Efficacy of Optimization of Vitamin D in Preventing Osteoporosis and Osteoporotic Fractures: A Systematic Review

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Abstract

Increased intake or supplementation of vitamin D is often recommended for normal bone health; however, its preventive effect on osteoporosis has not been fully evaluated. The aim of this review is to gather evidence of the efficacy of the optimization of vitamin D nutrition in preventing osteoporosis and osteoporotic fractures. PubMed was used for searching the relevant literature using the MeSH terms “Bone Density (limited to “human”, “female”, and “English” literature)” or “Fractures (limited to “human”, “age ≥45 years”, and “English” literature)”, and “Vitamin D”. The searches yielded 19 randomized controlled trials (RCTs), nine cohort studies, 19 case-control studies, 19 cross-sectional studies, and one meta-analysis. We attempted to answer three questions: 1) does increased vitamin D intake prevent bone loss in peri- and postmenopausal women?, 2) does increased vitamin D intake prevent osteoporotic fractures in the elderly?, and 3) does increased vitamin D intake positively affect peak bone mass attainment in young women? The answer to questions 1 and 2 is that a vitamin D intake of 10–17.5 μg/day (400–700 IU/day) or more is effective in preventing bone loss in late postmenopausal women and an intake of 17.5–20 μg/day (700–800 IU/day) or more is effective in preventing bone loss in late postmenopausal women and an intake of 17.5–20 μg/day (700–800 IU/day) or more together with a calcium supplement reduces the risk of osteoporotic fractures. For question 3, some lines of evidence support the negative effect of low vitamin D nutrition on the attainment of peak bone mass in young women. Further studies are needed to clarify the effect of vitamin D in this age group.

Key words: bone density, fractures, osteoporosis, systematic review, vitamin D

Introduction

Vitamin D and its metabolites play an important role in the maintenance of normal bone metabolism in humans, principally by increasing calcium absorption in the intestine and regulating parathyroid hormone (PTH) secretion (1). Vitamin D stores in the body are replenished by vitamin D in both food and supplements and vitamin D produced in the skin in response to exposure to ultraviolet B radiation. After vitamin D enters the blood stream, it is promptly converted to its stable form, 25-hydroxyvitamin D [25(OH)D] in the liver, and thus serum 25(OH)D levels are generally regarded as an indicator of vitamin D nutritional status. 25(OH)D in the blood is ultimately converted to 1,25-dihydroxyvitamin D [1,25(OH)\textsubscript{2}D] in the kidney, which is the most activate form among the vitamin D metabolites. Adequate vitamin D nutrition is essential for the maintenance of normal bone metabolism for the following reasons: 1) consistently low levels of serum 25(OH)D elevate PTH levels, which causes a decrease in bone mass (2), 2) 25(OH)D has recently been found to facilitate Ca absorption in the intestine mediated by stimulation of the nuclear vitamin D receptor (3), and 3) low levels of 25(OH)D is associated with reduced muscle function, and consequently with falls, which are a risk factor for fractures in the elderly (4). For these reasons, increased vitamin D intake or vitamin D supplementation is often recommended; however, its preventive effect on osteoporosis has not been fully evaluated.

There are three major strategies for preventing osteoporosis: prevention of bone loss in middle and old ages, prevention of fractures in the elderly, and attainment of maximal peak bone mass in young people (5). In this review, we tried to answer the following three questions corresponding to those strategies: 1) does increased vitamin D intake prevent bone loss in peri- and postmenopausal women?, 2) does increased vitamin D intake...
prevent osteoporotic fractures in the elderly?, and 3) does increased vitamin D intake positively affect peak bone mass attainment in young women? We limited our review to females to answer questions 1 and 3, because bone mass decrease is a much more serious problem in women than in men.

The efficacies of the active forms of vitamin D (1,25(OH)2D and its analogues), which are often used for treating osteoporosis, have been thoroughly investigated and reviewed (6). However, the nonhydroxylated forms of vitamin D, including cholecalciferol and ergocalciferol, are present in various foods, and they are commonly used as supplements. Because the effects of cholecalciferol or ergocalciferol on bone mass and osteoporotic fractures have not been well evaluated or systematically reviewed to date, we specifically reviewed vitamin D intake and vitamin D nutrition in relation to osteoporosis prevention. In some studies, blood 25(OH)D concentrations were measured and served as a good indicator of vitamin D nutrition instead of assessing vitamin D intakes, and these studies were also included in this review.

The aim of this review was to gather evidence on the efficacy of the optimization of vitamin D nutrition in preventing osteoporosis and osteoporotic fractures by attempting to answer three specific questions, and on the basis of evidence in the literature, we intended to propose a practical regimen of vitamin D nutrition.

**Literature search**

The online PubMed web site provided by the United States National Library of Medicine was used to search the literature. The MeSH terms of “Bone Density (limited to “humans”, “female”, and “English” literature)” or “Fractures (limited to “humans”, “age ≥45 years”, and “English” literature)”, and “Vitamin D” retrieved 1118 articles. The inclusion criteria for articles were as follows: 1) original human epidemiologic studies that targeted subjects with no specific or serious diseases except osteoporosis, and 2) studies that explore associations between vitamin D intake or blood 25(OH)D concentrations and bone density or the occurrence of low-energy traumatic fractures. The 1118 articles that were retrieved included 13 randomized controlled trials (RCTs), six cohort studies, and 19 cross-sectional studies that were useful in answering the questions about “Bone Density”, and eight RCTs, three cohort studies, and 19 case-control studies that were useful in answering the questions about “Fracture”. Searches for “Review”, “Meta-analysis”, and “Clinical guideline” in relation to the MeSH term “Vitamin D” were also conducted to obtain relevant systematic reviews and/or meta-analyses, and one meta-analysis was relevant.

**Level of evidence**

The body of literature on which we based our answers to the three questions was ranked with one of the following levels of evidence: (level I), evidence obtained from systematic reviews or meta-analyses; (level II), evidence obtained from RCTs; (level III), evidence obtained from nonrandomized controlled trials; (level IVa), evidence obtained from cohort studies; (level IVb), evidence obtained from case-control studies; (level IVc), evidence obtained from case series, and (level V), evidence obtained from case reports or case series; and (level VI), evidence obtained from opinions or descriptions without scientific data (7).

**Question 1: Does increased vitamin D intake prevent bone loss in peri- and postmenopausal women?**

Thirty-two articles contain evidence that is useful for answering this question (Table 1). In thirteen RCTs, the effects of vitamin D supplementation on bone loss were investigated. Vitamin D supplementation at 10 μg/day significantly prevented loss of bone mineral density (BMD) in the femoral neck and lumbar spine in postmenopausal women in the United States (mean age, 62 years) (8), and in the femoral neck of postmenopausal women in the Netherlands (aged 70 years and older) (11). Another RCT showed that vitamin D supplementation at 17.5 μg/day significantly prevented BMD loss in the femoral neck of postmenopausal women in the United States (mean age, 64 years) more than vitamin D supplementation at 2.5 μg/day (10). On the other hand, four RCTs showed negative effects of vitamin D supplementation. BMD loss was not prevented by vitamin D supplementation at 20 μg/day in British women aged between 24 and 70 years (mean age, 47 years) (19), by vitamin D supplementation at 20 μg/day in postmenopausal British women between 47 and 70 years (mean age, 59 years) (18), by vitamin D supplementation at 250 μg/week in early postmenopausal Australian women (mean age, 56 years) (20), or by vitamin D supplementation at 7.5 μg/day in Finnish postmenopausal women (mean age, 53 years) (12, 16). A meta-analysis (published in 2002) (6) wherein RCTs were evaluated showed that a small but significant positive effect of vitamin D therapy on BMDs of the lumbar spine (1-year trial only) and femoral neck.

In four studies that showed a negative effect of vitamin D supplementation, the subjects mainly consisted of premenopausal women (19) or early postmenopausal women (16, 18, 20), whereas three studies that showed a positive effect mainly targeted late postmenopausal women, and the average age of their subjects was higher than that of the subjects in the four “negative” studies. Vitamin D supplementation appears to be advantageous to older people who have a tendency to develop vitamin D insufficiency. The amounts of vitamin D supplementation in the three “positive studies” ranged from 10 to 17.5 μg/day, and these amounts or higher amounts of vitamin D intake are considered to be effective.

Four of the 13 RCTs have shown a positive effect of combining vitamin D and calcium supplementation on BMD. Supplementation with 20 μg/day of vitamin D and 1200 mg/day of Ca significantly decreased the rate of BMD loss in the proximal femur in French women (aged 64–99 years) (9); supplementation with 17.5 μg/day of vitamin D and 500 mg/day of Ca decreased the rate of BMD loss in the lumbar spine, femoral neck, and whole body in US women aged 65 years and older (13); and supplementation with 14 μg/day of vitamin D and 1000 mg/day of Ca increased spinal BMD in Danish postmenopausal women (aged 58–67 years) (15). A