showed no statistically significant

increase in bone mineral densities in the lumbar spine, total hip, or femoral neck. The other

study that noted increases in bone mineral density was a comparison of effects of denosumab,

a monoclonal antibody that binds and inhibits the receptor activator of nuclear

factor-jB ligand (RANKL), with either active or native vitamin D.

Studied intervention	Number	Duration	BTM	LS BMD	TH BMD	FN BMD	Reference
Calcium, vitamin D, vitamin K2	210	18 months	0	0	n/a	0	(10)
Multispecies probiotic supplement	50	6 months	-	0	0	n/a	(11)
Denosumab with active vitamin D or native vitamin D	56	12 months	n/a	+	+	+	(12)
Folic acid	40	6 months	-	n/a	n/a	n/a	(13)
Vitamin D and calcium	279	24 months	0	n/a	n/a	n/a	(14)
Soy isoflavones	70	6 months	+	n/a	n/a	0	(15)
Phytochemicals, vitamin D and vitamin K	51	14 weeks	-	n/a	n/a	n/a	(16)
Vitamin K	440	48 months	0	0	0	n/a	(17)
Calcium and vitamin D with and without clodronic acid	79	36 months	0	-	n/a	-	(18)
Vitamin K2	325	36 months	n/a	0	n/a	n/a	(19)
Phylloquinone	21	84 days	-	n/a	n/a	n/a	(20)
Calcium (chicken eggshell powder)	85	12 months	-	0	n/a	+	(21)

Table 1. Overview of results of records included in systematic review. Abbreviations: BTM – bone turnover markers, LS BMD – lumbar spine bone mineral density, TH BMD – total hip bone mineral density, FN BMD – femoral neck bone mineral density. Number – number of study participants. N/a – not recorded or not available in original study.

DISCUSSION:

In the articles contributing to this systematic review, it is noted that overall, the effects of

vitamin supplements, soy isoflavones, or probiotics have favorable effects in decreasing the

measured markers of bone turnover in studies with a treatment period ranging from 84 days to

48 months. Studies involving the evaluation of calcium, vitamin D, and vitamin K on bone health

showed that supplementation did not affect bone mineral density of the lumbar spine, total

hip, or femoral neck (10) (11). Compared to baseline, the maintenance of bone mineral density

over a period of 6 to 48 months is a considerable achievement in postmenopausal women, as

bone resorption increases with age and hormonal changes. As evidenced in the study

evaluating the difference between fortified dairy products with calcium, vitamin D, and vitamin K, there were no differences in lumbar spine and femoral neck bone mineral density, most notably meaning no significant decreases in bone mineral density (10). In this period of 18 months, the bone mineral density appears to be maintained through the supplementation of dairy products, although no significant difference was found between the dairy formulations. These results indicate that supplementation with dairy products delays bone loss. Similarly, favorable effects of multispecies probiotic supplementation on bone mineral density maintenance are shown (11).

It is important to take into consideration the widely positive increase in bone mineral density of lumbar spine, total hip, and femoral neck as shown in the study evaluating the effects of denosumab with vitamin D, which is an outlier compared to the other articles in this review. The difference in effect is proposed to be because of the use of denosumab in conjunction with vitamin D. Although vitamin D supplementation is crucial for efficacy during the treatment period with denosumab, it must be noted that the significant increases in bone mineral density are due to denosumab (12). Another outlier in data appears to be the effect of soy isoflavones on markers of bone turnover. The randomized, placebo-controlled trial that studied the effect of soy isoflavones with vitamins D3 and K1 showed significantly increased levels of bone-specific alkaline phosphatase and N-telopeptide in comparison with baseline and placebo groups, meaning there appeared to be increased bone turnover (15). However, the authors proposed that this unexpected increase in bone turnover markers were linked to the soy isoflavones initiating bone formation, as osteocalcin and deoxypyridinoline remained the same. Thus, this shows that a combination of soy isoflavones with vitamins D3 and K1 can reduce

bone loss in postmenopausal women, although it is unknown to what extent each of the components have independently on bone mineral density (15).

Supplementation with probiotic supplements, folic acid, vitamin K, calcium, and phytochemicals with vitamins D and K are shown to be beneficial to bone health with evidence that bone turnover markers are decreased in these treatment groups. In regards to vitamin K, dietary phylloquinone must be taken at levels up to five times the recommended vitamin K AI level to result in a statistically significant decrease in serum N-telopeptides of collagen cross-links (20). In regards to probiotic supplements, bone resorption and turnover are suppressed when treated with multispecies probiotics for six months (11), and calcium supplements alone at a level of 500mg twice daily suppress markers of bone turnover (21). These findings demonstrate that vitamin or probiotic supplementation are not effective in increasing bone mineral density, as bisphosphonates are effective in doing, but that these dietary supplements significantly decrease various bone turnover markers. This appears to be the main effect of vitamins on bone health.

There are weaknesses of this systematic review that should be taken into account when interpreting the findings. In regards to outcome measures, most studies reported outcomes as levels of bone turnover markers, or bone mineral density, not changes in the incidence of fractures, either vertebral or non-vertebral. Patient-related outcomes, such as fractures, should be the primary outcome that is recorded. Also important to note is that no two studies used the same agents. Methodological weaknesses include the possible presence of publication bias, as only published randomized-controlled trials in English were selected for use in this systematic

review. Including unpublished data from clinical trials would serve to decrease the presence of

publication bias. Also, the scope of studies could be expanded to include more than one

database to ensure that the systematic review includes as many relevant studies as possible.

Finally, there were many differences in the types of bone turnover markers that were measured

in the studies included. Independent analysis of levels of each bone turnover marker would

provide a more precise representation of the effects of certain interventions.

References:

1. Jadad, Alejandro R., et al. "Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary?" *Controlled Clinical Trials*, vol. 17, no. 1, 1996, pp. 1–12., doi:10.1016/0197-2456(95)00134-4.

2. Kanis, J. A., Melton, L. J., Christiansen, C., Johnston, C. C., & Khaltaev, N. (2009). The diagnosis of osteoporosis. *Journal of Bone and Mineral Research, 9*(8), 1137-1141. doi:10.1002/jbmr.5650090802

3. Soen, S., Fukunaga, M., Sugimoto, T., Sone, T., Fujiwara, S., Endo, N., . . . Tomomitsu, T. (2013). Diagnostic criteria for primary osteoporosis: year 2012 revision. *Journal of Bone and Mineral Metabolism, 31*(3), 247-257. doi:10.1007/s00774-013-0447-8

4. Seifert-Klauss, V., & Prior, J. C. (2010). Progesterone and Bone: Actions Promoting Bone Health in Women. *Journal of Osteoporosis, 2010*, 1-18. doi:10.4061/2010/845180

5. Ajibade, D. V., Dhawan, P., Fechner, A. J., Meyer, M. B., Pike, J. W., & Christakos, S. (2010). Evidence for a Role of Prolactin in Calcium Homeostasis: Regulation of Intestinal Transient Receptor Potential Vanilloid Type 6, Intestinal Calcium Absorption, and the25-Hydroxyvitamin D31α HydroxylaseGene by Prolactin. *Endocrine Reviews, 31*(3), 404-404. doi:10.1210/edrv.31.3.9994

6. Morita, R., Yamamoto, I., Fukunaga, M., Dokoh, S., Konishi, J., Kousaka, T., . . . Motohashi, T. (1979). Changes in Sex Hormones and Calcium Regulating Hormones with Reference to Bone Mass Associated with Aging. *Endocrinologia Japonica, 26*(Supplement), 15-22. doi:10.1507/endocrj1954.26.supplement_15

7. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004:79:362–71

8. Prosser, D., & Jones, G. (2004). Enzymes involved in the activation and inactivation of vitamin D. *Trends in Biochemical Sciences, 29*(12), 664-673. doi:10.1016/j.tibs.2004.10.005

9. Palacios, C. (2006). The Role of Nutrients in Bone Health, from A to Z. *Critical Reviews in Food Science and Nutrition, 46*(8), 621-628. doi:10.1080/10408390500466174

10. Barnuevo, Marií Dolores, et al. "In Vivo Randomized Trial of Three Marketed Milk Preparations Enriched with Calcium and Vitamins (D and K) on Bone Mass and Bone Turnover Markers from Biological Fluids in Premenopausal Caucasian Women." *Nutrición Hospitalaria*, vol. 35, no. 5, 2018, p. 1174., doi:10.20960/nh.1800.

11. Jafarnejad S, Djafarian K, Fazeli MR, Yekaninejad MS, Rostamian A, Keshavarz SA. Effects of a multispecies probiotic supplement on bone health in osteopenic postmenopausal women: a randomized, double-blind, controlled trial. J Am Coll Nutr. 2017;36(7):497-506.

12. Suzuki T., Nakamura Y., Tanaka M., Kamimura M., Ikegami S., Uchiyama S. Comparison of the effects of denosumab with either active vitamin D or native vitamin D on bone mineral density and bone turnover markers in postmenopausal osteoporosis. Mod Rheumatol. 2018;28:376–379.

13. Salari P, Abdollahi M, Heshmat R, Meybodi HA, Razi F. Effect of folic acid on bone metabolism: a randomized double blind clinical trial in postmenopausal osteoporotic women. *Daru*. 2014;22(1):62. Published 2014 Sep 16. doi:10.1186/s40199-014-0062-9

14. Dawson-Hughes B, Harris SS, Ceglia L, Palermo NJ. Effect of supplemental vitamin D and calcium on serum sclerostin levels. *Eur J Endocrinol*. 2014;170(4):645–650. Published 2014 Mar 13. doi:10.1530/EJE-13-0862

15. Lappe J, Kunz I, Bendik I, et al. Effect of a combination of genistein, polyunsaturated fatty acids and vitamins D3 and K1 on bone mineral density in postmenopausal women: a randomized, placebo-controlled, double-blind pilot study. *Eur J Nutr*. 2013;52(1):203–215. doi:10.1007/s00394-012-0304-x

16. Lamb J.J., Holick M.F., Lerman R.H., Konda V.R., Minich D.M., Desai A., Chen T.C., Austin M., Komberg J., Chang J.L., et al. Nutritional supplementation of hop rho iso-a-acids, berberine, vitamin D_3, and vitamin K_1 produces a favorable bone biomarker profile supporting healthy bone metabolism in postmenopausal women with metabolic syndrome. Nutr. Res. 2011;31:347–355. doi: 10.1016/j.nutres.2011.03.016.

17. Cheung AM, Tile L, Lee Y, et al. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial [published correction appears in PLoS Med. 2008 Dec;5(12):e247]. *PLoS Med*. 2008;5(10):e196. doi:10.1371/journal.pmed.0050196

18. Tanakol R, Yarman S, Bayraktaroglu T, et al. Clodronic acid in the treatment of postmenopausal osteoporosis. Clin Drug Invest. 2007;27(6):419–33.

19. Knapen MH, Schurgers LJ, Vermeer C. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. *Osteoporos Int*. 2007;18(7):963–972. doi:10.1007/s00198-007-0337-9

20. Martini LA, Booth SL, Saltzman E, do Rosario Dias E, de Oliveria Latorre M, Wood RJ. Dietary phylloquinone depletion and repletion in postmenopausal women: Effects on bone and mineral metabolism. Osteoporos Int. 2006;17:929–935.

21. Schaafsma A., Van Doormaal J. J., Muskiet F. A. J., Hofstede G. J. H., Pakan I., & Van Der Veer E. (2002). Positive effects of a chicken eggshell powder-enriched vitamin-mineral

supplement on femoral neck bone mineral density in healthy late post-menopausal

Dutch women. British Journal of Nutrition, 87(3), 267–275. 10.1079/BJNBJN2001515