Vitamin D Supplementation and Fracture Incidence in Elderly Persons

A Randomized, Placebo-Controlled Clinical Trial

Paul Lips, MD; Wilco C. Graafmans, MS; Marcel E. Ooms, MD; P. Dick Bezemer, PhD; and Lex M. Bouter, PhD

Objective: To determine whether vitamin D supplementation decreases the incidence of hip fractures and other peripheral bone fractures.

Design: Prospective, double-blind trial.

Setting: Community setting (Amsterdam and surrounding area).

Patients: 2578 persons (1916 women, 662 men) 70 years of age and older (mean age ± SD, 80 ± 6 years) living independently, in apartments for elderly persons, or in homes for elderly persons.

Intervention: Participants were randomly assigned to receive either vitamin D_3, 400 IU in one tablet daily, or placebo for a maximum of 3.5 years.

Measurements: Dietary calcium intake and serum 25-hydroxyvitamin D [25(OH)D] were estimated in a subset of participants. During follow-up, attention was concentrated on hip fractures and other peripheral fractures. The maximal follow-up period was 4 years. The results were evaluated by survival analysis.

Results: Mean dietary calcium intake from dairy products was 868 mg/d. Mean serum 25(OH)D concentration in the third year of the study was 23 nmol/L in the placebo group and 60 nmol/L in the vitamin D group. Median follow-up was 3.5 years, and total follow-up was 8450 patient-years. During follow-up, 306 persons in the placebo group and 282 persons in the vitamin D group died ($P = 0.20$). Hip fractures occurred in 48 persons in the placebo group and 58 persons in the vitamin D group ($P = 0.39$, intention-to-treat analysis). Other peripheral fractures occurred in 74 persons in the placebo group and 77 persons in the vitamin D group ($P = 0.86$).

Conclusion: Our results do not show a decrease in the incidence of hip fractures and other peripheral fractures in Dutch elderly persons after vitamin D supplementation.

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From Vrije Universiteit, Amsterdam, the Netherlands. For current author addresses, see end of text.

Vitamin D deficiency is common in elderly persons, especially those with hip fracture (1, 2). It is caused by low exposure to sunshine, decreased synthesis of vitamin D_3 in the aging skin, and a diet low in vitamin D (3, 4). The mean vitamin D intake in elderly persons in the Netherlands is about 100 IU/d, half that of elderly persons in the United States (5). Most of this vitamin D comes from margarine, which is the only vitamin D–supplemented food in the Netherlands (3 IU/g). In vitamin D deficiency, the low serum concentration of 25-hydroxyvitamin D [25(OH)D] leads to a low 1,25-dihydroxyvitamin D [1,25(OH)2D] concentration and then to a higher serum parathyroid hormone concentration, especially in the winter (6–10). Histologically, the increased parathyroid activity is associated with high bone turnover, leading to cortical bone loss and low density bone (5, 11), which may lead to hip fracture.

We previously studied the effects of vitamin D supplementation in residents of a home for the elderly and residents of a nursing home (10). Vitamin D_3, 400 IU/d, led to an adequate increase of the serum 25(OH)D concentration, to a small but significant increase of the serum 1,25(OH)2D concentration, and to a decrease of the serum concentration of intact parathyroid hormone. It was recently observed (12, 13) that bone mineral density at the hip is positively related to serum 25(OH)D concentration in postmenopausal and elderly women. Therefore, it might be expected that vitamin D supplementation would increase bone mineral density in elderly persons deficient in vitamin D. In line with this expectation, it was shown that vitamin D supplementation prevented bone loss from the spine during the winter in postmenopausal women (14).

These results suggest that vitamin D supplementation may reduce the incidence of hip fractures, because bone strength shows a strong correlation with bone mineral density (15). However, increasing bone mineral density through a therapeutic intervention does not necessarily lead to increased bone strength, as has been shown with sodium fluoride (16). Bone structure and bone quality are also determinants of bone strength (17), and falls are a risk factor for hip fractures (18). Therefore, hip fracture

should be the outcome criterion in studies on the effect of vitamin D supplementation. Intervention studies on the prevention of osteoporotic fractures necessitate large numbers of patients, because the outcome has an annual incidence of 0.5% to 4% in the elderly population (19). We report the results of a large-scale, prospective study on the effect of vitamin D supplementation on the incidence of hip and other osteoporotic fractures.

Methods

Participants

The study included 2578 persons (1916 women and 662 men) 70 years of age and older (mean age ± SD, 80 ± 6 years; range, 70 to 97 years). Participants were recruited from general practitioners, from apartment houses for elderly persons, and from homes for elderly persons in Amsterdam and its vicinity. Persons recruited from practitioners were living independently; those recruited from apartment houses and homes were receiving some care, but less than they would have received in a nursing home. Participants had to be reasonably healthy and able to give informed consent. Persons with a history of hip fracture or total hip arthroplasty, known hypercalcemia, sarcoidosis, or recent urolithiasis (< 5 years earlier) were excluded. Patients who had diseases or who used medications that influence bone metabolism (such as thyroid disease or glucocorticoid medication) were not excluded. The spontaneous use of vitamin D supplements and multivitamins was discouraged, but the prescription practices of the general practitioners were not altered. All vitamin use was carefully documented. The study was approved by the Ethical Review Board of the Vrije Universiteit Hospital, and all participants gave informed consent.

Study Design

After checking the inclusion and exclusion criteria and obtaining informed consent, the participants were randomly assigned to receive either active treatment with vitamin D_3 or placebo. The study was double-blind, and randomization was done in blocks of 10 per general practice, apartment house, or home. Randomization lists were made using a computerized random-number generator. Lists in sealed envelopes were sent to the hospital pharmacy for assignment. Each participant took either one tablet per day that contained vitamin D_3, 400 IU, or one placebo tablet per day that was identical in appearance and taste to the vitamin tablet. After enrollment, the participants received the first container of tablets (210 tablets). The container was replaced every 6 months with a full container. All participants were also advised in writing to consume at least three servings of dairy products per day (for example, 1 glass of milk, 1 cup of yogurt, and 1 slice of cheese) to ensure a calcium intake of at least 800 to 1000 mg/d.

The study was started in August 1988. The last participant was enrolled in December 1990, and all participants had stopped using study medication by December 1993. The follow-up period had been planned to last no more than 3 years, but because the number of hip fractures during the study was lower than expected, a 6-month extension was planned. The study participants thus received medication for 3 to 3.5 years; those who received it for 3.5 years were those who consented to the 6-month extension. Total follow-up was to a maximum of 4 years.

Data collected at baseline included an outdoor activity score (1 = going outdoors less than once a week; 2 = going outdoors 1 or 2 times per week; and 3 = going outdoors 3 times per week or more) and a score for sunshine exposure (when outside: 1 = in the shade as much as possible; 2 = sometimes in sunshine; 3 = much exposure to sunshine). These scores show a positive relation with serum 25(OH)D concentration (3). Mobility was estimated by a walking score that ranged from 1 (unable to walk) to 5 (walks independently a fair distance on any surface) (20). The dietary calcium intake from dairy products was estimated in a subset of 348 women by using a questionnaire, as described previously (21).

The participants were evaluated annually with a questionnaire on hip fractures, other peripheral fractures, outdoor score, sunshine exposure score, use of vitamin supplements, and walking score. Each general practitioner or caretaker was asked to immediately report change of address, hip fracture, or death. Hip fracture and death were verified by the general practitioner. All participants were followed for the maximal period of 4 years if possible, even if they had stopped using the trial medication, had sustained a fracture, or had moved to another city. To investigate possible selection bias, 267 potential participants in a home for the elderly and its adjunct apartments (all residents of the institution) were studied for baseline characteristics, including age, sex, sunshine exposure score, outdoor score, walking score, and reasons for nonparticipation.

Compliance was checked when the tablet containers were replaced (every 6 months), by questionnaire (every year), and by measurement of the serum 25(OH)D concentration. Serum 25(OH)D concentration was measured at baseline and after 1 year in 270 persons who participated in a substudy investigating the effect of vitamin D supplementation on

bone mineral density and bone turnover variables. This substudy included a nonrandom sample of participants from several apartment houses and homes for the elderly and is described in detail elsewhere (21). In the same substudy, dietary calcium intake from dairy products was assessed. Serum 25(OH)D concentration was also estimated during the third year of the study in February and March in a random sample of 96 participants drawn from the remaining study population. These participants received a letter giving them an appointment within 10 days; the blood samples were drawn at home. Serum 25(OH)D concentration was measured by competitive protein binding assay after being purified by gradient high-pressure liquid chromatography. The intra- and interassay coefficients of variation were 5% and 6%, respectively (22).

Statistical Analysis

Baseline data of the vitamin D group and the placebo group were compared using *t*-tests (age, calcium intake), chi-square tests (sex, residence), and Wilcoxon rank-sum tests (scores). The serum 25(OH)D concentrations of both groups were compared using *t*-tests.

Data on fractures and mortality were analyzed by survival analysis using log-rank tests, Cox proportional hazards regression, and hazard rate ratios (23). Hip fractures are presented using the Kaplan–Meier method. All participants were kept in the study as long as possible. The data were analyzed in two ways. The intention-to-treat analysis included all randomly assigned participants for either the total follow-up period or until fracture, death, or loss to follow-up. The active treatment analysis included the participants as long as they stated that they were using the trial medication. Thus, the participants were included in the active treatment analysis until they stopped using the trial medication, regardless of whether a fracture occurred after they had stopped. Age, sex, and residence were added in both analyses as covariates to the Cox regression model. Because outdoor score, sunshine score, and walking score were interrelated (correlation coefficients ranging from 0.21 to 0.59) and were likely to indicate "general health" or "mobility," they were averaged over the years and added up to a sum score. For this purpose, the walking score was simplified (1, 2, or 3 = 1; 4 = 2; 5 = 3), because the lower walking scores applied to a few participants only. The resulting total score, ranging from 3 to 9, was entered as a covariate in the model. The level of compliance (weekly intake as reported on the questionnaire) was also added as a covariate to the active treatment analysis. Separate survival analyses were done for hip fractures and other peripheral fractures. In the analysis for hip fractures, we used the time to the first hip fracture, regardless of other peripheral fractures. In the analysis for other peripheral fractures, we used the time to the first peripheral fracture, regardless of hip fractures. The analyses were repeated after we excluded participants who used vitamin D or multivitamin supplements other than the trial medication.

Table 1. Baseline Characteristics of Participants Randomly Assigned to Receive Placebo or Vitamin D*

Characteristic	Patients Receiving Placebo (n = 1287)	Patients Receiving Vitamin D (n = 1291)
Mean age ± SD, *y*	80.0 ± 6.0	80.0 ± 5.9
Sex, *n*		
Female	958	958
Male	329	333
Residence, *n*		
Independent	528	519
Apartment for the elderly	253	252
Home for the elderly	506	520
Outdoor score, *n*†		
1 (outdoors < once per week)	152	153
2 (outdoors 1–2 times per week)	153	144
3 (outdoors ≥3 times per week)	981	993
Sunshine score, *n*†		
1 (in the shadow)	343	323
2 (sometimes in sunshine)	506	501
3 (much sunshine exposure)	436	466
Walking score, *n*†		
1 (unable to walk)	7	8
2 (able to walk between two persons)	24	17
3 (walks with mechanical aid [supervised])	65	66
4 (walks a limited distance)	336	355
5 (walks independently)	855	844
Median calcium intake, *mg/d*‡ (25th–75th percentile)	859 (644–1099)	876 (638–1101)

* There were no statistically significant differences between the group receiving placebo and the group receiving vitamin D.
† Fewer than 0.5% missing values.
‡ Calcium intake from dairy products estimated in a subset of 348 women.

Results

Baseline data for the participants are presented in Table 1. There were no important differences in baseline characteristics between the groups. A study of nonparticipation in 267 potential participants from one institution showed that 30 potential participants had had to be excluded on the basis of exclusion criteria. Of the remaining 237 persons, 54 (23%) consented to participate. The mean ages of the 54 participants (83.2 years) and the 183 nonparticipants (83.0 years) did not differ, nor did the sex ratios of the two groups. The outdoor, sunshine, and walking scores tended to be lower in the nonparticipants than in the participants. For example, the walking score was lower than 4 in 11% of the participants and 17% of the nonparticipants. Reasons for not giving consent were primarily "infor-

Table 2. Mortality, Cessation of Treatment, Loss to Follow-up, and Active Treatment at 3 Years of Study

Variable	Patients Receiving Placebo	Patients Receiving Vitamin D	*P* Value
	n		
Death	251	223	0.16
Cessation of treatment*	237	227	0.54
Active treatment†	792	834	
Loss to follow-up	7	7	
Total	1287	1291	

* Determined from participants' self-report on questionnaires.
† Determined from participants' self-report.

mation not received or forgotten," "other commitments," "illness," and "no interest."

At the start of the study, 133 participants were taking a vitamin or multivitamin preparation that usually contained 90 to 400 IU of vitamin D. During the study, 73 participants (37 in the placebo group and 36 in the vitamin D group) were found to be taking a vitamin or multivitamin supplement that contained vitamin D at two or more follow-up visits.

Data on mortality, cessation of trial medication, loss to follow-up, and active treatment at 3 years after randomization are presented in Table 2. The number of participants who died or stopped using the trial medication was higher (although not significantly higher) in the placebo group than in the vitamin D group. It can be seen that 1626 participants, or 63% of the 2578 participants at the start of the study, completed 3 years of the study. After 3 years, the 1313 participants who had started early within the inclusion period were asked to continue, and 1194 of these participants consented to enter the 6-month extension period. This group was, on average, 1 year younger than the remaining study sample. The maximal follow-up period was 4 years (6 months after medication was stopped). The median duration of follow-up was 3.5 years, and the total follow-up time was 8450 patient-years. During the total follow-up period, 306 participants in the placebo group and 282 participants in the vitamin D group died ($P = 0.20$ by survival analysis).

Compliance was considered to be adequate if the participants reported on the questionnaire that they took the tablets 5 or more days per week. This occurred in 85% of the participants; compliance was similar in both groups. The serum 25(OH)D concentrations measured at baseline and after 1 year of treatment in a sample of 270 residents of apartment houses or homes for the elderly and those measured in 96 randomly selected participants in the third year of our study are shown in Table 3. The overlap in the distribution of concentrations between participants receiving placebo and participants receiving vitamin D was small. The contrast in serum 25(OH)D concentrations between the placebo group and the vitamin D group was greater in institutionalized than in independent elderly persons.

During the total follow-up period, 111 hip fractures occurred in 106 participants; 5 participants had a hip fracture on each side. There were 157 other peripheral fractures in 151 participants. Eleven participants sustained both a hip fracture and another fracture. The fracture data are presented in Table 4; the hip fracture data are shown in Figure 1. The vitamin D group had slightly more hip fractures than the placebo group, but the difference was not statistically significant. This is apparent in the Kaplan–Meier curve in the top panel of Figure 1. The unadjusted hazard rate ratio for hip fractures (vitamin D compared with placebo) according to the intention-to-treat analysis was 1.18 (95% CI, 0.81 to 1.71). When the residents of apartment houses and homes for elderly were analyzed as a separate subgroup, 36 hip fractures occurred in the placebo group, and 49 hip fractures occurred in the vitamin D group (hazard rate ratio according to intention-to-treat analysis, 1.3 [CI, 0.84 to 2.0]). When participants 80 years of age and older were analyzed as a separate subgroup, the results were similar (hazard rate ratio, 1.13 [CI, 0.70 to 1.80]). Including age, sex, residence, and sum score (outdoor, sunshine, and walking scores) as covariates did not change the results. Excluding persons who regularly used vitamin or multivitamin supplements did not change the results. The unadjusted hazard rate ratio for other peripheral fractures (vitamin D compared with placebo) was 1.03 (CI, 0.75 to 1.40). Adjustment for covariates and the exclusion of per-

Table 3. Serum 25-Hydroxyvitamin D Concentrations in Residents of Apartments or Homes for the Elderly at Baseline and after 1 Year of Treatment and in Randomly Selected Participants in the Third Year of the Study during Winter

Variable	Patients Receiving Placebo	Patients Receiving Vitamin D	*P* Value
	nmol/L (25th–75th percentile)		
Residents of apartments and homes for the elderly ($n = 270$)*			
Baseline	26 (19–37)	← 27 (19–36)	
After 1 year	23 (17–31)	→ 62 (52–70)	0.001
Random sample ($n = 96$) during third year of study	23 (17–28)	54 (43–61)	0.001
Independent elderly persons ($n = 46$)	26 (18–35)	49 (41–62)	
Residents of apartments and homes for elderly persons ($n = 50$)	21 (15–26)	55 (45–60)	

* Part of a substudy on the effect of vitamin D on bone mineral density and bone turnover (21).

40nmol/L

Table 4. Patients with Hip Fractures and Other Peripheral Fractures in the Placebo and Vitamin D Group*

Fracture	Patients Receiving Placebo	Patients Receiving Vitamin D	*P* Value†
	n		
Hip fracture	48	58	0.39
Other fractures	74	77	0.86
Colles	22	20	
Humerus	12	10	
Ankle, foot, or leg	17	20	
Other	23	27	

* Maximal follow-up was 4 years.
† According to intention-to-treat analysis (log-rank test).

sons who regularly used vitamin or multivitamin supplements did not change the results.

Data on the active treatment analysis, in which participants were included as long as they used the trial medication, are shown in the bottom panel of Figure 1. This figure shows that the curves of the placebo group and the vitamin D group are similar. The unadjusted hazard rate ratio for hip fractures (vitamin D compared with placebo) according to the active treatment analysis was 1.10 (CI, 0.71 to 1.70). For other peripheral fractures, it was 1.02 (CI, 0.73 to 1.40). The inclusion of age, sex, residence, sum score, and compliance as covariates did not change the results.

Discussion

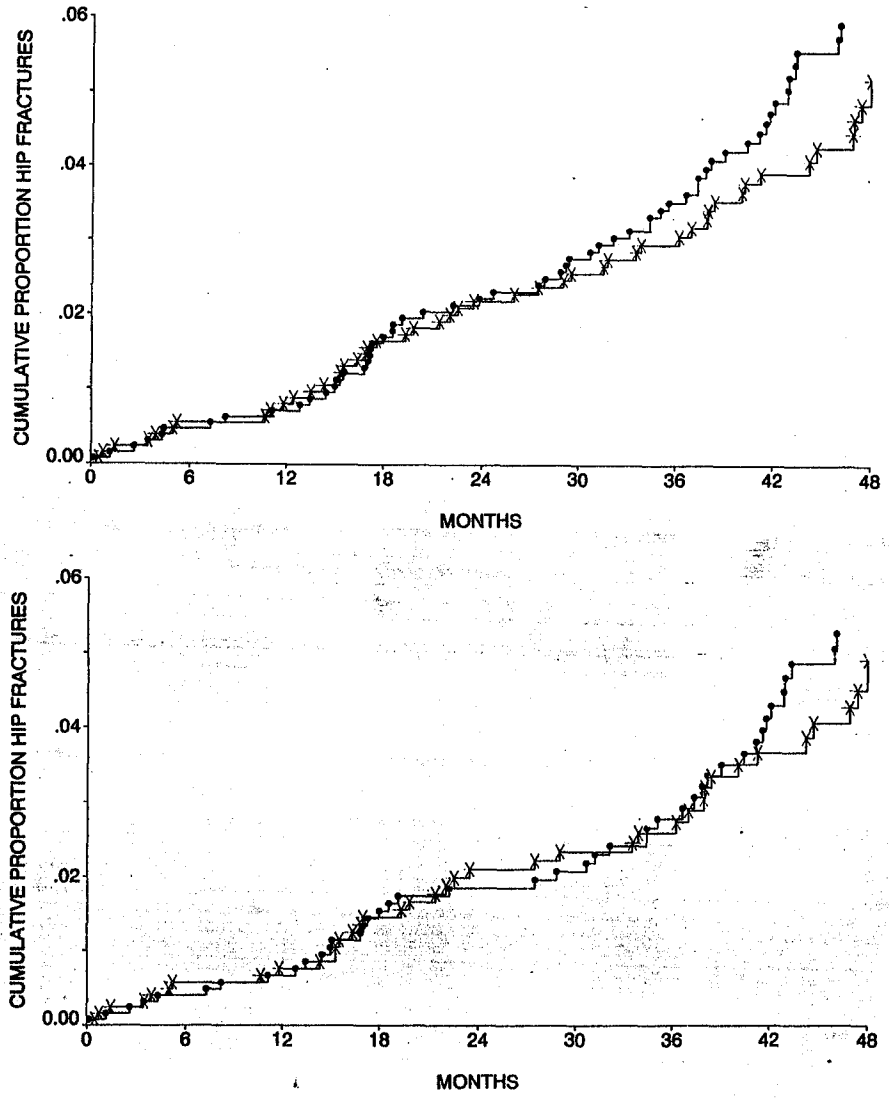
Vitamin D supplementation did not decrease the incidence of hip fractures in our study population. The hypothesis of a protective effect of vitamin D had been based on previous studies done in the Netherlands (10, 24), which showed that vitamin D supplementation in elderly persons deficient in vitamin D led to an adequate improvement of vitamin D status, as determined by significant increases of the serum 25(OH)D and 1,25(OH)2D concentrations and a decrease of the serum parathyroid hormone concentration. In contrast, vitamin D supplementation in nursing home residents in the United States who were replete with vitamin D (mean serum 25(OH)D concentration > 40 nmol/L) did not significantly decrease the parathyroid hormone concentration (25). A positive effect of vitamin D was also suggested by the results of the substudy done in 248 women from the present study (13). This substudy showed that bone mineral density in the hip at baseline correlated positively with the serum 25(OH)D concentration below a threshold level [serum 25(OH)D < 30 nmol/L]. After 2 years of vitamin D supplementation, the bone mineral density of the femoral neck had increased 2.3% in the vitamin D group compared with the placebo group (21). According to Cummings and coworkers (26), a decrease of 1 standard deviation in bone mineral density of the hip increases hip fracture risk by a factor (risk ratio) of 2.6. When these data are combined, it can be calculated that a 2.3% increase in bone mineral density of the femoral neck might result in a decrease in hip fracture incidence of about 15% and a risk ratio of 0.85 (27). We could have missed such a decrease because it is within the 95% CIs of the observed hazard rate ratio. The power of our study was such that a decrease in the hip fracture incidence of 20% or more could have been shown.

Our study may also have underestimated the effect of vitamin D supplementation in other ways. The 248 participants who had repeated bone mineral density measurements were women living in apartment houses and homes for the elderly. This sample was not random and did not contain men or elderly persons living independently. Vitamin D supplementation may have less effect in elderly persons living independently, because these persons are younger and have higher serum 25(OH)D concentrations than residents of homes for the elderly. The visible effect of vitamin D supplementation in our study may also have been decreased by the 73 participants who regularly used vitamin or multivitamin supplements. However, excluding these participants did not change our results. We chose to include these persons and to do the additional analysis because it is difficult to completely eliminate the use of vitamin supplements.

The effect of vitamin D supplementation by intramuscular injection has been studied in Finland (28). A decrease in the incidence of upper limb fractures was found, in contrast to our results. However, the participants in the Finnish study were all residents of nursing homes.

The effect of vitamin D, 800 IU/d, and calcium, 1200 mg/d, compared with double placebo was studied in 3270 elderly women in Lyon, France, by Chapuy and colleagues (29). These investigators observed a 25% decrease (intention-to-treat analysis) in the incidence of hip fractures and other peripheral fractures. Important differences between our study conditions and those of Chapuy and colleagues include a considerably lower dietary calcium intake in France than in the Netherlands and the use of a calcium supplement in the French study. The participants in the French study were an average of 3 years older (at baseline) than our participants, were all women, and were all residents of nursing homes.

Hip fracture incidence was higher in the French study than in our study. The incidence in our study was 25 per 1000 participants per year in women living in homes for the elderly and 29 per 1000 participants per year in women older than 85 years



intention to treat

active

Figure 1. Cumulative proportion of participants with first hip fracture (Kaplan–Meier method) in the placebo group (X) and the group assigned to receive vitamin D_3 treatment (•). Top. According to intention-to-treat analysis. **Bottom.** According to active treatment analysis.

of age. In the French prevention study, the incidence was 40 per 1000 participants per year in women older than 85 years of age (29). The vitamin D dosage in the French study was higher (800 IU/d) than in our study. However, as we have shown previously (10), the difference between the effects of 400 and 800 IU of vitamin D_3 per day is almost negligible. Serum 25(OH)D concentration in the French study was similar to that in ours, but the measurement technique used by Chapuy and colleagues was different from the one we used. Cross-calibration of the assays suggests that the participants in the French study had greater vitamin D deficiencies than our participants (30). The decrease in serum parathyroid hormone concentration in a sample of the French study was about 50% after calcium and vitamin D treatment (29), whereas this concentration decreased slightly more than 15% in a nonrandom sample from our study after vitamin D supplementation (21). The difference in bone mineral density of the hip between the treatment group and the control group was more than 6% in the French study and only 2.3% in a nonrandom sample from our study (21). In sum, the changes in parathyroid activity and bone mineral density of the hip indicate that a larger treatment effect occurred in the French study.

Participants in our study may have been more active than the average, because the incidence of fractures in our study was lower than expected. About 60% of the more than 60 homes for the elderly in Amsterdam participated in our study, but the percentage of persons in each home who participated varied from 5% to 30%. We gained the impression that frailer elderly persons more often refrained from participation; this was also suggested by the results of our small nonparticipation study. However, analysis of the older and less active sub-

group did not show a trend toward a protective effect of vitamin D supplementation.

Our results do not show that vitamin D supplementation in elderly persons in the Netherlands decreases the incidence of hip fractures and other peripheral fractures. The data suggest that other risk factors are more important in our study population. Nevertheless, a positive effect of vitamin D supplementation is suggested by the small increase in bone mineral density of the femoral neck observed in a sample of this study (21). The effect of vitamin D supplementation might be greater when a calcium supplement is also used, as in the French study (29). The same results might not be found in the Netherlands, however, where dietary calcium intake is much higher than in France. A major difference between our study and the two previous studies in which vitamin D supplementation appeared to be effective (28, 29) may be the health status of the participants, which was generally better in our study. It may be that the effect of vitamin D supplementation on the incidence of fractures may only be apparent in an older, frailer population than ours. If so, vitamin D supplementation might therefore be considered primarily for frail elderly persons who do not go outdoors in the sunshine.

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Requests for Reprints: Paul Lips, MD, Department of Endocrinology, Academisch Ziekenhuis Vrije Universiteit, PO Box 7057, 1007 MB Amsterdam, the Netherlands.

Current Author Addresses: Dr. Lips: Department of Endocrinology, Academisch Ziekenhuis Vrije Universiteit, PO Box 7057, 1007 MB Amsterdam, the Netherlands.
Mr. Graafmans and Drs. Ooms, Bezemer, and Bouter: Institute for Research in Extramural Medicine (EMGO Institute), Medical Faculty, Vrije Universiteit, Van der Boechorststraat 7, 1081 BT Amsterdam, the Netherlands.

References

1. **McKenna MJ.** Differences in vitamin D status between countries in young adults and the elderly. Am J Med. 1992;93:69-77.
2. **Lips P, Obrant KJ.** The pathogenesis and treatment of hip fractures. Osteoporosis Int. 1991;1:218-31.
3. **Lips P, van Ginkel FC, Jongen MJ, Rubertus A, van der Vijgh WJ, Netelenbos JC.** Determinants of vitamin D status in patients with hip fracture and in elderly control subjects. Am J Clin Nutr. 1987;46:1005-10.
4. **Holick MF.** Vitamin D and the skin: photobiology, physiology and therapeutic efficacy for psoriasis. In: Heersche DN, Kanis JA, eds. Bone and Mineral Research. Amsterdam: Elsevier; 1990:313-66.
5. **Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD.** Vitamin D and bone health in the elderly. Am J Clin Nutr. 1982;36(5 Suppl):1014-31.
6. **Lips P.** Vitamin D nutrition in the elderly: problems and recommendations. In: Norman AW, Bouillon R, Thomasset M, eds. Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application. New York: Walter de Gruyter; 1991:757-64.
7. **Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK.** Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency. Am J Clin Nutr. 1987;45:755-63.
8. **Lips P, Hackeng WH, Jongen MJ, van Ginkel FC, Netelenbos JC.** Seasonal variation in serum concentrations of parathyroid hormone in elderly people. J Clin Endocrinol Metab. 1983;57:204-6.
9. **Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, Dawson-Hughes B.** Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. N Engl J Med. 1989;321:1777-83.
10. **Lips P, Wiersinga A, van Ginkel FC, Jongen MJ, Netelenbos JC, Hackeng WH, et al.** The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. J Clin Endocrinol Metab. 1988; 67:644-50.
11. **Lips P, Netelenbos JC, Jongen MJ, van Ginkel FC, Althuis AL, van Schaik CL, et al.** Histomorphometric profile and vitamin D status in patients with femoral neck fracture. Metab Bone Dis Relat Res. 1982;4:85-93.
12. **Khaw KT, Sneyd MJ, Compston J.** Bone density, parathyroid hormone and 25-hydroxyvitamin D concentrations in middle aged women. BMJ. 1992;305: 273-7.
13. **Ooms ME, Lips P, Roos JC, van der Vijgh WJ, Popp-Snijders C, Bezemer PD, et al.** Vitamin D status and sex hormone binding globulin: determinants of bone turnover and bone mineral density in elderly women. J Bone Miner Res. 1995;10:1177-84.
14. **Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G.** Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. Ann Intern Med. 1991;115:505-12.
15. **Melton LJ 3d, Eddy DM, Johnston CC Jr.** Screening for osteoporosis. Ann Intern Med. 1990;112:516-28.
16. **Riggs BL, Hodgson SF, O'Fallon WM, Chao EY, Wahner HW, Muhs JM, et al.** Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med. 1990;322:802-9.
17. **Mosekilde L, Mosekilde L, Danielsen CC.** Biomechanical competence of vertebral trabecular bone in relation to ash density and age in normal individuals. Bone. 1987;8:79-85.
18. **Cummings SR, Nevitt MC.** A hypothesis: the causes of hip fractures. J Gerontol. 1989;44:107-11.
19. **Kanis JA.** Treatment of osteoporotic fracture. Lancet. 1984;1:27-33.
20. **Lips P, van Ginkel FC, Netelenbos JC, Wiersinga A, van der Vijgh WJ.** Lower mobility and markers of bone resorption in the elderly. Bone Miner. 1990;9:49-57.
21. **Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ, Bouter LM, Lips P.** Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. J Clin Endocrinol Metab. 1995;80:1052-8.
22. **Jongen MJ, Kuiper S, van der Vijgh WJ, Lips P, Netelenbos JC.** Improvement in the simultaneous determination of calcidiol and calcitriol in human serum or plasma. J Clin Chem Clin Biochem. 1988;26:25-8.
23. **Armitage P, Berry G.** Statistical Methods in Medical Research. 2d ed. Boston: Blackwell Scientific; 1987.
24. **Chapuy MC, Chapuy P, Meunier PJ.** Calcium and vitamin D supplements: effects on calcium metabolism in elderly people. Am J Clin Nutr. 1987;46: 324-8.
25. **Himmelstein S, Clemens TL, Rubin A, Lindsay R.** Vitamin D supplementation in elderly nursing home residents increases 25(OH)D but not 1,25(OH)2D. Am J Clin Nutr. 1990;52:701-6.
26. **Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al.** Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet. 1993;341:72-5.
27. **Ooms ME.** Osteoporosis in Elderly Women: Vitamin D Deficiency and Other Risk Factors [PhD Thesis]. Amsterdam: Vrije Universiteit; 1994.
28. **Heikinheimo RJ, Inkovaara JA, Harju EJ, Haavisto MV, Kaarela RH, Kataja JM, et al.** Annual injection of vitamin D and fractures of aged bones. Calcif Tissue Int. 1992;51:105-10.
29. **Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al.** Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327:1637-42.
30. **Lips P, Chapuy MC, Dawson-Hughes B, Pols HA.** International comparison of serum 25-hydroxyvitamin D measurements [Abstract]. J Bone Miner Res. 1995;10:S496.