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Review Article

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 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$(OH)_2$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

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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 cross-sectional studies; (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

study of bone strength showed that supplementation with 22 μg/day of vitamin D and 1000 mg/day of Ca increased bone strength in the calcaneus of elderly Swiss women (62–98 years of age) (17). All the four RCTs in which both vitamin D (14–22 μg/day) and calcium were supplemented showed a positive effect on BMD.

Observational studies consisted of four cohort studies and 15 cross-sectional studies, and three of the cohort studies and nine of the cross-sectional studies showed a positive association between vitamin D nutritional status and BMD. The results of these observational studies are summarized in Table 1.

In summary, increased vitamin D intake is useful for preventing bone loss in elderly women (based on level-I evidence) and vitamin D supplementation at 10–17.5 μg/day (400–700 IU/day) is effective in late postmenopausal women (based on level-II evidence). Furthermore, a combination of vitamin D and calcium supplementation is more promising. However, the effects of vitamin D supplementation seem unclear in early postmenopausal women and younger women (based on level-II evidence). The answer to question 1 is that vitamin D supplementation at 10–17.5 μg/day (400–700 IU/day) or more is recommended to minimize bone loss in late postmenopausal women (at least one line of level-II evidence exist).

Question 2: Does increased vitamin D intake prevent fractures in the elderly?

Thirty articles contain evidence that is useful for answering this question (Table 2). In eight RCTs, the effect of vitamin D supplementation on the occurrence of fractures was investigated, and we therefore mainly focused on this issue on the basis of the results of the RCTs. A four monthly vitamin D supplementation at 2500 μg (equivalent to 28 μg/day) significantly reduced the 5-year incidence of fracture in elderly British men and women (aged 65–85 years) (relative risk=0.78) (45). By contrast, three RCTs, in which Netherlanders 70 years of age and older received vitamin D supplementation at 10 μg/day (41), elderly Norwegians (mean age, 85 years) received vitamin D supplementation at 10 μg/day (44), and Finnish postmenopausal women (mean age 53 years) received vitamin D supplementation at 7.5 μg/day (42), showed no decrease in fracture incidence.

There has been some lines of evidence showing that increased intake of vitamin D alone prevents subsequent fractures in the elderly. In the three RCTs showing a negative effect (41, 42, 44), the levels of vitamin D supplementation were ≤10 μg/day and may have been insufficient to prevent fractures. The results of the RCT with four monthly vitamin D supplementation of 2500 μg (45) that demonstrated fracture prevention suggest that higher doses of vitamin D might be effective in preventing fractures.

In some RCTs, the efficacy of a combination of vitamin D and Ca supplementation was tested. The Decalyos I study targeted elderly French women between 69 and 106 years of age and showed that supplementation of both vitamin D at 20 μg/day and Ca at 1200 mg/day decreased hip fracture occurrence by 43% compared with the placebo group over 1.5 years, and increased BMD (9). The results of the Decalyos I study were confirmed by their follow-up study (40), and the Decalyos II study (43) showed a similar trend (relative risk=0.59, 95%CI: 0.33, 1.04). Another RCT conducted in the United States (13) showed that supplementation of both vitamin D at 17.5 μg/day and Ca at 500 mg/day reduced the 3-year incidence of nonvertebral fractures (relative risk=0.4) in elderly people aged 65 year or older.

The combination of vitamin D and a calcium supplement has shown promise, because four RCTs showed a decrease in fracture occurrence in the combined supplementation group (vitamin D 17.5–20 μg/day). In three of them (9, 13, 40) the decrease was significant, and in the other RCT (43), the decrease was borderline significant. However, almost all the subjects in these studies were elderly people aged 65 years and older, who are at a high risk of vitamin D insufficiency, and thus the results may not be applicable to elderly populations with relatively good vitamin D nutrition status, such as younger elderly people.

The observational studies consisted of three cohort and 19 case-control studies. One of the cohort studies showed that increased vitamin D intake significantly decreased fracture incidence, and 12 of the case-control studies showed poorer vitamin D nutritional status in the cases than in the controls.

In summary, vitamin D supplementation at 7.5–10 μg/day (300–400 IU/day) is unlikely to reduce the risk of fractures in the elderly (based on level-II evidence), but vitamin D supplementation at 20 μg/day (800 IU/day) may possibly prevent fractures (based on level-II evidence). Vitamin D supplementation at 17.5–20 μg/day (700–800 IU/day), together with calcium supplementation reduces the risk of fractures (based on level-II evidence). The answer to question 2 is that vitamin D supplementation at 17.5–20 μg/day (700–800 IU/day) or more with sufficient calcium intake is recommended to reduce the risk of fractures in the elderly (at least one line of level-II evidence exist). However, vitamin D supplementation at 10 μg/day (400 IU/day) or less may not be effective (at least one line of level-II evidence exist).

Question 3: Does increased vitamin D intake positively affect peak bone mass in young women?

Ten articles contain evidence that is useful for answering this question (Table 3). An RCT (19) conducted among British women aged 24–70 years showed no significant differences in changes in BMDs of the lumbar spine, proximal femur, or whole body between a vitamin D supplement (20 μg/day) group and a placebo group.

Among the observational studies, one cohort study and eight cross-sectional studies were relevant. A cohort study (68) of 171 Finnish female adolescents showed a positive association between serum 25(OH)D concentrations and 3-year changes in BMD in the lumbar spine (P=0.01). Bischoff-Ferrari et al. (39) conducted an extensive cross-sectional study of 7515 men and women in the United States aged 20 to 49 years and showed that serum 25(OH)D concentrations with the reference range (22.5–94 nmol/L) were positively associated with femoral BMD, particularly in white women. However, another cross-sectional study (70) in 259 Icelandic women

Table 1 Published papers related to answer to question 1, "Does increased vitamin D intake prevent bone loss in peri- and postmenopausal women?"

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(8)	RCT	1991	249 postmenopausal US women (mean age: 62 years)	10 μg/day of vitamin D and 377 mg/day of Ca in the supplement group, and 377 mg/day of Ca in the control group	1-year ΔBMDs of the lumbar spine and whole body	The amount of increase in spinal BMD of the supplement group (+0.85%) was larger (P=0.04) than that in the control group (+0.15%)	+	
(9)	RCT	1992	56 elderly French women (mean age: 84 years)	20 μg/day of vitamin D and 1200 mg/day of Ca in the supplement group, and a placebo in the control group	1.5-year ΔBMD of the proximal femur	The ΔBMDs of the femoral neck (+2.9%, P=0.036), total proximal femur (+2.7%, P<0.001), and trochanter (−1.0%, P=0.044) in the supplement group were different from those in the control group (+1.8%, −4.6%, −6.4%, respectively)	+	
(10)	RCT	1995	247 postmenopausal US women (mean age: 64 years)	17.5 μg/day of vitamin D and 500 mg/day of Ca in the supplement group, and 2.5 μg/day of vitamin D and 500 mg/day of Ca in the control group	2-year ΔBMDs of the lumbar spine, femoral neck, and whole body	The amount of decrease in femoral neck BMD of the supplement group (−1.1%) was smaller (P=0.003) than that in the control group (−2.5%)	+	
(11)	RCT	1995	348 elderly Dutch women 70 years of age and older (mean age: 80 years)	10 μg/day of vitamin D_3 in the supplement group and a placebo in the control group	2-year ΔBMDs of the distal radius and proximal femur	The ΔBMDs of the left and right femoral necks in the supplement group (+1.6% and +1.2%, respectively) were different (P=0.01 and P=0.001, respectively) from those in the control group (−0.3% and −1.4, respectively)	+	
(12)	RCT	1997	213 randomly sampled postmenopausal Finnish women 47–56 years of age	7.5 μg/day of vitamin D_3 and 93 mg/day of Ca in the supplement group, and 93 mg/day of Ca in the control group	2.5-year ΔBMDs of the lumbar spine and femoral neck	There was no significant difference in ΔBMD between the two groups	−	
(13)	RCT	1997	389 elderly US men and women 65 years of age and older (mean age: 71 years)	17.5 μg/day of vitamin D_3 and 500 mg/day of Ca in the supplement group, and a placebo in the control group	3-year ΔBMDs of the lumbar spine, femoral neck, and whole body	The ΔBMDs of the lumbar spine (+2.1%, P=0.02), femoral neck (+0.5%, P=0.04), and whole body (+0.06%, P<0.001) in the supplement group were different from those in the control group (+1.2%, −0.7%, −1.1%, respectively)	+	

Abbreviations: RCT, randomized controlled trial; CS, cross-sectional study; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density.

Table 1 (continued)

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(14)	RCT	1997	81 elderly Dutch women 70 years of age and older (mean age: 78 years)	10 μg/day of vitamin D in the supplement group, and a placebo in the control group	2-year ΔBMD of the femoral neck	The ΔBMD of the femoral neck in the supplement group was different from that in the control group in subjects with BB (+4.4%, P=0.04) and Bb (+4.2%, P=0.007) genotypes of vitamin D receptor *Bsm*I polymorphism	+	
(15)	RCT	1998	197 postmenopausal Danish women 58–67 years of age	14 μg/day of vitamin D_3 and 1000 mg/day of Ca in the supplement group, and a placebo in the control group	2-year ΔBMDs of the forearm, lumbar spine, and proximal femur	The ΔBMD of the lumbar spine in the supplement group (+1.6%) was different ($P<0.05$) from that in the control group (no change)	+	
(16)	RCT	1999	224 randomly sampled postmenopausal Finnish women 47–56 years of age (mean age: 53 years)	7.5 μg/day of vitamin D_3 and 93 mg/day of Ca in the supplement group, and 93 mg/day of Ca in the control group	5-year ΔBMDs of the lumbar spine and femoral neck	There was no significant difference in ΔBMD between the two groups	−	
(17)	RCT	1999	248 institutionalized Swiss women 62–98 years of age (mean age: 85 years)	22 μg/day of vitamin D_3 and 1000 mg/day of Ca in the supplement group, and a placebo in the control group	1-year change in ultrasound parameters of the calcaneus	The changes in broadband ultrasound attenuation (BUA) in the supplement group (+1.6%) was different ($P<0.01$) from those in the control group (−2.3%)	+	
(18)	RCT	2000	79 postmenopausal British monozygotic pair 47–70 years of age (mean age: 59 years)	20 μg/day of vitamin D_3 in the supplement group and a placebo in the control group	2-year ΔBMDs of the lumbar spine, proximal femur, and whole body, and ultrasound parameters in the calcaneus	There was no significant difference in ΔBMD or ultrasound parameters between the two groups	−	
(19)	RCT	2001	70 British women 24–70 years of age (mean age: 47 years)	20 μg/day of vitamin D in the supplement group and a placebo in the control group	1-year ΔBMDs of the lumbar spine, femoral neck, and whole body	There was no significant difference in ΔBMD between the two groups	−	
(20)	RCT	2003	187 early postmenopausal Australian women (mean age: 56 years)	250 μg/week of vitamin D_2 and 1000 mg/day of Ca in the supplement group, and 1000 mg/day of Ca in the control group	2-year ΔBMDs of the forearm, lumbar spine, and proximal femur	There was no significant difference in ΔBMD between the two groups	−	
(21)	Cohort study	1992	38 US women 38–45 years of age	Vitamin D intake and serum 25(OH)D concentration	5-year ΔBMDs of the distal and proximal radius	Vitamin D intake correlated with ΔBMD of the distal radius ($r=0.509$, $P=0.02$), but serum 25(OH)D was not significantly associated with any ΔBMDs	±	Possible confounders not adjusted for, and conflicting results

Abbreviations: RCT, randomized controlled trial; CS, cross-sectional study; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density.

Table 1 (continued)

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(22)	Cohort study	1998	218 US white women 65 years of age and older (mean age: 71 years)	Serum 25(OH)D concentration	3.5-year ΔBMDs of the total proximal femur and 5.9-year ΔBMD of the calcaneus	The ΔBMD (–0.1%) in the total proximal femur in women in the highest quartile of serum 25(OH)D (≥80 nmol/L) was significantly different ($P<0.05$) from that in women (–0.7%) in the lowest quartile (<21 nmol/L)	+	
(23)	Cohort study	1999	216 elderly British men and women 60–75 years of age	Serum 25(OH)D concentration	ΔBMDs of the lumbar spine and femoral neck	Serum 25(OH)D was not significantly associated with ΔBMD	–	
(24)	Cohort study	2002	139 Italian women 45–79 years of age (mean age: 58 years)	Serum 25(OH)D concentration	2-year ΔBMDs of the lumbar spine and femoral neck	Serum 25(OH)D was positively associated with ΔBMDs of the lumbar spine ($P=0.04$) and femoral neck ($P=0.04$)	+	
(25)	CS	1985	324 US women 55–80 years of age	Vitamin D intake	BMD of the mid radius	Vitamin D intake was positively associated with radial BMD ($P=0.0104$)	+	
(26)	CS	1992	138 British women 45–65 years of age (mean age: 57 years)	Serum 25(OH)D concentration	BMD of the lumbar spine and proximal femur	Serum 25(OH)D was positively associated with BMD of the lumbar spine ($r=0.18$, $P<0.05$), femoral neck ($r=0.22$, $P<0.01$), and trochanter ($r=0.19$, $P<0.05$)	+	
(27)	CS	1994	213 elderly Chinese women 60 years of age and older (mean age: 76 years)	Serum 25(OH)D concentration	BMDs of the lumbar spine and proximal femur	Serum 25(OH)D was not significantly associated with BMD	–	
(28)	CS	1995	330 elderly Dutch women 70 years of age and older (mean age: 80 years)	Serum 25(OH)D concentration	BMDs of the distal radius and proximal femur	Serum 25(OH)D was positively associated with BMD of the proximal femur ($R^2=0.114$, $P=0.0052$)	+	
(29)	CS	1996	206 German women 50–80 years of age	Serum 25(OH)D concentrations in summer and winter	BMDs of the lumbar spine and proximal femur	Summertime serum 25(OH)D was associated with femoral neck BMD ($P<0.05$)	±	

Abbreviations: RCT, randomized controlled trial; CS, cross-sectional study; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density.

Table 1 (continued)

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(30)	CS	1998	77 native-American women 19–85 years of age	Serum 25(OH)D concentration	BMDs of lumbar spine and femoral neck	Serum 25(OH)D was positively associated with spinal BMD (P=0.05)	+	
(31)	CS	1999	510 Danish women 45–58 years of age (mean age: 51 years)	Serum 25(OH)D concentration	BMDs of the lumbar spine and proximal femur	Serum 25(OH)D was positively associated with BMD of the lumbar spine (P=0.02)	+	
(32)	CS	1999	165 Czech women (mean age: 62 years)	Serum 25(OH)D concentration	BMDs of the lumbar spine, total proximal femur, and Ward's triangle	Serum 25(OH)D was positively associated with BMDs of the total proximal femur (P=0.0488) and Ward's triangle (P=0.0054)	+	
(33)	CS	2000	418 Icelandic women 70 years of age	Serum 25(OH)D concentration	BMDs of the lumbar spine, femoral neck, and whole body	Serum 25(OH)D was not significantly associated with BMD	−	
(34)	CS	2001	198 Argentinean female outpatients 37–87 years of age (mean age: 61 years)	Serum 25(OH)D concentration	BMD of the lumbar spine and femoral neck	Serum 25(OH)D was positively associated with femoral neck BMD (R^2=0.026, P=0.024)	+	
(35)	CS	2001	70 Japanese women 19–49 years of age	Serum 25(OH)D concentration	BMD of the distal forearm	Serum 25(OH)D was not significantly associated with BMD	−	
(36)	CS	2001	117 Japanese women 46–80 years of age (mean age: 66 years)	Serum 25(OH)D concentration	BMD of the distal forearm	Serum 25(OH)D was not significantly associated with BMD	−	
(37)	CS	2003	58 postmenopausal Canadian women 45–75 years of age	Vitamin D intake	BMDs of the lumbar spine, femur, and whole body	Vitamin D intake was not significantly associated with BMD	−	
(38)	CS	2003	136 postmenopausal US women (mean age: 69 years)	Serum 25(OH)D concentration	BMDs of the forearm, lumbar spine, femur, and whole body	Serum 25(OH)D was not significantly associated with BMD	−	
(39)	CS	2004	5917 US men and women 50 years of age and older	Serum 25(OH)D concentration	BMDs of the total proximal femur	Serum 25(OH)D was positively associated with BMD throughout the reference range (22.5–94 nmol/L) of serum 25(OH)D	+	

Abbreviations: RCT, randomized controlled trial; CS, cross-sectional study; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density.

Table 2 Published papers related to answer to question 2, "Does increased vitamin D intake prevent fractures in the elderly?"

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(9)	RCT	1992	3270 elderly French women 69–106 years of age (mean age: 84 years)	20 μg/day of vitamin D_3 and 1200 mg/day of Ca in the supplement group, and a placebo in the control group	Occurrence of femoral and nonvertebral fractures over 1.5 years	The incidences of femoral neck fracture (43%, P=0.043) and nonvertebral fractures (32%, P=0.015) in the supplement group were significantly lower than those in the control group	+	
(40)	RCT	1994	3270 elderly French women 69–106 years of age (mean age: 84 years)	20 μg/day of vitamin D_3 and 1200 mg/day of Ca in the supplement group, and a placebo in the control group	Occurrence of femoral and nonvertebral fractures over 3 years	The RR of femoral fractures in the supplement group to the control group was 0.70 (95%CI: 0.62, 0.78), and the RR of nonvertebral fractures was 0.70 (95%CI: 0.51, 0.91)	+	
(41)	RCT	1996	2578 Dutch men and women 70–97 years of age	10 μg/day of vitamin D_3 in the supplement group, and a placebo in the control group	Occurrence of hip and peripheral bone fractures over 3.5 years	The hazard ratio of femoral neck fracture in the supplement group to the control group was 1.18 (95%CI: 0.81, 1.71), and the hazard ratio of other fractures was 1.03 (95%CI: 0.75, 1.40)	–	
(13)	RCT	1997	389 elderly US men and women 65 years of age and older (mean age: 71 years)	17.5 μg/day of vitamin D_3 and 500 mg/day of Ca in the supplement group, and a placebo in the control group	Occurrence of nonvertebral fracture over 3 years	The RR of femoral neck fracture in the supplement group to the control group was 0.5 (95%CI: 0.2, 0.9), and the RR of nonvertebral fractures was 0.4 (95%CI: 0.2, 1.0)	+	
(42)	RCT	1998	226 randomly sampled postmenopausal Finnish women 47–56 years of age (mean age: 53 years)	7.5 μg/day of vitamin D_3 and 93 mg/day of Ca in the supplement group, and 93 mg/day of Ca in the control group	Occurrence of nonvertebral fractures over 5 years	The RR of nonvertebral fracture in the supplement group to the control group was 0.47 (95%CI: 0.20, 1.14)	–	
(43)	RCT	2002	610 French women 64–99 years of age	20 μg/day of vitamin D and 1200 mg/day of Ca in the supplement group, and a placebo in the control group	Occurrence of femoral fracture over 2 years	The RR of femoral neck fracture in the supplement group to the control group was 0.59 (95%CI: 0.33, 1.04)	–	
(44)	RCT	2002	1144 elderly Norwegian men and women (mean age: 85 years)	10 μg/day of vitamin D in the supplement group, and a placebo in the control group	Occurrence of fractures in the proximal femur and peripheral bones over 2 years	The RR of femoral neck fracture in the supplement group to the control group was 1.09 (95%CI: 0.73, 1.63), and the RR of other fractures was 0.92 (95%CI: 0.66, 1.27)	–	

Abbreviations: RCT, randomized controlled trial; CC, case-control study; 25(OH)D, 25-hydroxyvitamin D; RR, relative risk.

Table 2 (continued)

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(45)	RCT	2003	2886 British men and women 65–85 years of age	2500 μg/4 month of vitamin D_3 in the supplement group, and a placebo in the control group	Occurrence of fractures over 5 years	The RR of fractures in the supplement group to the control group was 0.78 (95%CI: 0.61, 0.99), and the RR of fractures in the proximal femur, wrist, forearm, or vertebra was 0.67 (95%CI: 0.48, 0.93)	+	
(46)	Cohort study	1997	9704 elderly US women 65 years of age and older	Use of vitamin D supplement	Occurrence of fractures over 6.6 years	The RRs of fractures in the supplement group to the control group ranged from 0.7–1.2 with no significant difference	−	
(47)	Cohort study	2003	72337 female US nurses 60 years of age	Vitamin D intake	Occurrence of femoral fractures over 18 years	The RR of femoral fractures in the high-vitamin D-intake group (≥12.5 μg/day) to the low-intake group (<3.5 μg/day) was 0.63 (95%CI: 0.42, 0.94)	+	
(48)	Cohort study	2003	60689 Swedish women 40–74 years of age	Vitamin D intake	Occurrence of fractures over 11.1 years	Vitamin D intake was not significantly associated with the occurrence of fractures	−	
(49)	CC	1975	67 Danish patient 60–95 years of age and 41 controls 60–95 years of age	Plasma 25(OH)D concentration	Occurrence of femoral fractures	Plasma 25(OH)D level in the fracture group was not significantly different from that in the control group	−	Possible confounders not adjusted for
(50)	CC	1978	22 British cases (mean age: 75 years) and 22 age-unmatched controls (mean age: 76 yeas)	Serum 25(OH)D concentration	Occurrence of femoral neck fracture	Serum 25(OH)D level in the fracture group was lower than that in the control group ($P<0.05$)	+	Possible confounders not adjusted for
(51)	CC	1979	98 female white British patients (mean age: 80 years) and 76 age- and sex-matched controls (mean age: 79 yeas)	Plasma 25(OH)D concentration	Occurrence of femoral neck fracture	Plasma 25(OH)D level in the fracture group was lower than that in the control group ($P<0.001$)	+	Possible confounders not adjusted for
(52)	CC	1979	18 female elderly Japanese patients and 35 age-matched controls (age unknown)	Serum 25(OH)D concentration	Occurrence of vertebral or femoral fracture	Serum 25(OH)D level in the fracture group was lower than that in the control group ($P<0.01$)	+	Possible confounders not adjusted for
(53)	CC	1982	58 Finnish patients with fracture (mean age: 77 years) and 41 age- and sex-matched outpatient with nonorthopedic diseases (mean age: 78 years) as controls	Serum 25(OH)D concentration	Occurrence of femoral neck fracture	Serum 25(OH)D level in the fracture group was lower than that in the control group in winter ($P\leq0.02$) and spring ($P\leq0.01$)	+	Possible confounders not adjusted for

Abbreviations: RCT, randomized controlled trial; CC, case-control study; 25(OH)D, 25-hydroxyvitamin D; RR, relative risk.

Table 2 (continued)

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(54)	CC	1984	67 female Australian patients (mean age: 78 years) and 50 ambulant female controls (mean age: 72 years)	Serum 25(OH)D concentration	Occurrence of femoral neck fracture	Serum 25(OH)D level in the fracture group was lower than that in the control group ($P<0.001$)	+	Possible confounders not adjusted for
(55)	CC	1986	40 female Finnish inpatients with fracture (mean age: 77 years) and 25 gynecological outpatients as controls (mean age: 74 years)	Serum 25(OH)D concentration	Occurrence of femoral neck fracture	Serum 25(OH)D level in the fracture group was lower than that in the control group ($P<0.01$)	+	Possible confounders not adjusted for
(56)	CC	1986	10 postmenopausal British patients 62–75 years of age with fracture, and 10 patients 54–75 years of age who underwent hip joint replacement for osteoarthritis as controls	Plasma 25(OH)D concentration	Occurrence of femoral fracture	Plasma 25(OH)D level in the fracture group was not significantly different from that in the control groups	−	Small sample size
(57)	CC	1987	125 Dutch patients (mean age: 76 years) and 74 controls (mean age: 76 years)	Vitamin D intake and serum 25(OH)D concentration	Occurrence of femoral fracture	Serum 25(OH)D level in the fracture group was lower than that in the control group ($P<0.001$), but vitamin D intake was not significantly different between the two groups	+	Possible confounders not adjusted for
(58)	CC	1989	200 Chinese patients 49–93 years of age, and 427 controls 60–90 years of age	Plasma 25(OH)D concentration	Occurrence of femoral fractures	Plasma 25(OH)D level in the fracture group was lower than that in the control group ($P<0.001$)	+	Possible confounders not adjusted for
(59)	CC	1989	37 Finnish patients 65 years of age or older with fracture and 24 age- and sex-matched nonorthopedic outpatients	Vitamin D intake and serum 25(OH)D concentration	Occurrence of femoral neck fracture	Vitamin D intake in the fracture group was lower than that in the control group ($P<0.05$), but serum 25(OH)D level was not significantly different between the two groups	±	Possible confounders not adjusted for, and conflicting results
(60)	CC	1989	41 female British patients and 40 (age-unmatched) female controls, aged between 50–93 years	Serum 25(OH)D concentration	Occurrence of femoral fractures	Serum 25(OH)D level in the fracture group was lower than that in the control group ($P<0.01$)	+	Possible confounders not adjusted for
(61)	CC	1990	69 female Chinese patients (mean age: 78 years) and 28 controls (mean age: 71 years)	Vitamin D intake and plasma 25(OH)D concentration	Occurrence of femoral neck fracture	Serum 25(OH)D level in the fracture group was significantly lower than that in the control group	+	Possible confounders not adjusted for

Abbreviations: RCT, randomized controlled trial; CC, case-control study; 25(OH)D, 25-hydroxyvitamin D; RR, relative risk.

Table 2 (continued)

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(62)	CC	1995	57 French patients 71–91 years of age with fracture and 68 patients with a disease unrelated to bone status as controls	Serum 25(OH)D concentration	Occurrence of femoral fractures	Serum 25(OH)D level in the fracture group was lower than that in the control group (P<0.003)	+	Possible confounders not adjusted for
(63)	CC	1995	1634 patients aged 50 years and older and age- and sex-matched controls in 14 European countries	Use of vitamin D supplements	Occurrence of femoral fracture	The adjusted odds ratio of femoral fractures in the supplement user to the nonuser was 0.74 (95%CI: 0.53, 1.03)	−	
(64)	CC	1997	117 Belgium patients 60–95 years of age and 117 controls 70–90 years of age	Serum 25(OH)D concentration	Occurrence of femoral fractures	Serum 25(OH)D level in the fracture group was lower than that in the control group (P=0.001)	+	
(65)	CC	1997	179 French patients aged 50 years or older, 180 age- and sex-matched hospital controls, and 55 community controls	Serum 25(OH)D concentration	Occurrence of femoral fractures	Overall, the serum 25(OH)D level in the fracture group was significantly lower than that in the control group, and the serum 25(OH)D level in the male fracture group was lower than that in the hospital control group (P=0.02), but the serum 25(OH)D level in the female hospital fracture group was not significantly different between the three groups	±	Possible confounders not adjusted for
(66)	CC	1998	271 female US patients and 359 controls aged 65 years and older	Serum 25(OH)D concentration	Occurrence of vertebral and femoral fractures	The adjusted odds ratios of femoral and vertebral fractures in the low-25(OH)D group (≤47 nmol/L) to the high-25(OH)D group were 1.2 (95%CI: 0.7, 1.9) and 1.1 (95%CI: 0.6, 1.8), respectively	−	
(67)	CC	2002	21 female Turkish patients 65–82 years of age and 20 age- and sex-matched controls	Serum 25(OH)D concentration	Occurrence of femoral fractures	Serum 25(OH)D level in the fracture group was not significantly different from that in the control group	−	Possible confounders not adjusted for

Abbreviations: RCT, randomized controlled trial; CC, case-control study; 25(OH)D, 25-hydroxyvitamin D; RR, relative risk.

Table 3 Published papers related to answer to question 3, "Does increased vitamin D intake positively affect peak bone mass in young women?"

Ref.	Design	Year	Subjects	Predictor variables (intervention)	Outcome variables	Results	Effect	Comment
(19)	RCT	2001	70 British women 24–70 years of age	20 μg/day of vitamin D in the supplement group and a placebo in the control group	1-year ΔBMDs of the lumbar spine, femoral neck, and whole body	There was no significant difference in ΔBMD between the two groups	−	
(68)	Cohort study	2002	171 female Finnish adolescents 9–15 years of age	Serum 25(OH)D concentration	3-year ΔBMDs of the lumbar spine and femoral neck	Serum 25(OH)D tertiles were positively associated with ΔBMD of the lumbar spine (P=0.01)	+	
(69)	CS	1992	371 US men and women 20–23 years of age	Vitamin D intake	BMD of the forearm	Serum 25(OH)D was not significantly associated with BMD	−	
(70)	CS	1998	259 Icelandic women 16–20 years of age	Serum 25(OH)D concentration	BMDs of the forearm, lumbar spine, proximal femur, and whole body	Serum 25(OH)D was not significantly associated with any BMD	−	
(31)	CS	1998	77 native-American women 19–85 years of age	Serum 25(OH)D concentration	BMDs of the lumbar spine and femoral neck	Serum 25(OH)D was associated with spinal BMD (P=0.05)	+	
(71)	CS	2001	196 Finnish women 31–43 years of age	Serum 25(OH)D concentration	BMD of the forearm	Serum 25(OH)D was not significantly associated with BMD	−	
(35)	CS	2001	70 Japanese women 19–49 years of age	Serum 25(OH)D concentration	BMD of the forearm	Serum 25(OH)D was not significantly associated with BMD	−	
(72)	CS	2001	178 female Finnish adolescents 14–16 years of age	Serum 25(OH)D concentration	BMD of the distal forearm	Serum 25(OH)D was not significantly associated with BMD	−	
(73)	CS	2004	92 Indian men and women 24–53 years of age	Serum 25(OH)D concentration	BMDs of the distal forearm, lumbar spine, and proximal femur	Serum 25(OH)D correlated with BMDs of the femoral neck (r=0.46, P=0.037) and Ward's triangle (r=0.50, P=0.020)	+	Possible confounders not adjusted for
(39)	CS	2004	7515 US men and women 20–49 years of age	Serum 25(OH)D concentration	BMD of the total proximal femur	Serum 25(OH)D was positively associated with BMD throughout the reference range (22.5–94 nmol/L) of serum 25(OH)D, and the association was maintained beyond the reference range in white and Mexican Americans (not in black adults)	+	

Abbreviations: RCT, randomized controlled trial; CS, cross-sectional study; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density.

aged between 16–20 years showed no significant association between serum 25(OH)D concentrations and BMD at any bone sites, and three other cross-sectional studies (69, 71, 72) with a medium sample size showed no association between either vitamin D intake or serum 25(OH)D concentrations and forearm BMD. Other cross-sectional studies with relatively small sample sizes included two studies that showed a positive association (31, 73) and one that showed a negative association (35).

To date, evidence to support a positive association between vitamin D nutritional status and BMD has been insufficient. Recent studies have showed that many female adolescents and young adults are vitamin D insufficient (35, 68, 72), and further studies are needed to confirm that vitamin D insufficiency in young women is associated with changes in bone metabolism and BMD.

In summary, vitamin D nutritional status may affect the attainment of peak bone mass in young women (based on level-IVa evidence). The answer to question 3 is that the amount of vitamin D supplement in young women should be as high as that recommended for peri- and postmenopausal women (although insufficient scientific evidence exists).

Limitations

In this paper, we attempted to systematically review the literature on vitamin D nutrition and bone health by searching PubMed with the MeSH terms of “Vitamin D”, “Bone Density”, and “Fractures”. The search yielded 1118 articles, and they were examined to determine whether they met the inclusion criteria. Although this process should be appropriate for selecting relevant articles with good specificity, these MeSH terms may not retrieve all of the relevant literature, and studies showing negative results may not have been be retrieved, and this may have biased the results toward positive effects in general.

“Publication bias”, i.e., the tendency for negative data not to be published, is always a problem in systematic reviews. The answers to questions 1 and 2 were drawn mostly from RCTs, and the answers may not be biased, because RCTs with negative data are usually published. However, bias may have occurred in relation to question 3 because our answer was based on observational studies.

In this paper, we have reviewed RCTs to determine the optimal intake of vitamin D, but it was difficult to evaluate subjects’ baseline vitamin D nutritional status, which is determined by both vitamin D intake in the diet and vitamin D production in the skin in response to ultraviolet ray exposure, as a modifier of the effect of vitamin D supplementation. Baseline vitamin D nutritional status should be taken into account when evaluating vitamin D supplementation in future studies.

The literature cited in this review is mostly from European and North American countries, and there were fewer studies in Asia, where habitual calcium intake is much lower. We searched for articles written in Japanese in PubMed and in *Igakuchuozassi*, the database for medical scientific papers published in Japan, but no relevant literature was found. Therefore, the optimum amounts of supplemental vitamin D and calcium for Asians is uncertain. Asians are thought to have adapted to low calcium intake, and thus smaller supplements may be effective. Further studies targeting populations with low calcium intake are needed.

Perspectives

The effects of vitamin D supplementation in middle and old ages have been well studied. However, there have been some lines of evidence showing that enhanced vitamin D intake or increased vitamin D nutritional status is associated with high BMD in young people. The effects of vitamin D on the attainment of maximal peak bone mass in young women should be further studied in the future.

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