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Vitamin D Deficiency and Secondary Hyperparathyroidism in the Elderly: Consequences for Bone Loss and Fractures and Therapeutic Implications

PAUL LIPS

Department of Endocrinology, Institute for Endocrinology, Reproduction and Metabolism (EVM-Institute) and Institute for Research in Extramural Medicine (EMGO-Institute), Vrije Universiteit Medical Center, 1007 MB Amsterdam, The Netherlands

Vitamin D deficiency is common in the elderly, especially in the housebound and in geriatric patients. The establishment of strict diagnostic criteria is hampered by differences in assay methods for 25-hydroxyvitamin D. The synthesis of vitamin D_3 in the skin under influence of UV light decreases with aging due to insufficient sunlight exposure, and a decreased functional capacity of the skin. The diet contains a minor part of the vitamin D requirement. Vitamin D deficiency in the elderly is less common in the United States than elsewhere due to the fortification of milk and use of supplements. Deficiency in vitamin D causes secondary hyperparathyroidism, high bone turnover, bone loss, mineralization defects, and hip and other fractures. Less certain consequences include myopathy and falls. A diet low in calcium may cause an increased turnover of vitamin D metabolites and thereby aggravate vitamin D deficiency. Prevention is feasible by UV light exposure, food fortification, and supplements. Vitamin D_3 supplementation causes a decrease of the serum PTH concentration, a decrease of bone turnover, and an increase of bone mineral density. Vitamin D_3 and calcium may decrease the incidence of hip and other peripheral fractures in nursing home residents. Vitamin D_3 is recommended in housebound elderly, and it may be cost-effective in hip fracture prevention in selected risk groups. (*Endocrine Reviews* 22: 477–501, 2001)

Abbreviations: CPB, Competitive protein binding assay; DBP, vitamin D binding protein; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; RDA, recommended dietary allowance; RR, risk ratio.

I. Introduction

A. History; association of hip fractures with osteomalacia

VITAMIN D is widespread in nature and photosynthesized in most plants and animals exposed to sunlight (1, 2). Its major role in vertebrate animals and humans is to increase the absorption of calcium and phosphate for the mineralization of the skeleton. In the case of vitamin D deficiency in children, the cartilage is not calcified, causing rickets. In adults, the newly formed bone matrix (the osteoid) is not mineralized, causing osteomalacia (3). The first classical description of rickets traces back to Whistler and Glisson in the middle of the 17th century (1). The association between lack of sunshine and rickets was first recognized in the be-

ginning of the 19th century (1, 4). A hundred years later, around 1920, rickets was experimentally cured by exposure of children to sunshine or UV light (1, 2, 5). Since then, rickets has almost disappeared in the western world because of the use of cod liver oil or vitamin D preparations and by adequate sunshine exposure. About 50 yr later, it was recognized in 1967 by Chalmers *et al.* (6) that osteomalacia was more common than expected, especially in elderly women. They also reported that hip fractures often were often associated with osteomalacia (7). While rickets and osteomalacia are rare outside certain risk groups, less severe vitamin D deficiency is quite common, especially in elderly people (8, 9). This less severe form, often described as vitamin D insufficiency or inadequacy (10, 11), causes stimulation of the parathyroid glands, which may lead to high bone turnover, bone loss, and hip fractures (8, 12). Over the last 20 yr, numerous papers have been published on vitamin D deficiency and its consequences in elderly people. The aim of this paper is to review the prevalence of vitamin D deficiency in the elderly, its consequences, and its prevention and treatment, including public health aspects.

B. Physiology of vitamin D and bone mineralization

Vitamin D_3, or cholecalciferol, is synthesized in the skin. Its precursor, 7-dehydrocholesterol, is converted by the UV light of the sun (UVB 290–315 nm) into previtamin D_3, which is slowly isomerized to vitamin D_3 (13). Vitamin D binding protein (DBP) binds vitamin D and its metabolites and transports them in the bloodstream (14). Some nutrients also contain vitamin D_3, *e.g.*, fatty fish, eggs, and dairy products. Vitamin D_2, or ergocalciferol, originates from irradiation of ergosterol, a major plant sterol (13), and has been added to dairy products and (multi)vitamin preparations. More and more, however, it is being replaced by vitamin D_3. Vitamin D_2 is also transported in the circulation by DBP, and its metabolism is similar to that of vitamin D_3.

Vitamin D is hydroxylated in the liver into 25-hydroxyvitamin D [25(OH)D], which is the major circulating metabolite (15, 16). Further hydroxylation into 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] occurs primarily in the kidney. The hydroxylation in the kidney is stimulated by PTH and suppressed by phosphate. While 25(OH)D has limited biological activity, 1,25-$(OH)_2$D is the most active metabolite stimulating the absorption of calcium and phosphate from the gut. The production of 1,25-$(OH)_2$D is under tight feedback control, directly by serum calcium and phosphate and indirectly by calcium via a decrease of serum PTH (15–17). When serum calcium and phosphate are sufficiently high, the production of 1,25-$(OH)_2$D diminishes in favor of another metabolite, 24,25-dihydroxyvitamin D. The function of this metabolite in humans is still unclear (15). The free serum 1,25-$(OH)_2$D concentration is very low, as 1,25-$(OH)_2$D is more than 99% bound to DBP and albumin (14). The active metabolite 1,25-$(OH)_2$D acts through the vitamin D receptor (VDR), a specific nuclear receptor, related to the T_4 and steroid hormone receptors (15, 17, 18). The VDR is present in the intestine where 1,25-$(OH)_2$D, after binding to the VDR, stimulates the synthesis of several proteins in the intestinal cells, which participate in the transport of calcium from the intestinal lumen into the bloodstream (16, 17). The VDR is also present in many other organs such as bone, muscle, pancreas, and pituitary (19). The active metabolite 1,25-$(OH)_2$D influences muscle function and stimulates cell differentiation and immunological function in general (19, 20). Rapid nongenomic effects of 1,25-$(OH)_2$D (not involving the VDR) have been observed in the intestine, the osteoblast, the parathyroid gland, and other tissues (21). The action of 1,25-$(OH)_2$D on bone is not well understood. It stimulates the osteoblasts to produce osteocalcin and alkaline phosphatase and decreases the production of type I collagen by fetal rat calvaria (17). On the other hand, 1,25-$(OH)_2$D stimulates bone resorption *in vitro* (15, 16). The effects of 1,25-$(OH)_2$D on bone mineralization appear to be indirect by stimulating the calcium and phosphate supply, mainly by absorption from the gut.

The bone remodeling sequence by which new osteons are formed starts with osteoclasts resorbing existing bone (22). Thereafter, osteoblasts appear and construct the new unmineralized bone matrix, the osteoid. Subsequently, the osteoid is mineralized. The mineralization of the osteoid occurs in two phases. During primary mineralization, about half of the bone mineral accumulates within a few days, increasing the density to 1.4 g/cm^3. The secondary mineralization proceeds more slowly during 6 months or more and increases the density to 1.9 g/cm^3. When mineralization is normal, the mineral content of an osteon depends on its age. Young, low-density bone is more prevalent when bone turnover is high. Older, completely mineralized high-density bone is associated with low bone turnover (23).

II. Vitamin D Status in the Elderly

A. Assessment of vitamin D status

Before serum measurement of vitamin D metabolites became feasible, vitamin D deficiency was suspected in patients with symptoms of bone pain and muscle weakness and was diagnosed by low serum calcium and phosphate levels and elevated alkaline phosphatase activity (3, 24). In addition, urine calcium excretion in these patients was low. Clinical signs used in the screening of elderly people were those pointing to proximal muscle weakness, such as standing up from a chair. During the last two decades, measurement of serum 25(OH)D has become common practice for the assessment of vitamin D status and the detection of vitamin D deficiency (25). Although this practice has made the diagnosis comparatively easy, the assays for 25(OH)D still lack sufficient standardization as indicated by international comparative studies (26–28). In the most recent study (28), serum 25(OH)D was measured in two laboratories in 104 samples from a vitamin D supplementation study by a competitive protein binding assay (CPB), RIA, and a CPB after purification by HPLC. The mean serum 25(OH)D measured by CPB was 80% higher than that measured by HPLC, while the RIA gave intermediate values. The correlation between CPB and HPLC was moderate ($r = 0.69$, $P < 0.01$). Of the serum 25(OH)D values measured by HPLC in the lowest quartile, 25% and 21% were not recognized to be in the lowest quartile by CPB and RIA, respectively. Similar discrepancies were observed in the highest quartile. In the second part of the

same study, serum 25(OH)D was measured in up to eight serum samples by five laboratories using their routine assay methods (CPB or RIA). The difference between the mean values of the highest and the lowest laboratory was 38%. The individual values are shown in Fig. 1. It can be concluded from these interlaboratory comparisons that serum 25(OH)D levels from different regions or countries cannot be compared satisfactorily as long as the assays have not been cross-calibrated. Another problem is that different investigators have used various reference populations. Reference values have been based on healthy adults, such as blood donors, or on more or less representative samples of the population.

The use of population-based reference values may be less appropriate for another reason. The serum 25(OH)D concentration is not subject to homeostatic control, but depends on life style and environmental characteristics. It is more apt to base reference values for serum 25(OH)D on adverse health outcomes such as secondary hyperparathyroidism or increased bone turnover. Health-based reference values for serum 25(OH)D are higher than population-based values and are more suitable to define vitamin D deficiency, vitamin D insufficiency, and a vitamin D-replete state (see also *Section V*).

B. Determinants of vitamin D status

Vitamin D_3 (cholecalciferol) is synthesized in the skin under the influence of UV light (13). The UV range stimulating the formation of vitamin D_3 is rather small (290–315 nm). During winter at northern latitudes, the sunlight must pass a much longer distance through the atmosphere, and most UV light is absorbed. In the northern part of the United States and Canada, as well as in northwestern Europe, vitamin D production is virtually absent between October and March (29), but this may be different in more southern countries. UV radiation is effectively absorbed by glass and most plastics (1). Clothing prevents the photosynthesis of vitamin D_3 (30).

Sunscreens such as *p*-aminobenzoic acid also interfere with the cutaneous production of vitamin D_3 (31). The mean serum concentration of 25(OH)D was much lower in chronic sunscreen users than in control subjects (40 *vs.* 91 nmol/liter, Ref. 32). The cutaneous synthesis of vitamin D_3 is much lower in highly than in lightly pigmented skin (33). It is positively correlated with skin thickness (34).

The formation of vitamin D_3 in the skin is much less efficient in the elderly than in younger people. Total body irradiation with artificial UV light in six white young adults and six white elderly people with the same skin type showed that the increase of the serum vitamin D_3 concentration in young adults was about 4 times more than that in the elderly (35) (Fig. 2). However, even in the elderly, cutaneous vitamin D_3 production remains very effective. UV irradiation of 1,000 cm^2 of the skin on the back increases serum 25(OH)D from 20 to 60 nmol/liter in 3 months time, with an exposure time of 3–7 min three times per wk (36). This suggests that a 10-min exposure of head and arms (unprotected) three times per week, is adequate to prevent vitamin D deficiency.

When sunshine exposure is not adequate, dietary compensation should occur. Vitamin D intake in the elderly is around 100 IU/d or less in most European countries (37). Fatty fish is an important source of vitamin D_3. Serum 25(OH)D is higher in elderly subjects who regularly consume fatty fish than in those who do not (37). Vitamin D intake is much higher in the United States, due to fortification of milk with vitamin D (400 IU per quart) or to the use of (multi) vitamin supplements (8, 38). The diet and (multi) vitamin D tablets may contain either vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol). Separate measurement of vitamin D_2 and vitamin D_3 metabolites allows the estimation of the contribution of the diet to vitamin D status, at least when most vitamin D in the diet is vitamin D_2. Serum 25(OH)D_2 was more prominent in institutionalized than in ambulatory

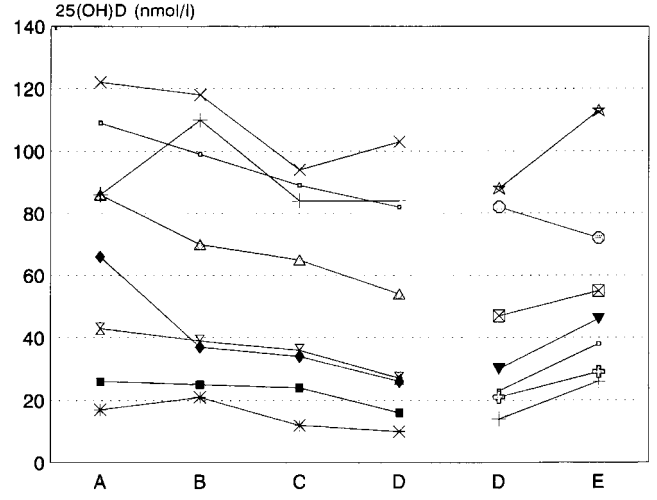

FIG. 1. International comparison of serum 25(OH)D measurements in three European and two US laboratories. The points represent individual values of serum 25(OH)D measured by four laboratories in eight serum samples and by two laboratories in seven other serum samples. [Reproduced with permission from P. Lips *et al.*: *Osteoporos Int* 9:394–397, 1999 (28). © International Osteoporosis Foundation and National Osteoporosis Foundation.]

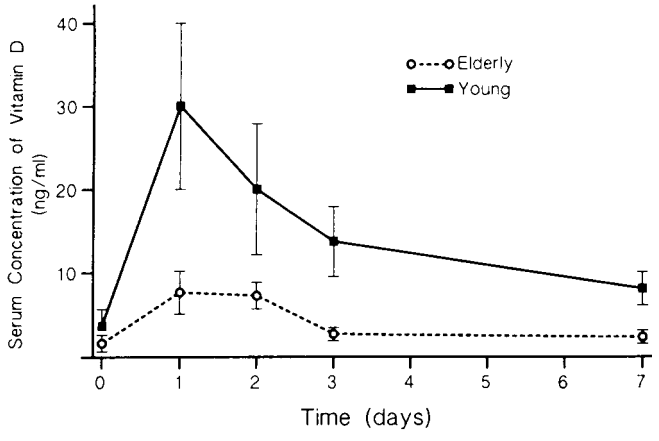

FIG. 2. Serum vitamin D_3 concentration after total body exposure to artificial sunlight (UV 260–360 nm) in six white young adults (20–30 yr) and six white elderly people (62–80 yr) with skin type III. Serum vitamin D_3 concentration was measured for 7 d. The area under the curve for serum vitamin D_3 suggests that the production of vitamin D_3 in the skin in the elderly is about 25% of that in young adults. [Reproduced with permission from M. F. Holick *et al.*: *Lancet* 2:1104–1105, 1989 (35). © The Lancet Ltd.]

TABLE 1. Studies on vitamin D status and vitamin D intake in elderly people

Ref	Country	Study population	n	Age (mean ± SD) (yr)	Vitamin D intake (mean IU/d) ± SD	25(OH)D[a]		Vitamin D deficiency (%)	Comments
						Lower ref. limit (nmol/liter)	Mean ± SD (nmol/liter)		
47	UK	Geriatric patients	36	86	40	20	3.3	90	
48	UK	Geriatric patients	62	65–95	55		11		
49	UK	Geriatric patients	43	81 ± 6	42 ± 31	10	12 ± 8	49	4 Subjects had hypocalcemia and osteomalacia
		Outpatients	37	77 ± 7	60 ± 40	10	18 ± 17	42	
50	UK	Hip fracture patients	41	77 ± 9		10	24 ± 14	15	
51	UK	Postmenopausal women	138	56.6 ± 4.7			28.9 ± 11.6		
52	UK	Elderly Asians	37	67–91		15	23 ± 20	57	
		Elderly whites	19	67–83		15	55 ± 14	6	
53	Ireland	Independent	30	69 ± 5		25	21	50	Studied in winter
		Nursing home	51	79 ± 8		25	9	84	Studied in winter
54	Sweden	Home for elderly	47	84		20	25	35	
55	Denmark	Geriatric patients	94	81 ± 9	70	12.5	24 ± 20	44	
37	Netherlands	Independent	74	76 ± 4	114 ± 44	20	33 ± 14	16	
		Hip fractures	125	76 ± 11	116 ± 63	20	19 ± 11	62	
56	Netherlands	Home for elderly	70	84 ± 6		20	24 ± 13	38	Serum $1,25(OH)_2D$ was lower in nursing home than in home for elderly
		Nursing home	72	81 ± 9		20	24 ± 9	32	
57	Netherlands	Home for elderly	348	80 ± 6		20	28 ± 13	34	Serum 25(OH)D < 30 nmol/liter in 65% of patients
58	Belgium	Geriatric patients	240	78 ± 7		12.5	29 ± 21	15	Reference limit for osteomalacia
59	Belgium	Male hip fracture	40	73 ± 6		30	26 ± 22	62	Free 25(OH)D index lower in fracture patients than in controls
		Male controls	40	72 ± 5		30	47 ± 18	18	
60	France	Outpatients	57	61–90			30 ± 25		
61	France	Outpatients	89	74 ± 6	<200		43 ± 18		
		Geriatric patients	104	81 ± 7	<200		21 ± 11		
62	France	Independent women	440	80 ± 3		30	43 ± 25	39	EPIDOS population sample from 5 French cities
10	France	Adults	1569	50 ± 6	136	30	61 ± 30	14	
63	Germany	Population-based sample	580	50–81		25	50 ± 25	24	
64	Italy	Postmenopausal women	570	59 ± 8		30	45 ± 20	28	
65	Italy	Postmenopausal women	25	62 ± 7		30	46 ± 29	32	Studied in winter
		Hospital patients	42	70 ± 10		30	27 ± 18	71	
		Neurological patients	17	74 ± 4		30	23 ± 12	82	
66	Spain	Home for elderly	21	80		12.5	37	0	
		Geriatric patients	31	79		12.5	10	75	
67	Switzerland	Geriatric patients	193	80 ± 9		30	18 ± 18	86	All subjects studied in winter
45	Europe	Independent women	410	73		30	29	47	Studied in winter
		Independent men	414	73		30	34	36	Population sample from 12 countries, central laboratory
68	Israel	Geriatric patients	338	78 ± 8	<100	12.5	33 ± 22	13.6	Mean serum 25(OH)D 12.5 nmol/liter in bedridden patients
69	Saudi Arabia	Elderly	24	62 ± 13		12.5	9 ± 3	83	Completely covered skin
70	Australia	Hip fractures	283	80 ± 9		30	45 ± 26	32	48% vitamin D deficiency in nursing home patients
71	New Zealand	Elderly women	38	76 ± 6		40	52 ± 23	24	In winter 69% vitamin D deficient
72	Hong Kong	Healthy women	28	71 ± 6	48 ± 16	50	55	30	
		Hip fractures	69	78 ± 10	40 ± 16	50	44 ± 12	49	
73	Japan	Severe Parkinson's disease	51	70 ± 8	103 ± 36	25	22 ± 8	78	
74	Japan	Alzheimer's disease	46	81 ± 5	82 ± 35	25	18 ± 10	80	

[a] Conversion factor for serum 25(OH)D: 1 nmol/liter = 0.40 ng/ml.

TABLE 1. Continued

Ref	Country	Study population	n	Age (mean ± SD) (yr)	Vitamin D intake (mean IU/d) ± SD	25(OH)D[a]		Vitamin D deficiency (%)	Comments
						Lower ref. limit (nmol/liter)	Mean ± SD (nmol/liter)		
75	Canada	Independent	186	73 ± 5	80 ± 10	43	39	>50	78% vitamin D intake < 100 IU/d
38	USA	Independent elderly	304	72	190		39 ± 18		60% vitamin D intake <100 IU/d
76	USA	Postmenopausal women	333	58 ± 6	112	20	80 ± 27	0	89 women took vitamin D supplement
77	USA	Nursing home	30	81			45		
78	USA	Healthy adults	281	20–94		35	85	3	No decrease with age of serum 25(OH)D and 1,25$(OH)_2$D
79	USA	Nursing home	35	74 ± 12	232 ± 66		43 ± 13		Serum 25(OH)D < 30 nmol/liter in 17%
80	USA	Geriatric patients	109	82	379	10	45	0	
41	USA	Homebound elderly	52	>65 yr	121 ± 132	25	26 ± 13		
		Geriatric patients	64	>65 yr	282 ± 146	25	36 ± 18		
81	USA	Independent women	469	67–95	±200	25	71 ± 29	4.1	Framingham cohort
		Independent men	290		±200	25	82 ± 29	2.4	
82	USA	Independent women	500	71 ± 4	150 ± 95	30	74 ± 24	3.3	NIA STOP/IT trial
		Independent men	235	71 ± 4	175 ± 112	30	86 ± 26	0.4	
40	USA	Hospital in-patients	290	62 ± 19	300 ± 292	37	37 ± 22	57	Serum 25(OH)D < 20 nmol/liter in 22%
83	USA	Hip fracture, women	30	80 ± 9		30	32	50	N-telopeptide higher in hip fracture
		Total hip replacement, women	68	66 ± 9		30	32		

[a] Conversion factor for serum 25(OH)D: 1 nmol/liter = 0.40 ng/ml.

elderly patients (39). However, when dairy products or supplements are not consumed, serum 25(OH)D may be very low in elderly patients in the United States (40, 41). In the Amsterdam vitamin D study, 133 of 2,578 elderly subjects (≥ 70 yr) were taking a (multi) vitamin preparation that contained between 90 and 400 IU of vitamin D (42). Higher vitamin D intakes, associated with consumption of fatty fish and vitamin supplements, are reported from Scandinavian countries (43).

C. Prevalence of vitamin D deficiency

Vitamin D deficiency can be defined according to population-based reference limits for serum 25(OH)D or biological indices, *e.g.*, hypocalcemia and elevated alkaline phosphatase or PTH levels (health-based limits). The former will depend on the reference population and country, determined by sunshine exposure and nutrition. We have defined reference limits in a population of healthy blood donors in Amsterdam with nonparametric estimation of 95% confidence limits (44, 37). The lower reference limits for serum 25(OH)D were 20 nmol/liter in winter (October-March) and 30 nmol/liter in summer (April-September).[1] Population-based reference limits will be higher when sunshine exposure is higher or when the diet contains more vitamin D. A similar lower reference limit of 30 nmol/liter (12 ng/ml) for serum 25(OH)D was reported in the Euronut SENECA (Survey in Europe on Nutrition and the Elderly, a Concerted Action) study (45) and SUVIMAX study (10). A somewhat higher reference limit of 37 nmol/liter was reported in the United States (40).

Extensive reviews on vitamin D status in young adults and the elderly have been published (9, 46). An overview of studies on vitamin D status in the elderly is presented in Table 1. The mean values of these studies are graphically presented according to geographical region or to subject/patient category in Fig. 3. These studies were performed in postmenopausal women, independent healthy elderly subjects, outpatients of general or geriatric clinics, hospital inpatients, geriatric patients, residents of homes for the elderly or nursing homes, and patients with hip fracture. The selection of study subjects is not always clear. Some studies were done in a population sample, *e.g.*, Framingham (81), Baltimore Aging Study (78), EPIDOS (62), Euronut (45). The serum 25(OH)D concentrations vary widely between different studies. Only part of this variation may be explained by assay differences. Serum 25(OH)D concentrations are lower in European countries than in the United States. The levels are lower in hospital patients and residents of nursing homes than in independent elderly subjects. Low serum levels were also observed in patients with severe Parkinson's and Alzheimer's disease in Japan (73, 74) and in patients with hip fracture in various countries. Serum 25(OH)D measured with one assay (HPLC followed by CPB assay) (84) in several groups in Amsterdam showed a gradual decline from healthy adults, to independent elderly, institutionalized elderly, and patients with hip fractures (Fig. 4) (37, 56, 85). While the picture in Fig. 3B may not be entirely reliable

[1] Conversion factor: 1 nmol/liter = 0.40 ng/ml.

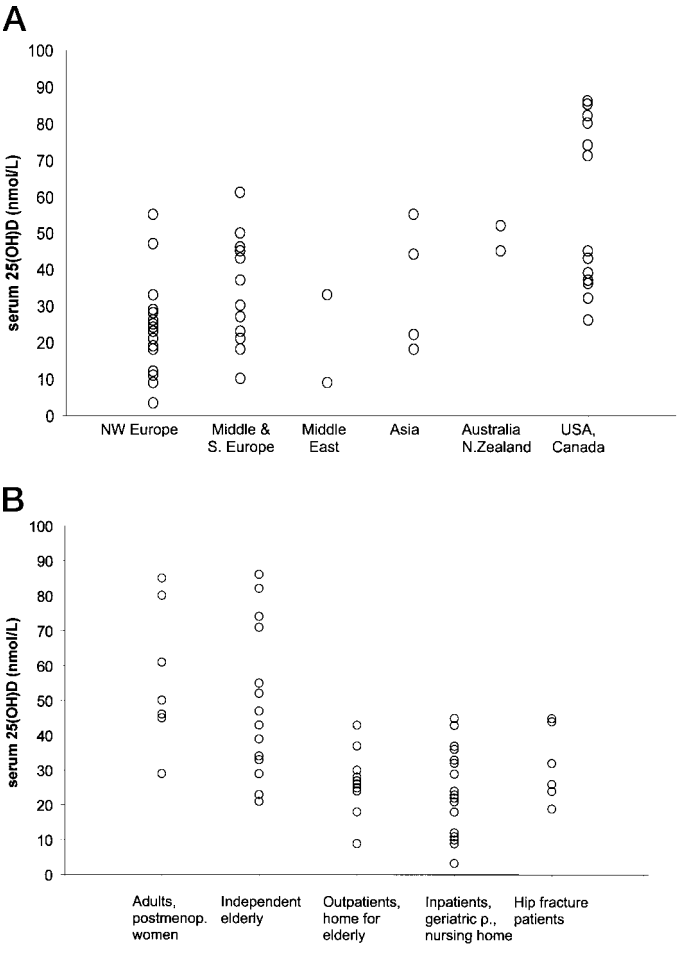

FIG. 3. Mean values of serum 25(OH)D from the studies in Table 1 according to geographical region (Fig. 3A) or to subject/patient/residence category (Fig. 3B).

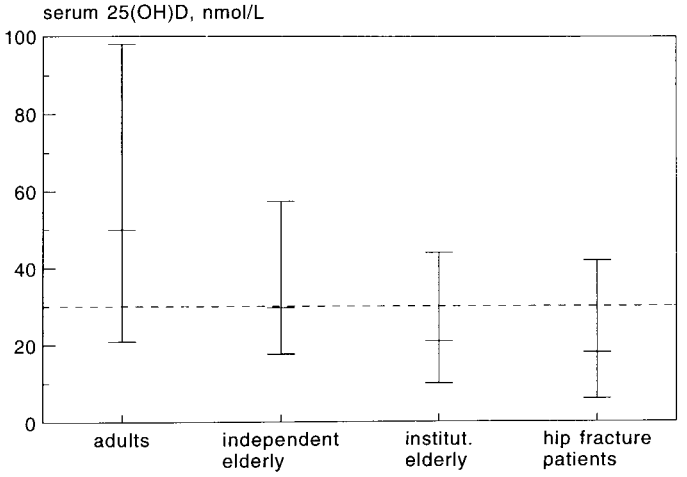

FIG. 4. Serum 25(OH)D (median, 5th-95th percentile) in 250 healthy adults (blood donors), 74 independent elderly subjects, 142 institutionalized elderly patients, and 125 patients with hip fracture. The samples in all groups were collected throughout the year. All measurements were performed by HPLC followed by competitive protein binding assay (data from Refs. 37,56,85). [Reproduced with permission from M. E. Ooms: Thesis. Vrije Universiteit Amsterdam, 1994 (105).]

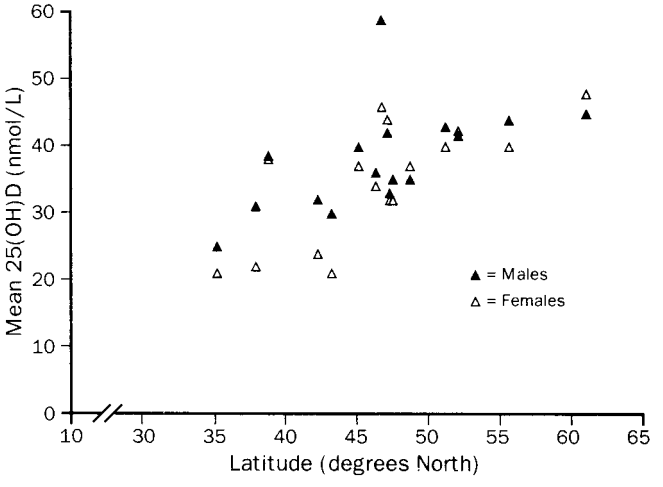

FIG. 5. Serum 25(OH)D measured in elderly people in 16 European centers participating in the Euronut SENECA Study. The *points* represent the mean values of each center for males and females according to northern latitude. The lowest values were found in Greece, Spain, and Italy. [Reproduced with permission from R. P. J. Van der Wielen *et al.*: *Lancet* 346:207–210, 1995 (45). © The Lancet Ltd.]

because of assay differences, Fig. 4, with all data from one assay method, gives a similar impression, which is reassuring. The lowest serum 25(OH)D concentrations were observed in geriatric patients in the United Kingdom and Ireland (48, 49, 53), but vitamin D deficiency also appears to be very common in institutionalized elderly patients in Switzerland (67). However, low levels were also found in Southern Europe. The European Euronut SENECA study was done in 15 centers in 11 countries using a central laboratory facility. Mean serum 25(OH)D varied from 22 nmol/liter in a study center in Greece to 46 nmol/liter in a center in Norway (45). Unexpectedly, serum 25(OH)D correlated positively with the degree of northern latitude (Fig. 5). The prevalence of vitamin D deficiency depends on the study population and the lower reference limit. In some studies this limit was set at 10 or 12.5 nmol/liter, and the investigators stated that this was the reference limit for osteomalacia (55, 58). In one of these studies, four subjects had hypocalcemia and osteomalacia (49). Vitamin D intake was around 100 IU/d or less in European studies, but twice as high or more in the United States Other remarkable observations are the high prevalence of vitamin D deficiency (serum 25(OH)D $<$ 30 nmol/liter) in healthy adults (14%) and independent elderly (39%) in France (10, 62). Very low levels of serum 25(OH)D were observed in inhabitants of Saudi Arabia, who tend to avoid sunlight and remain fully covered outside (69). Vitamin D deficiency also occurred in Australian hip fracture patients (70).

The very low serum 25(OH)D in patients with hip fracture might be partly due to trauma. Serum DBP was lower in patients with hip fracture than in controls (86). However, the free 25(OH)D index, (ratio 25(OH)D/DBP), an estimate for the free serum 25(OH)D concentration, was also lower in patients with hip fracture than in controls (3.0 ± 1.6 *vs.* 4.6 ± 2.0, $P < 0.001$) indicating real vitamin D deficiency.

One may conclude that vitamin D deficiency is very com-

mon in patients with hip fracture and in institutionalized elderly in European countries, but it also occurs in hospital patients and homebound elderly in the United States (40, 41). Vitamin D intake is very low in European countries, but low intakes are also encountered in the United States.

D. Changes in vitamin D metabolism with aging

As stated above, the efficiency of vitamin D production in the skin from its precursor 7-dehydrocholesterol decreases with aging (Fig. 2). The absorption of vitamin D is adequate even at very advanced ages. Oral vitamin D_2, 50,000 IU, led to similar increases of serum vitamin D_2 concentration in elderly subjects and young adults (39). In a study in 142 elderly subjects (mean age 82 yr) in a home for the elderly and a nursing home, a vitamin D supplement of 400 or 800 IU/d increased serum 25(OH)D from 24 to 65 or 75 nmol/liter, respectively (56). The serum 25(OH)D concentrations increased to more than 40 nmol/liter in all subjects who received a supplement. This indicates that absorption of vitamin D_3 is very adequate in the elderly. Of course, malabsorption such as that found in celiac disease may compromise the absorption of vitamin D_3. On the other hand, the pathogenesis of osteomalacia in malabsorption also involves poor calcium absorption and increased vitamin D turnover due to secondary hyperparathyroidism (87).

Vitamin D is hydroxylated in the liver to 25(OH)D. This hydroxylation step is well preserved in old age, but may be compromised by liver disease (88, 89). Further hydroxylation to 1,25-$(OH)_2$D occurs in the kidney. The renal 1α-hydroxylase activity may decrease with aging parallel to the decrease of renal function (90). The increase of serum 1,25-$(OH)_2$D after infusion of human PTH for 24 h (1–34) was lower in elderly patients with vertebral fractures than in younger adults (91). The increase of serum 1,25-$(OH)_2$D after PTH infusion correlated negatively with age and positively with glomerular filtration rate and was lower in patients with hip fracture than in healthy elderly patients (92). However, in the Baltimore Aging Study, serum 1,25-$(OH)_2$D was not lower in very healthy elderly subjects than in young and middle-aged adults (78). Experimentally, the age-related loss of 1α-hydroxylase activity was reversible in old rats on a low phosphorus or low calcium diet when infused with IGF-I (93, 94). This indicates that aging in itself does not necessarily cause a decrease of serum 1,25-$(OH)_2$D.

The age-related decrease in intestinal calcium absorption has been attributed to the decrease in serum 1,25-$(OH)_2$D. However, it appears that the decrease of calcium absorption with aging is partly independent of vitamin D (95). The serum concentration of 1,25-$(OH)_2$D is tightly controlled by negative feedback. When serum 1,25-$(OH)_2$D increases, gut calcium absorption also increases. The relatively high serum calcium decreases the secretion of PTH, leading to a lower production of 1,25-$(OH)_2$D. In case of severe vitamin D deficiency, serum 25(OH)D is low, and the production of 1,25-$(OH)_2$D may be restricted by lack of substrate (37, 56, 58). In vitamin D-deficient elderly and in patients with hip fracture, a positive correlation between serum 25(OH)D and serum 1,25-$(OH)_2$D has been observed, indicating substrate-dependent synthesis of 1,25-$(OH)_2$D (56, 58, 96). Serum DBP decreases with aging similarly to serum albumin. The lower serum 25(OH)D and 1,25-$(OH)_2$D concentration in frail elderly people and in patients with hip fracture could be due to the decrease of DBP, because, for the most part, the vitamin D metabolites are bound to DBP (14, 97). However, the free 25(OH)D index and free 1,25-$(OH)_2$D index [ratio 25(OH)D/DBP and 1,25-$(OH)_2$D/DBP] were lower in patients with hip fracture than in healthy elderly controls, indicating real deficiency in patients with hip fracture (86). In conclusion, vitamin D metabolism is relatively normal in healthy elderly people, but chronic diseases may interfere with it. The formation of 1,25-$(OH)_2$D may be restricted by impairment of renal function and by lack of substrate in the case of vitamin D deficiency.

III. Consequences of Vitamin D Deficiency

A. Secondary hyperparathyroidism and high bone turnover

A low serum 25(OH)D concentration is the hallmark of vitamin D deficiency. The low serum 25(OH)D concentration leads to a small decrease of serum 1,25-$(OH)_2$D and calcium absorption. The lower serum calcium concentration causes an increase of PTH secretion, which stimulates the production of 1,25-$(OH)_2$D. By this mechanism serum 1,25-$(OH)_2$D is kept at (nearly) normal levels at the expense of a higher serum PTH concentration, which is referred to as "secondary hyperparathyroidism." It implicates that serum PTH is relatively high for the associated serum calcium concentration, although it may still be within normal reference limits. As a consequence of the seasonal variation of serum 25(OH)D, vitamin D deficiency, when present, is most marked at the end of the winter months. As can be expected, serum PTH was observed to exhibit an inverse seasonal variation with high levels at the end of winter and low levels at the end of summer when serum 25(OH)D is at its maximum (76, 98). The increased serum PTH causes an increase of bone turnover, which is usually associated with (primarily cortical) bone loss. As is known from studies in primary hyperparathyroidism, the trabecular bone is relatively preserved: the bone mineral density in most patients with primary hyperparathyroidism is normal in the lumbar spine, while it is lower in the femoral neck (99). This was confirmed by histomorphometric studies (100, 101).

Secondary hyperparathyroidism has been proposed as the principal mechanism whereby vitamin D deficiency could contribute to the pathogenesis of hip fractures. Many investigators have observed increased serum PTH concentrations in elderly people with or without hip fractures associated with vitamin D deficiency (37, 56, 61, 70, 102). Serum PTH correlated negatively with serum 25(OH)D in many studies (10, 37, 56, 57, 61), usually with a correlation coefficient between 0.20 and 0.30 (Fig. 6). The correlation coefficient may be somewhat higher when restricted to the low range of serum 25(OH)D and when confounding variables (*e.g.*, serum creatinine) are controlled. The latter is important as many two-site intact PTH (1-84) assays may actually also measure inactive fragments such as PTH (7-84) accounting for more than 50% of the observed value in case of impaired renal function (103). The inverse relationship between serum

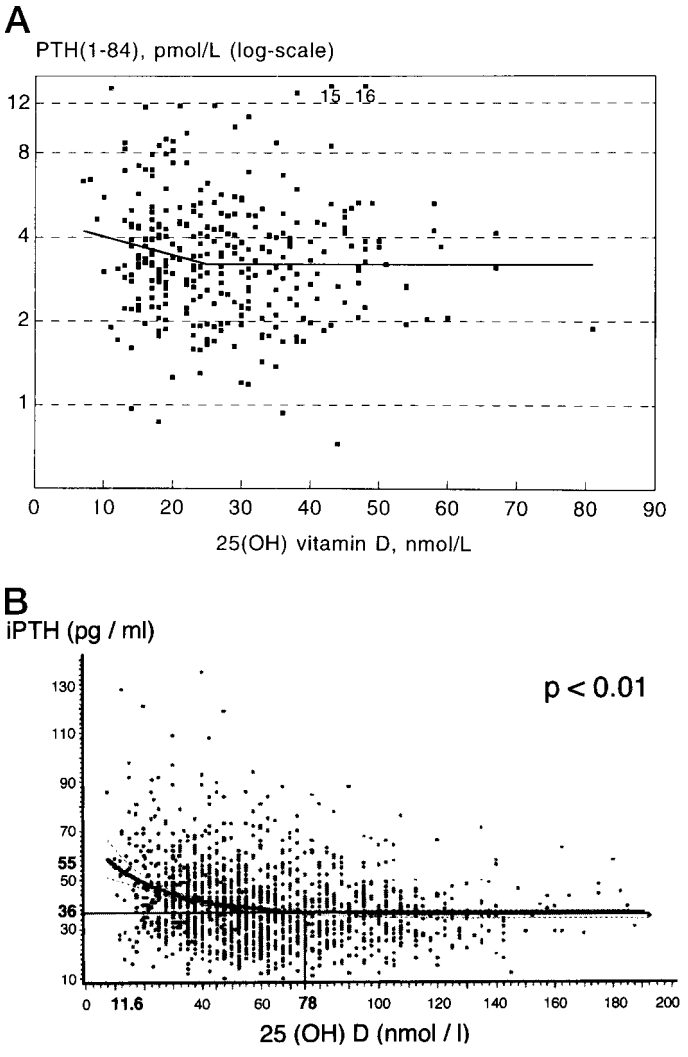

FIG. 6. A, Negative relationship between serum PTH and serum 25(OH)D in 330 elderly women (>70 yr) in Amsterdam. The best fit was obtained by a linear regression model with a threshold for serum 25(OH)D at 25 nmol/liter with a negative correlation below the threshold ($P = 0.02$) and no significant correlation above the threshold. B, Negative relationship between serum PTH and serum 25(OH)D in 1,569 adults (50 ± 6 yr) from the SUVIMAX study. The best fit was obtained by nonlinear regression analysis ($P < 0.01$). A plateau for serum PTH was reached at serum 25(OH)D above 78 nmol/liter. Below this level, serum PTH started to rise. [Panel A reproduced with permission from M. E. Ooms: Thesis. Vrije Universiteit Amsterdam, 1994 (105); panel B reproduced with permission from M. C. Chapuy *et al.*: *Osteoporos Int* 7:439–443 1997 (10). © International Osteoporosis Foundation and National Osteoporosis Foundation.]

25(OH)D and serum PTH has been observed not only in the elderly but also in postmenopausal women aged 45–65 yr (10, 76, 102).

A seasonal variation of biochemical markers of bone turnover was observed in a population-based sample of 580 adults in Germany, with higher values of bone alkaline phosphatase and urinary pyridinoline in winter than in summer, an indication of higher bone turnover in winter (63). Markers of bone resorption (urine hydroxyproline excretion) and bone formation (alkaline phosphatase activity, serum osteocalcin) were significantly increased in patients with osteomalacia compared with healthy controls, and serum osteocalcin correlated significantly with osteoid surface (104). In the Amsterdam vitamin D study, serum osteocalcin was significantly higher in patients with serum 25(OH)D < 30 nmol/liter than in the other patients, and a negative correlation ($P = 0.04$) between serum osteocalcin and serum 25(OH)D was observed below the threshold for serum 25(OH)D of 30 nmol/liter (57, 105). Recently, markers of bone turnover were measured in 119 active community-dwelling elderly women (106). Vitamin D insufficiency was defined by a serum 25(OH)D between 15 and 30 nmol/liter, observed in 27% of the group. Serum PTH correlated significantly with serum 25(OH)D ($r = -0.42$, $p < 0.01$). The serum concentration of osteocalcin and bone alkaline phosphatase activity and urinary excretion of hydroxyproline and deoxypyridinoline were significantly higher in the vitamin D-insufficient women than in the vitamin D-replete group. Bone mineral density in the total hip was significantly lower in the vitamin D-insufficient group. In about half of the patients with vitamin D insufficiency, one or more bone markers were elevated above the upper reference limit. The increase of serum PTH and bone resorption and formation markers is consistent with increased bone turnover and bone loss in patients with vitamin D deficiency. Biochemical markers of bone turnover may be useful in the future to diagnose high bone turnover and bone loss in patients with various grades of vitamin D deficiency.

B. Bone histology in patients with hip fractures

About 30 yr ago, Chalmers and colleagues (6, 7) pointed to the frequent occurrence of osteomalacia in elderly women, often occurring after gastrectomy and often associated with hip fractures. Since then, many reports have been published on increased osteoid tissue (hyperosteoidosis) and osteomalacia in patients with hip fracture. Osteomalacia can only be diagnosed reliably in a nondecalcified bone biopsy, labeled with tetracycline before the biopsy to assess mineralization. Osteomalacia is characterized by an increase of the bone surface covered by osteoid seams and an increase of the osteoid thickness, which usually measures more than 4 lamellae (3, 12). The cornerstone of the diagnosis of osteomalacia is the demonstration of a reduction in mineral apposition rate, mineralization surface, and bone formation rate, which can be measured after the administration of double tetracycline labels before the bone biopsy (107). Absence of double fluorescent labels and a low mineralization surface combined with increased osteoid thickness indicates severe osteomalacia (108). Bone biopsies have been extensively studied in patients with hip fracture because they can easily obtained during the operation. However, tetracycline labels cannot be administered before the hip fracture, implicating that the mineral apposition rate cannot be measured. Studies of bone biopsies in patients with hip fracture are summarized in Table 2. The incidence of osteomalacia in these studies ranges from 0 to 37%. However, comparison between these studies is hampered by the use of different criteria for osteomalacia. One may avoid this problem by referring to the increased amount of osteoid tissue as "hyperosteoidosis." Many studies show an increase of osteoid surface and eroded

TABLE 2. Hyperosteoidosis in patients with hip fracture according to histomorphometric studies of iliac crest or femoral head histology

First or only author	Ref.	Country	No. of Patients	Percentage "osteomalacia"	Criteria[a]	Comments[a]
Chalmers (1969)	7	UK	130	20	OV/BV > 6%	12% Radiological or biochemical abnormalities 6 Patients Looser zones
Hodkinson (1971)	109	UK	35	0	O.Th	10% O.Th > 15 μm in patients with osteoarthritis
Jenkins (1973)	110	UK	45	30	OV/TV > 0.5%	5 Patients frank osteomalacia (9%)
Aaron (1974)	111	UK	125	37	OS/BS > 25% or calcif. front < 60%	Both present in 21% of patients
Faccini (1976)	112	UK	51	"many"	Not specified	
Wootton (1979)	113	UK	80	8	Osteoid lamellae ≥ 4	
Wilton (1987)	114	UK	201	4	OV/BV > 5%	
Hordon (1990)	115	UK	78	12	OS/BS ≥ 25% O.Th > 13 μm	9/78 With osteomalacia mean O.Th. 20.9 μm, mean OV/BV 12.5%
Compston (1991)	116	UK	49	2	O.Th > 15 μm and Calcification front < 60%	
Robinson (1992)	117	UK	81	0	OV/BV > 5% or OS/BS > 25%	
Alhava (1974)	118	Finland	104	6	Histology, x-rays, alk. phosphatase	Decalcified biopsies
Hoikka (1982)	119	Finland	50	24	OV/BV > 3.4%	
Lund (1982)	120	Denmark	20	5	O.Th > 12 μm	Serum 25(OH)D 48 nmol/liter in osteomalacic patients
Lips (1982)	96	Netherlands	89	0	O.Th > 15 μm	
Eid (1978)	121	Qatar	69	26	O.Th.	5 Patients Looser zones
Evans (1981)	122	Australia	31	10%	OS/BS ↑, tetracycline surface ↓	
Wicks (1982)	123	Australia	95	0		abs. osteoid vol. < 0.1% in all biopsies
Sokoloff (1978)	124	USA	31	26	OS/BS > 8.6%	Low grade osteomalacia
Johnston (1985)	125	USA	32	15	OV/BV > 5%	

[a] OV/BV, Osteoid volume; O.Th, osteoid thickness; OV/TV, absolute osteoid volume; OS/BS, osteoid surface; abreviations are according to ASBMR histomorphometry nomenclature committee (107).

surface (resorption surface) compatible with high bone turnover associated with secondary hyperparathyroidism. In 89 biopsies of patients with hip fractures from The Netherlands, high turnover characterized by osteoid surface > 18% and eroded surface > 6% was observed in 22% of the biopsies (96). In this study osteoid thickness was not increased in any biopsy. Six studies report the measurement of osteoid thickness, and in three of these osteoid thickness was increased in 5 to 12% of the patients (113, 115, 120). In series from the United Kingdom, increased osteoid values appear more common than in series from other countries (126). The excess osteoid tissue shows a seasonal variation with the highest values in spring and the lowest in autumn, reversed to the seasonal variation of serum 25(OH)D, as may be expected (127). A more recent well documented study (115) reported osteomalacia in 12% of the patients with hip fracture, and these biopsies had increased osteoid volume (mean 12.5%) and osteoid thickness (>13 μm) associated with severe vitamin D deficiency [mean serum 25(OH)D 10.6 nmol/liter]. Frank osteomalacia with radiographically demonstrated Looser zones was reported in several series of patients with hip fracture (7, 110, 118, 121) or subtrochanteric fracture (128). A very sunny climate as in Qatar does not exclude osteomalacia where Looser zones were observed in 6 of 69 patients with hip fracture (121).

Hyperosteoidosis is not uncommon in patients with hip fracture. Most of these patients can be diagnosed as having secondary hyperparathyroidism. Overt osteomalacia with increased osteoid thickness, when present, is observed in a small percentage of bone biopsies of patients with hip fracture, usually less than 5% but in some series up to 10%. In series that report higher percentages (111), the diagnosis could have been secondary hyperparathyroidism in many cases. Definitions in many studies are incomplete. In a detailed histological analysis of bone biopsies, Parfitt *et al*. (108) distinguished three stages of hypovitaminosis D osteopathy. The criteria used were osteoid surface and osteoid seam thickness, mineral apposition rate, mineralizing surface, and bone formation rate measured with double tetracycline labeling. The first stage of hypovitaminosis D osteopathy could not be distinguished from the histological picture seen in primary hyperparathyroidism. The second stage was characterized by increased osteoid surface and thickness, but tetracycline labels were still visible and the mineral apposition rate could be measured. The third stage was overt osteomalacia with increased osteoid seam thickness and no tetracyline labels precluding measurement of mineral apposition rate and bone formation rate. However, mineral apposition rate and bone formation rate cannot be measured in patients with hip fracture, because the tetracycline labels cannot be administered before the fracture. The best evidence for osteomalacia can be obtained by combining osteoid seam thickness and mineral apposition rate. However, these may be normal in mild degrees of vitamin D deficiency where the histological picture resembles that of hyperparathyroid bone disease (108). Screening for osteomalacia at the time of hospital admission by measuring alkaline phosphatase has been suggested by some investigators, but the rate of false positive

results was very high (129). Two recent studies suggest that the prevalence of osteomalacia in patients with hip fracture has decreased in the United Kingdom to 0 to 2% (116, 117). However, severe degrees of vitamin D deficiency were recently reported in geriatric patients in several countries, *e.g.*, France, Spain, and Japan (see Table 1), indicating that osteomalacia still may occur and may be overlooked when no attention is given to this possibility.

C. Vitamin D status and bone mineral density

In cross-sectional studies, a positive relationship has been observed between serum 25(OH)D and bone mineral density (BMD) of the hip. In 330 elderly women in Amsterdam, a threshold was observed (57). The positive correlation was significant when serum 25(OH)D was lower than 30 nmol/liter, but above this level the relationship was no longer significant (Fig. 7). The relationship appeared to be stronger for cortical bone (femoral neck) than for trabecular bone (trochanter). As can be seen in Fig. 7, the BMD at the femoral neck was 5 or 10% lower than average when serum 25(OH)D was 20 or 10 nmol/liter, respectively. A positive relationship between serum 25(OH)D and BMD of the hip was also observed in middle-aged women in the United Kingdom (45–65 yr) (51) and in elderly women in New Zealand (71). Similarly, a negative relationship has been observed between BMD of the hip and serum PTH (51, 130, 131).

Bone mineral loss is caused by several mechanisms. Bone loss includes a reversible and an irreversible component. In overt osteomalacia, the newly formed osteoid is not mineralized, which may cause a considerable mineral deficit (3). In secondary hyperparathyroidism, the increase in osteoid tissue is rather small, but the mean age of osteons is lower than average due to the high bone turnover. While the initial mineralization of osteoid tissue proceeds rather quickly, secondary mineralization may take 6 months or longer (23). When the mean age of osteons is younger as it is in hyperparathyroidism, the degree of mineralization is lower. In addition, when more osteons are remodeled at the same time, the temporary bone deficit (*i.e.*, remodeling space) is higher than usual (132). The bone mineral loss due to 1) osteoid accumulation, 2) lower mineralization degree of mineralized osteons, and 3) increased remodeling space is reversible.

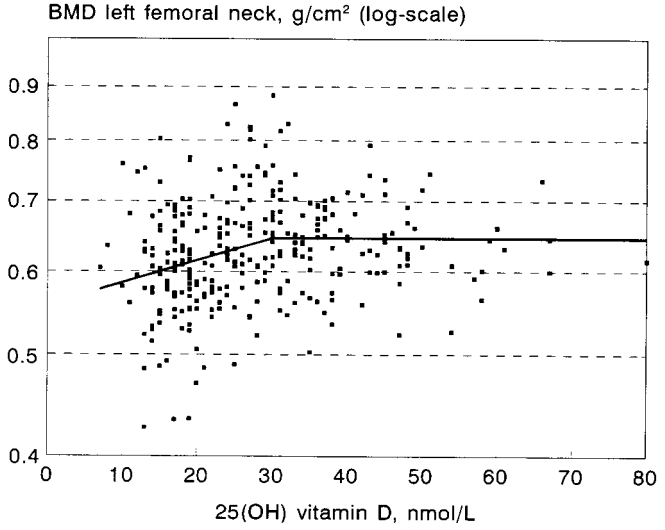

FIG. 7. Relationship between serum 25(OH)D and BMD of the femoral neck in 330 elderly women. The best fit was obtained by a linear regression model with a threshold for serum 25(OH)D at 30 nmol/liter. The correlation was significant ($P < 0.001$) when serum 25(OH)D < 30 nmol/liter. With higher values of serum 25(OH)D, the correlation with BMD was no longer significant. [Reproduced from M. E. Ooms *et al.*: *J Bone Miner Res* 10:1177–1184, 1995 (57) with permission from the American Society for Bone and Mineral Research.]

In addition, there is an irreversible component of bone loss. Remodeling balance per osteon usually is negative in the elderly. In a state of high turnover, the negative remodeling balance is multiplied by the high number of remodeling osteons, whereas in low turnover states, bone loss due to negative remodeling balance is much lower (23). Quantitative observations on the irreversible bone loss in osteomalacia were made by Parfitt *et al.* (133) in 28 patients who were treated with vitamin D and calcium. The osteoid volume decreased by 80% in cortical (from 6 to 1.5%) and trabecular bone (from 30 to 6%). Cortical porosity decreased from 10.3 to 7.8%. Mineralized bone volume increased by 7.5% in cortical and 40% in trabecular bone. The mineral deficits decreased after treatment from 42 to 36% in cortical and from 32 to 6% in trabecular bone. At the end, the irreversible cortical bone loss was due to cortical thinning (endosteal resorption) caused by secondary hyperparathyroidism (133). The bone mineral deficit in osteomalacia is much larger than that in milder degrees of vitamin D deficiency. The bone loss of 5 to 10%, due to secondary hyperparathyroidism in vitamin D-deficient elderly, is quite comparable to the bone loss in primary hyperparathyroidism, which is reversible after successful parathyroidectomy (134).

Another interpretation of the association between low serum 25(OH)D and low BMD is a sedentary life style. This would cause bone loss due to immobility as well as reduced exposure to sunlight. Indeed, frail elderly subjects are often vitamin D deficient and are physically not very active. However, immobility is associated with increased bone resorption, which causes suppression of parathyroid activity and a low serum PTH (135).

D. Vitamin D deficiency as a risk factor for fractures in epidemiological studies

Epidemiological data on vitamin D deficiency as a predictor for bone loss or osteoporotic fractures are scarce. In the Study of Osteoporotic Fractures, a study in four US centers, risk factors for osteoporosis were studied prospectively in 9,704 elderly women. Vitamin D deficiency as a risk factor was studied using the case-cohort approach in 133 women with first hip fracture and 138 women with a new vertebral fracture (136). Mild vitamin D deficiency [serum 25(OH)D < 47 nmol/liter, prevalence 22%] was not associated with an increased risk for hip or vertebral fracture. A low serum 1,25-$(OH)_2$D (≤ 57 pmol/liter) was associated with an increased risk for hip fracture [risk ratio (RR) 2.1 adjusted for age and weight]. Serum PTH was not a risk factor in this study, but low estradiol and high SHBG were both associated with an increased risk for hip and vertebral fracture. In the

Study of Osteoporotic Fractures, severe vitamin D deficiency was rare, and this may be the reason that vitamin D deficiency was not associated with an increased risk for osteoporotic fractures in this study. In Oslo, Norway, 246 patients with hip fracture and a similar number of controls were studied for risk factors. A vitamin D intake lower than 100 IU/d was associated with an increased risk for hip fracture [RR 3.9, confidence level (CI) 1.7–9.3] (137).

Bone loss from the femoral neck was prospectively studied during 16 yr in 304 women aged 30–49 yr from Rochester, Minnesota. Independent predictors of bone loss in elderly women included dietary vitamin D intake, hormone replacement therapy, and serum osteocalcin (138). However, vitamin D intake was not a risk factor for bone loss in pre- or postmenopausal women in this study. The efficacy of drugs preventing hip fracture was investigated in a retrospective case-control study (MEDOS) in 2,086 women with hip fracture and 3,532 controls (139). Estrogen, calcium, and calcitonin significantly reduced the risk, but vitamin D compounds did not. However, only 4% used vitamin D preparations. Subgroup analysis of these data showed that the relative risk of hip fracture was significantly lower in women aged above 80 yr when using vitamin D (RR 0.63, CI 0.40–0.98) and in women with a body mass index (BMI) below 20 kg/m^2 when using vitamin D (RR 0.45, CI 0.24–0.84) (140).

Vitamin D deficiency is less common in the elderly in the United States than in most European countries. This is an argument against vitamin D deficiency as a risk factor for hip fractures. However, within a country, hip fractures may be more frequent in vitamin D-deficient than in vitamin D-replete elderly subjects. More prospective epidemiological studies on risk factors for osteoporotic fractures including vitamin D deficiency are underway, *e.g.*, the European Prospective Osteoporosis Study, the Rotterdam Study, and the Longitudinal Aging Study Amsterdam.

E. Vitamin D deficiency and myopathy

Vitamin D deficiency is associated with muscle weakness. Muscle contraction and relaxation are abnormal in vitamin D deficiency, and these are corrected by vitamin D independently of changes in mineral levels (20). Improvement of myopathy occurs after very low doses of 1,25-$(OH)_2$D. Treatment of patients with osteoporosis with 1α-hydroxyvitamin D increased succinate dehydrogenase and phosphorylase activity and increased the number of IIA muscle fibers (141). Muscle weakness and hypotonia were observed as initial manifestation of severe vitamin D deficiency in an intensive care patient (142). Muscle strength correlated positively with serum 1,25-$(OH)_2$D in geriatric patients and with serum 25(OH)D in elderly male patients (143). Serum 25(OH)D was lower, and serum PTH was higher in Australian nursing home residents who fell than in other residents who did not fall (144). The association between falling and serum PTH persisted after multiple adjustments. A prospective study on risk factors for falls was done in 354 elderly subjects participating in a double blind clinical trial to evaluate the effect of vitamin D_3 supplementation on the incidence of hip fractures (Amsterdam Vitamin D Study). The incidence of falls and recurrent falls was similar in the vitamin D and placebo groups (145). The results of intervention studies with vitamin D on muscle strength are conflicting (see below).

F. Other consequences of vitamin D deficiency

During the last 20 yr many new actions of vitamin D metabolites, especially 1,25-$(OH)_2$D, have been discovered. The presence of the vitamin D receptor has been demonstrated in many organs, often without direct relevance for vitamin D action (17). New actions have been reviewed extensively (19, 21, 146). Some of these actions might decline in vitamin D-deficient elderly subjects. Although it is not the main subject of this review, some actions may be very relevant because of the frequent occurrence of vitamin D deficiency in the elderly. The active metabolite, 1,25-$(OH)_2$D, has been shown in numerous systems to decrease cell growth and induce cell differentiation (19, 147). It has been tested in the treatment of cancer and lymphoma, and systemic and topical 1,25-$(OH)_2$D has been successful in the treatment of psoriasis (13). Epidemiological studies have suggested that vitamin D deficiency is associated with colon and breast cancer (148–150).

Vitamin D status may influence immunological function. Vitamin D deficiency is also associated with impaired macrophage function (151); it is associated with infection in children with rickets and in adults with disseminated tuberculosis and with anergy to skin testing (146).Vitamin D status also influences insulin secretion. Vitamin D deficiency results in a decreased insulin response to glucose, which is corrected by 1,25-$(OH)_2$D (152). Treatment of a vitamin D-deficient patient with vitamin D improved glucose tolerance and β-cell function (153). Inadequate vitamin D status has been implicated as a factor contributing to syndrome X, *i.e.*, insulin resistance, obesity, hypertension, glucose intolerance, and dyslipidemia, but response to vitamin D treatment has been variable (154). Vitamin D is also involved in other endocrine organs such as the pituitary and the testis, but deleterious effects of vitamin D deficiency are not established for these organs. Vitamin D deficiency has also been associated with progression of osteoarthritis in the Framingham Study (155) and with an unusual pain syndrome characterized by severe hyperesthesia, which resolved after vitamin D treatment (156). Although vitamin D deficiency may have potentially important consequences along these pathways, the effects on health status in the elderly are uncertain.

G. Racial differences in vitamin D and PTH metabolism

Interesting observations have been made in American blacks compared with whites. The incidence of hip fractures is considerably lower in black than in white people (157, 158). A higher BMD was observed consistently in blacks compared with whites (159, 160). When adult black and white women and men were compared, serum 25(OH)D was significantly lower and serum 1,25-$(OH)_2$D was significantly higher in blacks (161). Similar observations were made when black and white adolescents were compared (162). In later studies, a higher serum 1,25-$(OH)_2$D in blacks than in whites was observed by some investigators (163, 164) but not by others

(165, 166). A significant increase of serum PTH was found in some (161, 164, 165) but not in other studies (166, 167). Biochemical markers of bone turnover, such as serum osteocalcin, suggested a higher bone turnover in blacks than in whites (161) or a similar turnover (164). Urinary calcium excretion has consistently been lower in black than in white people (161, 162, 164, 166). A detailed study of calcium absorption in response to calcitriol (1,25-$(OH)_2$D) showed a lower response in blacks than in whites, suggesting a gut resistance to 1,25-$(OH)_2$D (164). Little data are available on vitamin D status and metabolism in elderly black people. Although the literature suggests changes in the vitamin D endocrine system, such as an increase of serum 1,25-$(OH)_2$D and serum PTH, conclusions on the relevance of these changes for the low incidence of hip fractures in blacks cannot yet be drawn.

IV. Other Causes of Secondary Hyperparathyroidism in the Elderly

A. Renal function

Renal function slowly decreases with aging. Population studies show a gradual decrease of the glomerular filtration rate from about 125 ml/min at age 20 to about 60 ml/min at age 80. This is associated with a gradual increase of serum PTH with age (168, 169). Serum PTH correlates positively with serum creatinine. Several mechanisms may explain this. The slight increase of serum phosphate directly increases parathyroid function. The lower formation of 1,25-$(OH)_2$D causes a small decrease in calcium absorption, and the lower serum calcium increases serum PTH. Multiple regression analysis in studies of elderly patients with hip fracture show both renal function and serum 25(OH)D as determinants of serum PTH (70, 170, 171). The commonly prescribed diuretic furosemide may also induce secondary hyperparathyroidism. In Australian nursing home residents, furosemide was a more important predictor of serum PTH than renal function and serum 25(OH)D (172). Furosemide increases calcium excretion and lowers ionized calcium by inducing alkalosis (173), thereby increasing serum PTH. Furosemide was a negative predictor for BMD of the hip in institutionalized elderly patients in Amsterdam (174).

B. Estrogen deficiency

Interactions between estrogen status and serum PTH have also been reported. The rise in serum PTH with aging does not occur in women receiving estrogen replacement therapy. In a cross-sectional study in 351 women from 20 to 90 yr of age, mean serum PTH increased from 1.8 to 3.2 pmol/liter. This increase was not observed in 54 women receiving estrogen replacement therapy (175). Estrogen status may also influence secondary hyperparathyroidism caused by vitamin D deficiency. In 348 elderly women participating in the Amsterdam Vitamin D Study, an interaction was observed between the serum concentration of sex hormone binding globulin (SHBG), which correlates negatively with the free estrogen concentration, and the relationship between serum PTH and 25(OH)D (57). Mean serum PTH was high in vitamin D-deficient elderly with high serum SHBG (associated with low free estrogen concentration), and normal in vitamin D-deficient elderly women with low serum SHBG (suggesting high free estrogen concentration). Thus, estrogen appeared to suppress secondary hyperparathyroidism in response to vitamin D deficiency. The interaction of serum SHBG with secondary hyperparathyroidism also was apparent in the BMD increase after treatment with vitamin D_3 (see below).

C. Low calcium nutrition

A low calcium intake also increases PTH secretion (176). In a study in postmenopausal women (mean age 70 yr), it was shown that increasing calcium intake from 800 to 2,400 mg/day caused a decrease of serum PTH of 30% during 24 h (177). It has been suggested that calcium intake modulates the age-related increase in serum PTH and bone resorption. In addition, a low calcium intake may influence vitamin D metabolism. It was observed that vitamin D deficiency occurs after partial gastrectomy even when sunshine exposure is normal (87). The low calcium intake (due to low dairy intake) after gastrectomy causes an increase of serum PTH and consequently of serum 1,25-$(OH)_2$D. Metabolic studies in rats on a low calcium intake demonstrated that these increases in serum PTH and 1,25-$(OH)_2$D were associated with increased metabolic clearance of 25(OH)D (178). In primary and secondary hyperparathyroidism, the half-life of serum 25(OH)D was inversely correlated to serum 1,25-$(OH)_2$D (87). The (relatively) high 1,25-$(OH)_2$D level in secondary hyperparathyroidism is associated with a high turnover of 25(OH)D (Fig. 8). A low calcium intake by causing a high serum 1,25-$(OH)_2$D thus may lead to an increased catabolism of

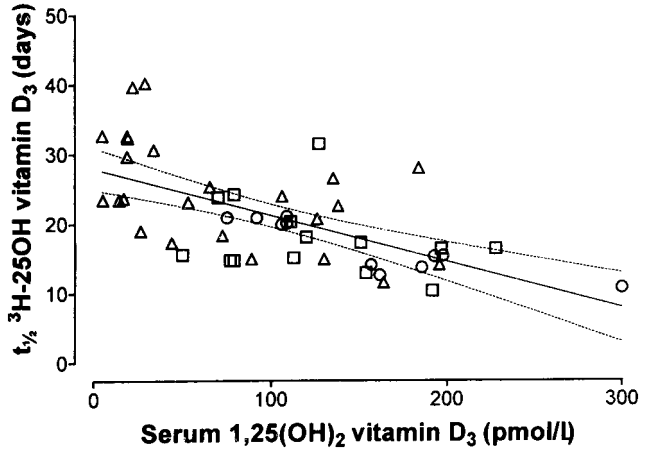

FIG. 8. Relationship between the half-life of ^{3}H-25(OH)D and the serum 1,25-$(OH)_2$D concentration in 49 patients shown as the regression line and 95% confidence limits. Correlation coefficient $r = -0.63$, $P < 0.001$. The data are from patients after gastrectomy (O), patients with primary hyperparathyroidism before and after surgery (□), and patients with other disorders of bone and mineral metabolism (Δ). When serum 1,25-$(OH)_2$D is high, the half-life of 25(OH)D is short, indicating an increased catabolism that may aggravate vitamin D deficiency. [Reproduced with permission from M. Davies *et al.*: *J Clin Endocrinol Metab* 82:209–212, 1997 (87) © The Endocrine Society.]

25(OH)D, thereby decreasing serum 25(OH)D and inducing or aggravating vitamin D deficiency. The reverse may also be true: a high calcium intake may suppress serum PTH, decrease serum 1,25-$(OH)_2$D, and thus have a vitamin D sparing effect (179, 180). A very low dietary calcium intake may cause histological osteomalacia. Three children of 4 to 13 yr presented with signs and symptoms of rickets. They had a normal serum 25(OH)D but a very low calcium intake of 125 mg/d (181). The bone biopsies showed high ostoid surface and thickness and a low bone formation rate. A clinical, biochemical, and histological cure was obtained by increasing calcium intake and calcium supplements. In conclusion, a low calcium intake aggravates vitamin D deficiency and its consequences, while a high calcium intake may reduce vitamin D requirement.

Secondary hyperparathyroidism thus appears to be the common intermediate pathway to compensate for low calcium bioavailability in the case of vitamin D deficiency, impaired renal function, furosemide treatment, low calcium intake, and estrogen deficiency (Fig. 9). The increased PTH secretion causes high turnover, which is harmful for the skeleton as can be concluded from BMD studies in hyperparathyroidism whether primary or secondary.

V. Functional Classification and Diagnosis of Vitamin D-Deficient States

A. Vitamin D deficiency and insufficiency

As is clearly visible from Table 1, there is no consensus on the borderline between a vitamin D-deficient and vitamin D-sufficient state. The lower reference limit for serum 25(OH)D in these reports ranges from 10 to 43 nmol/liter. Some authors define this limit as the lower limit of the adult reference range, while others mention the limit as below that in which osteomalacia occurs. As discussed earlier (*Section II.A*) it may be more appropriate to use health-based than population-based reference values for serum 25(OH)D, *i.e.*, reference limits based on avoidance of adverse health outcomes for the skeleton. A tendency is visible in recent studies to increase the lower reference limit as a consequence of the awareness that secondary hyperparathyroidism and bone loss occur at higher serum 25(OH)D than that associated with osteomalacia. Several investigators reserve the term "vitamin D deficiency" for a severe vitamin D-deficient state associated with osteomalacia, and use "vitamin D insufficiency" or "inadequacy" for moderate deficiency, which is associated with secondary hyperparathyroidism (10, 11).

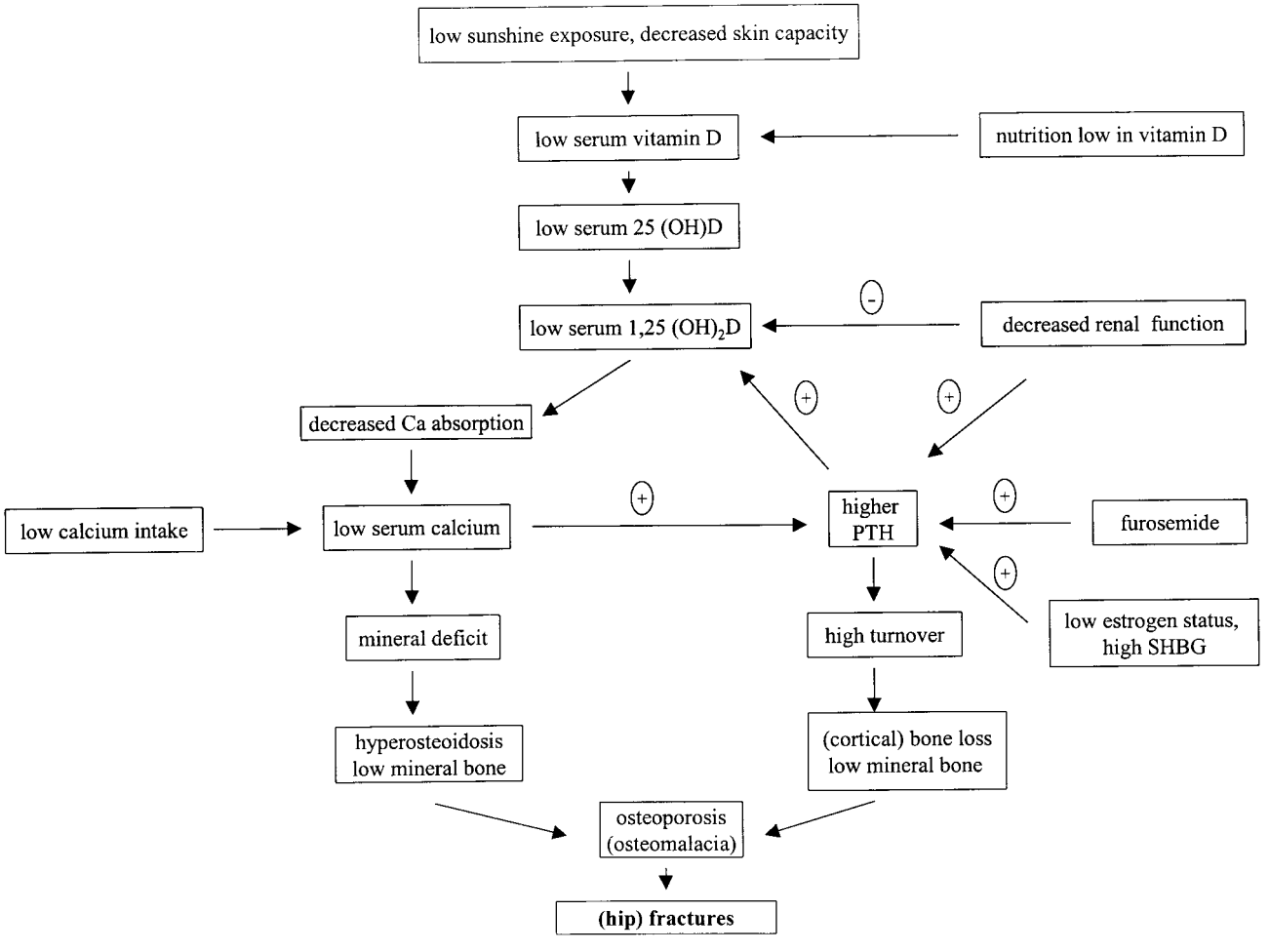

FIG. 9. Schematic presentation of pathways from vitamin D deficiency and secondary hyperparathyroidism to osteoporotic fractures.

Another point is the definition of secondary hyperparathyroidism. The increase of serum PTH is a compensatory or adaptive mechanism in response to a tendency for low serum calcium. Serum PTH changes during the day and between days in relationship with serum calcium, calcium intake, and calcium supplements (177, 179, 180). When serum PTH increases in winter after the decrease of serum 25(OH)D, this is in principle an adaptive physiological mechanism. This adaptive increase of serum PTH is usually called secondary hyperparathyroidism, although the mean values often are still in the normal reference range (76, 98). The seasonal variation of serum PTH occurs not only in the elderly but also in children (182). An inverse relationship between serum PTH and serum 25(OH)D occurs not only in elderly people but also in children in France and adults in Africa (183, 184).

B. Diagnostic criteria

The most common approach is to define a sufficient vitamin D state according to reference limits for serum 25(OH)D in healthy adults from the population (*e.g.*, blood donors) sampled throughout the year (85). However, this depends on climate, sunshine exposure, and clothing habits, leading to large differences between countries. A functional, health-based classification could be made using serum PTH. This is easy when serum PTH is increased to above the upper reference limit. However, the increases of serum PTH associated with vitamin D deficiency usually are within the normal reference ranges. In a study in Boston, the seasonal variation of serum PTH was no longer visible when serum 25(OH)D was higher than 90 nmol/liter, leading to the conclusion that serum 25(OH)D should be higher than this level to prevent secondary hyperparathyroidism (76). In a French population, serum PTH started to increase when serum 25(OH)D decreased below 78 nmol/liter, leading to a similar conclusion (10). However, in a large vitamin D study in Amsterdam, the negative relationship between serum PTH and serum 25(OH)D was only significant when serum 25(OH)D was lower than 30 nmol/liter (57, 105). Therefore, different data sets lead to different conclusions (Fig. 6). Of course, the differences may partly be due to differences in assays for 25(OH)D (28). Another modifying factor may be the dietary calcium intake. A relatively high calcium intake, as is usual in The Netherlands, may suppress serum PTH and influence the serum 25(OH)D level at which secondary hyperparathyroidism becomes manifest (179). Calcium nutrition by influencing serum PTH also influences the turnover of vitamin D metabolites. The half-life of serum 25(OH)D is shorter in hyperparathyroid states (87). In a vitamin D-deficient state, the synthesis of 1,25-$(OH)_2$D is substrate-dependent, *i.e.*, dependent on sufficient 25(OH)D, as shown by a positive correlation between serum 25(OH)D and serum 1,25-$(OH)_2$D (56, 58, 96). Treatment of women with postmenopausal osteoporosis with 25(OH)D showed a very significant increase of serum 1,25-$(OH)_2$D in those who responded with an increase of intestinal calcium absorption (185). After vitamin D supplementation in the elderly, 1,25-$(OH)_2$D may increase in parallel with serum 25(OH)D (58). In a study of elderly people in Amsterdam, serum 1,25-$(OH)_2$D increased only when serum 25(OH)D was lower than 30 nmol/liter (56).

Another parameter of mild vitamin D deficiency (or insufficiency) may be the decrease of serum PTH after vitamin D supplementation. When serum PTH decreases more than 15–20% after vitamin D supplementation, this may point to clinically relevant vitamin D deficiency, leading to bone loss and osteoporosis. In vitamin D supplementation studies, the decrease of serum PTH was 30% in severely vitamin D-deficient psychogeriatric patients (36), 15% in institutionalized elderly (56, 186), and negligible in vitamin D-replete elderly (77). When vitamin D and calcium supplementation are combined, serum PTH may decrease up to 50% (187). Vitamin D supplementation (50,000 IU/wk) with calcium (1,000 mg/d) in 35 elderly patients with a serum 25(OH)D between 25 and 62 nmol/liter decreased serum PTH by 22% (188). The decrease in serum PTH was significant when baseline serum 25(OH)D was lower than 50 nmol/liter. This is about the serum 25(OH)D level below which serum PTH started to rise in the large study of hospital inpatients (40). Similar conclusions can be drawn from the results in the placebo group of the multicenter raloxifene study consisting of 2,529 women treated with vitamin D (400–600 IU/d) and calcium (500 mg/d). In this study, serum PTH decreased by 12% when baseline serum 25(OH)D was lower than 50 nmol/liter (189).

It may be concluded that it is difficult to delineate sharp diagnostic criteria for mild vitamin D deficiency or insufficiency. When the required serum 25(OH)D level is set too high, it will result in a clinically irrelevant diagnosis and unnecessary supplementation. When the required serum 25(OH)D level is set too low, unnecessary bone loss will occur in many patients. A proposal for staging is presented in Table 3. A serum 25(OH)D lower than 50 nmol/liter might be called "mild vitamin D deficiency" or "insufficiency." This is associated with a slightly elevated serum PTH concentration and a mild increase of bone turnover. When serum 25(OH)D is lower than 25 nmol/liter, "moderate" vitamin D deficiency is diagnosed. Serum PTH is moderately increased (up to 30%) and high bone turnover is observed. Severe vitamin D deficiency occurs when serum 25(OH)D is lower than 12.5 nmol/liter. In these cases, serum PTH may be increased 30% or more, and a mineralization defect may occur, ultimately leading to frank osteomalacia.

TABLE 3. Proposal for staging of vitamin D deficiency

Stages	Serum 25(OH)D		Serum PTH increase	Bone histology
	nmol/liter	ng/ml		
Mild vitamin D deficiency (or insufficiency)	25–50	10–20	15%	Normal or high turnover
Moderate vitamin D deficiency	12.5–25	5–10	15–30%	High turnover
Severe vitamin D deficiency	<12.5	<5	>30%	Mineralization defect Incipient or overt osteomalacia

VI. Prevention and Treatment

Vitamin D deficiency can be treated by sunshine or UV irradiation, increase of dietary vitamin D intake, oral supplements, or injection. Again, comparison of results is hampered by interlaboratory differences in assays for 25(OH)D (27, 28). Results may be judged by considering the increase of serum 25(OH)D, the decrease of serum PTH, decrease of markers of bone turnover, increase in BMD, and decrease of fracture incidence. Since the half-life of 25(OH)D in the circulation is quite long (190), results of treatment may only be assessed after 3 to 6 months or more when a plateau is reached (56). When the outcome is fracture incidence, treatment results can only be assessed after 2 yr or more.

A. Sunshine and UV irradiation

Irradiation with UV light was used in a study in a nursing home to increase vitamin D status. For this purpose, UV fluorescent lighting tubes were suspended from the ceiling at 3 meter height in the day wards. The patients received irradiation for 3 h/d, resulting in an increase of serum 25(OH)D of 25 nmol/liter in 8 wk (191). More recently, a randomized controlled study was done in a psychogeriatric nursing home in The Netherlands. The patients received UV irradiation with half of the minimal erythematous dose on 1,000 cm^2 of the back three times per week, oral vitamin D_3 400 IU/d, or served as controls. Serum 25(OH)D increased from around 20 nmol/liter to 60 nmol/liter in both the UV group and the group that received oral vitamin D_3, while there was no change in the control group (Fig. 10). Serum PTH decreased about 30% in both treated groups (36).

B. Oral vitamin D supplementation

1. Effect on serum 25(OH)D and 1,25-$(OH)_2$D. Most studies have been done with vitamin D_3, but some have used vitamin D_2. Outcome parameters in these studies are the increase of serum 25(OH)D, decrease of serum PTH, decrease of bone resorption parameters, and change of bone mass or density. The effect of vitamin D supplementation was studied in 70 people living in a home for the elderly and 72 persons living in a nursing home in The Netherlands. The subjects were randomized in a control group, and groups taking vitamin D_3 (400 IU/d or 800 IU/d). Mean serum 25(OH)D increased from 24 nmol/liter to 60 or 70 nmol/liter, respectively, after 3 months (56). It increased to more than 40 nmol/liter in all supplemented subjects, and nonresponders were not observed. After 3 months treatment, the increase leveled off to a plateau at about 1 yr. The difference between 400 and 800 IU/d was rather small, indicating that the therapeutic margin is rather wide. The increase in serum 25(OH)D also depends on baseline serum 25(OH)D. In a recent multicenter study on the effect of raloxifene, a vitamin D supplement of 400–600 IU/d resulted in an increase of serum 25(OH)D in the placebo group from 70.8 ± 29.8 to 92.3 ± 28.6 nmol/liter. While the mean increase was 21.5 nmol/liter, it was 58.4 nmol/liter when baseline serum 25(OH)D was lower than 25 nmol/liter, and it was 39.4 and 13.5 nmol/liter with baseline serum 25(OH)D from 25–50 nmol/liter or higher than 50 nmol/liter, respectively (189).

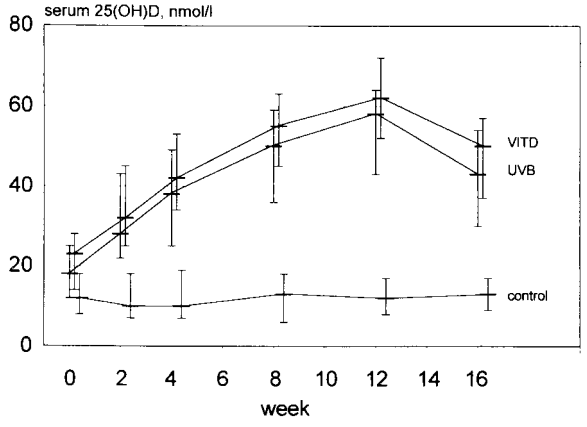

FIG. 10. Response of serum 25(OH)D to UV irradiation (UVB, half of the minimal erythematous dose, 3 times per week) on 1,000 cm^2 of the back of elderly women with vitamin D deficiency in comparison with the response to oral vitamin D_3 400 IU/d (vit D) and a control group (control). The study included 45 psycho-geriatric patients randomized in three groups. Data are expressed as median, 25th-75th percentile. [Reproduced from V. G. M. Chel *et al.* : *J Bone Miner Res* 13:1238–1242, 1998 (36) with permission of the American Society for Bone and Mineral Research.]

Vitamin D is stored in fat and slowly released, and the half-life of serum 25(OH)D is 3 wk. Therefore, vitamin D can also be given once per month or per 6 months or possibly once per year. A dose of 100,000 IU per 6 months increased serum 25(OH)D to adequate levels for many months (192).

An increase of serum 1,25-$(OH)_2$D has been observed after vitamin D supplementation in several studies (56, 58), while serum 1,25-$(OH)_2$D did not change in other studies (77). The increase of serum 1,25-$(OH)_2$D was related to baseline serum 25(OH)D, *i.e.*, serum 1,25-$(OH)_2$D only increased when baseline serum 25(OH)D was lower than 30 nmol/liter (56). It was not observed with relatively higher serum levels of 25(OH)D (56, 77). This is in agreement with the hypothesis of low serum 1,25-$(OH)_2$D in a vitamin D-deficient state due to substrate deficiency. When substrate [vitamin D_3 or 25(OH)D] is offered, serum 1,25-$(OH)_2$D can increase to the appropriate level.

2. Effect on parathyroid function. In vitamin D-deficient elderly subjects, serum PTH usually decreases after vitamin D supplementation. In the above mentioned study in a home for the elderly and nursing home, serum PTH decreased 15% (56). In another study in a nursing home, serum PTH did not decrease after vitamin D supplementation (77). In the latter study, however, baseline mean serum 25(OH)D was more than 40 nmol/liter, indicating a vitamin D-replete state in most patients. Decreases of serum PTH between 10 and 20% were also observed in other studies in elderly people in the United States, where serum 25(OH)D was higher than in European elderly subjects (102, 193). On the other hand, greater decreases of serum PTH were observed when baseline serum 25(OH)D was lower. In psycho-geriatric patients with a baseline serum 25(OH)D of 20 nmol/liter, serum PTH fell about 30% after vitamin D supplementation or UV irradiation (36). These observations indicate that the decrease of serum PTH after vitamin D supplementation depends on the degree of vitamin D deficiency. In the above mentioned

multicenter raloxifene study, 2,529 women in the placebo group received a vitamin D supplement of 400–600 IU/d and calcium 500 mg/d. The decrease of serum PTH was 18%, 12%, or 4% depending on baseline 25(OH)D lower than 25 nmol/liter, 25–50 nmol/liter, or higher than 50 nmol/liter, respectively (189). The combined administration of vitamin D_3 (800 IU/d) and calcium (1,200 mg/d) in French nursing home residents decreased serum PTH even more to about 45% lower than baseline values (187). This great decrease points to marked secondary hyperparathyroidism, which is probably caused by severe vitamin D deficiency in combination with a low calcium diet (194). A similar decrease of serum PTH of 50% was observed in 72 elderly women with vitamin D deficiency after supplementation with vitamin D_3 (800 IU/d) and calcium (1,000 mg/d) (195).

3. Effect on bone turnover. The decrease of parathyroid function caused by vitamin D supplements is followed by a decrease of bone turnover. A vitamin D_3 supplement of 400 IU/d led to a small decrease of serum osteocalcin in 330 elderly women in Amsterdam (186). The combination of vitamin D_3 and calcium may have a greater suppressing effect on bone turnover. A 6 weeks course of vitamin D_3 (1,000 IU/d) and calcium (1,500 mg/d) was followed by a 50% decrease of urinary *N*-telopeptide, a 20% decrease of serum osteocalcin, and a 10% decrease of bone alkaline phosphatase (196). Similar results, *i.e.*, a decrease in urinary C cross-linked telopeptide of 40% and 50%, was obtained after 3 and 6 months of therapy with vitamin D_3 (800 IU/d) and calcium (1,000 mg/d) in elderly women (mean age 83 yr) (197).

4. Effect on BMD. Vitamin D supplementation may increase BMD in several regions of the skeleton. A supplement of 800 IU increased BMD of the lumbar spine during winter months in postmenopausal women in comparison with the control group (102). In a later study from the same center, vitamin D (100 IU/d and 700 IU/d) were compared in a double-blind trial in postmenopausal women. The group receiving the higher vitamin D dose experienced less bone loss from the femoral neck than the group on the lower dose (−1.0% *vs.* −2.5%, $p<0.01$) (198). In the Amsterdam Vitamin D study, vitamin D_3 (400 IU/d) increased BMD of the femoral neck by 1.9% after 1 yr and 2.2% after 2 yr ($P < 0.01$), whereas BMD of the trochanter did not change significantly (Fig. 11) (186). This suggests a greater effect on cortical than on trabecular bone. The combined effect of vitamin D_3 (800 IU/d) and calcium (1200 mg/d) in the Qualyos study in French nursing home residents increased BMD of the total hip by more than 6% (187). In California, 12 elderly subjects with vitamin D deficiency (serum 25(OH)D < 35 nmol/liter) were supplemented with vitamin D_2 (50,000 IU) twice weekly and calcium carbonate (1,000 mg/d) for 5 weeks (199). Serum PTH decreased 50%, and BMD showed significant increases in the lumbar spine (4.1%) and femoral neck (4.9%). In a recent study in Indiana, 316 elderly women and 122 elderly men were randomized to 25(OH)D (15 μg/d) or calcium (750 mg/d), or placebo (200). Calcium prevented bone loss at the hip and femoral endosteal bone loss. The effect of 25(OH)D on bone loss was intermediate between that of calcium and placebo. In this study, baseline median serum 25(OH)D was 59 nmol/liter, a relatively high value. This study confirms that the effect of vitamin D treatment is small when vitamin D status is adequate.

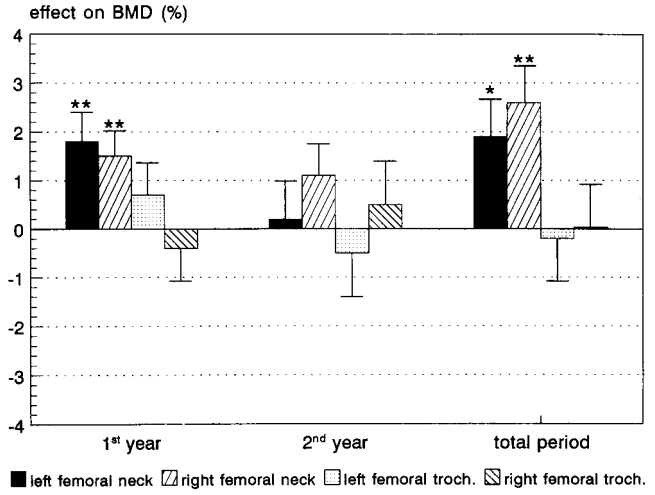

FIG. 11. Effect of vitamin D_3 400 IU/d in residents of apartment houses or homes for the elderly on bone loss in the femoral neck and trochanter. The difference in mean change (%) between the vitamin D and the placebo group is shown in the first year, second year, and total period. The SE is indicated by *error bars*. * $P < 0.05$; ** $P < 0.01$. [Reproduced with permission from M. E. Ooms *et al.*: *J Clin Endocrinol Metab* 80:1052–1058, 1995 (186). © The Endocrine Society.]

The increase of BMD may be explained by mineralization of excess osteoid in cases with more severe vitamin D deficiency and by decreasing parathyroid function and bone turnover. The decrease of bone turnover results in filling up of remodeling space and improving secondary mineralization by which the proportion of bone with high mineral content increases in comparison with bone with low mineral content (23, 132). The decrease of bone turnover will also decrease bone loss in the long term. According to these mechanisms, the increase in BMD will occur for the greater part in first year of vitamin D therapy. Indeed, the increase in BMD in the femoral neck in the Amsterdam vitamin D study was 1.9% in the first year and 0.3% in the second year (186). The increase of BMD after vitamin D supplements in vitamin D-deficient elderly may depend on genetic characteristics of the VDR (201). The VDR polymorphisms BB and Bb were associated with a 3% gain of BMD in the femoral neck after vitamin D supplementation in comparison with no change in the bb genotype (202).

5. Effect on muscle strength. As proximal muscle weakness is a symptom of osteomalacia, vitamin D supplementation may increase muscle strength and thereby decrease the incidence of falls. A randomized double-blind trial was done in 65 geriatric patients in the United Kingdom (mean age 82 yr) who were vitamin D deficient. Half of the patients received vitamin D_2 9,000 IU/day, increasing serum 25(OH)D from 17 to 150 nmol/liter, while no change occurred in the placebo group. There were no differences in muscle strength score or activities of daily living score between both groups (203). A randomized trial with vitamin D_2 in 32 geriatric patients with vitamin D deficiency (serum 25(OH)D < 37.5 nmol/liter)

showed a slight functional improvement assessed by the Frail Elderly Functional Assessment (FEFA) questionnaire (204).

A prospective study on risk factors for falls was done as a substudy to the Amsterdam Vitamin D Study. This substudy was done in 354 elderly living in homes or apartment houses for elderly people. Half of these elderly had been randomized to vitamin D_3 400 IU/d, while the other half was taking placebo. During the follow-up of 6 months, 251 falls were reported by 126 participants with no detectable difference between the elderly taking vitamin D and those taking placebo (145). Preliminary results from a German randomized study showed improved balance (decreased body sway) in healthy elderly women after vitamin D_3 treatment (205). One may conclude that some studies suggest some improvement of muscle function, but data are conflicting.

6. Effect on fracture risk. Intervention studies on the effect of vitamin D with hip fracture or other fractures as outcome need high numbers of study subjects and/or long follow-up to accumulate sufficient power (206). The incidence of hip fractures in 80-yr-old women is around 1% per year (207). Several intervention studies have been done, and these are summarized in Table 4.

The study of Heikinheimo *et al.* (208) included independently living elderly and residents of a home for the elderly, and these were randomized by month of birth to receive annually 150,000–300,000 IU of vitamin D_2 per injection or to serve as controls. After a follow-up during 2–5 yr, the investigators observed significantly less upper-limb fractures in the vitamin D group than in the control group, but there was no difference in hip fracture incidence between both groups.

A double-blind study with vitamin D_3, 800 IU/d, and calcium, 1,200 mg/d, or double placebo (Qualyos study) was done in 3,270 French female nursing home residents (187). This study resulted in a significant decrease of hip fractures and other nonvertebral fractures after 1½ years of treatment (Fig. 12). In the Amsterdam Vitamin D study, 2578 elderly, living independently or in apartment houses and homes for the elderly, were treated with vitamin D_3, 400 IU/d, or placebo (42). Serum PTH decreased 15% and BMD of the femoral neck increased 2.2% in comparison to the control group (186). However, there was no decrease in the incidence of hip and other nonvertebral fractures during follow-up of 4 yr (42).

The French and Dutch studies showed important differences. The people in the French study were 4 yr older than the Dutch (mean age 84 *vs.* 80 yr). The French subjects were nursing home residents and had a much lower calcium intake than the participants in the Dutch study (500 mg/d *vs.* 1,000 mg/d). The vitamin D and calcium treatment in the French study resulted in a considerable decrease of serum PTH (−45%) and increase of BMD of the total hip (+6%), whereas the PTH decrease (−15%) and BMD increase (+2.2%) in the Dutch study were moderate. The outcome of these intermediary parameters may explain the different fracture outcomes of both studies (194). The French elderly had a higher serum 25(OH)D than the Dutch. However, after careful cross-calibration of the assays by measuring 104 serum samples in both centers, it turned out that the French elderly were more vitamin D deficient than the Dutch (mean serum 25(OH)D 18 *vs.* 26 nmol/liter) (28).

The last study was done in 389 independently living elderly in the United States (193). They received either vitamin D_3 ,700 IU/d, and calcium, 500 mg/d, or double placebo. The treatment resulted in a significant decrease of the total number of nonvertebral fractures after 3 yr. A puzzling issue is that the serum 25(OH)D concentration was normal in most participants and that the decrease of serum PTH and increase

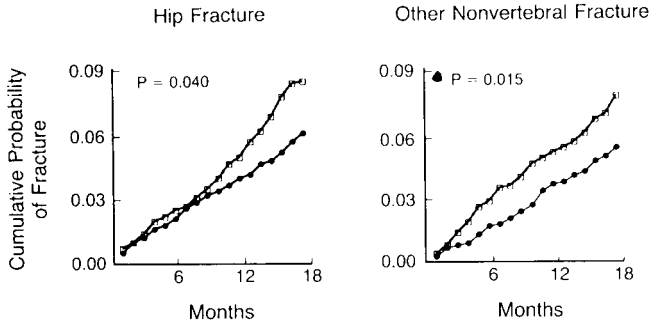

FIG. 12. Effect of vitamin D_3, 800 IU/d, and calcium, 1,200 mg/d, *vs.* double placebo on the incidence of hip fractures and other nonvertebral fractures in 3,270 French nursing home residents. The effect is presented as cumulative probability of fracture in the placebo group (□) and the group treated with vitamin D_3 and calcium (●), estimated by the life-table method and based on the length of time to the first fracture. The decrease was significant after 1.5 yr. [Reproduced with permission from M. C. Chapuy *et al.*: *N Engl J Med* 327:1637–1642, 1992 (187). © 1992 Massachusetts Medical Society. All rights reserved.]

TABLE 4. Clinical trials with vitamin D supplements (± calcium supplement) in elderly people with fracture as outcome

Ref.	Study type	n	Age m ± SD	Calcium intake (mg/d)	Supplement		25(OH)D (nmol/liter)		PTH decrease	BMD hip increase	Hip fractures (n)		Other fractures	
					Vitamin D (IU)	Ca (mg/d)	Baseline	Post			Treatment	Control	Treatment	Control
208		799	83		150,000–300,000/yr		13.6	44.8			25	43	10[a]	28
187	db	3270	84 ± 6	514	800 IU/d	1200 mg/d	40	100	45%	6%	80[b]	110	80[a]	105
42[c]	db	2578	80 ± 6	>1000[d]	400 IU/d		27	62[e]	15%	2.2%	58	48	77	74
193	db	389	71 ± 4	735	700 IU/d	500 mg/d	75	110	16%	1.2%	0	1	11[a]	26

db, Double-blind.
[a] $P < 0.05$ treatment *vs.* control.
[b] $P < 0.005$ treatment *vs.* control.
[c] Biochemical and bone density data in Ooms *et al*. 1995 (186).
[d] 868 mg/day from dairy products only.
[e] In random sample serum during third year of follow-up 25(OH)D 54 nmol/liter.

of BMD of the hip were very modest. This suggests that other unknown factors may play a role in the decrease of the fracture incidence. The 25(OH)D assay of the latter study was also cross-calibrated (28), but this did not result in important corrections. While vitamin D deficiency is less common in the United States than in Europe, the positive results of this study suggest that elderly in the United States may be vitamin D and/or calcium deficient and that this contributes to fractures.

One may conclude that the different outcomes in fracture incidence can be partly attributed to differences in baseline vitamin D status, calcium intake, serum PTH decrease, and increase in BMD of the hip. The vitamin D_3 dose might be important. However, the follow-up serum 25(OH)D was very similar in the French and the Dutch study [after cross-calibration serum 25(OH)D 55 *vs.* 62 nmol/liter]. The most important difference may be the addition of a calcium supplement. This may be confirmed by investigation of the PTH and BMD responses to either vitamin D_3 or calcium alone or to a combination of both. The efficacy of calcium in comparison to vitamin D supplementation is also suggested by a recent study from Indiana (200). The question remains whether the effect of treatment with vitamin D and calcium is mainly restricted to the first and second year or is sustained thereafter. The decrease of the incidence of hip fractures and other nonvertebral fractures in French nursing home residents (Qualyos study) was significant after 18 months (187). The study was continued up until 36 months, but the gain after 18 months was small. After 18 months, 114 hip fractures had occurred in women treated with vitamin D and calcium and 158 in the placebo group. After 36 months, 138 hip fractures had occurred in the vitamin D and calcium group, and 184 hip fractures had occurred in the placebo group, an increase from 18 to 36 months of 24 and 26 hip fractures, respectively (187, 209). Similar calculations can be made for all nonvertebral fractures. The number of nonvertebral fractures between 18 and 36 months was 71 in the group treated with vitamin D and calcium and 61 in the placebo group. Although the overall results over 36 months showed a significant decrease of hip fractures and all nonvertebral fractures ($p < 0.02$), the results from 18–36 months showed very similar fracture numbers in both groups. This implicates that the decrease of fracture incidence occurs within the first year or 1.5 yr, due to the increase of mineralization and reduction of bone turnover. The decrease thereafter is absent or small. However, it is probable that discontinuation of calcium and vitamin D treatment will increase the fracture incidence again. A meta-analysis on the treatment with vitamin D for prevention of osteoporotic fractures concludes that the effectiveness of vitamin D alone is uncertain (210). As mentioned before, an analysis of the MEDOS study suggested that vitamin D may prevent hip fractures in frail elderly, *i.e.*, women above 80 yr with low BMI (140).

C. Side effects and risks

The usually recommended doses of vitamin D_3 are 400 or 800 IU/d. These doses are safe, and side effects are virtually nonexistent. The tolerance is quite high because the conversion into 1,25-$(OH)_2D_3$ is under tight feed-back control. Higher doses seldom are necessary, but 100,000 to 300,000 IU by mouth or per injection have been used once every 6 months or once yearly because of the ease of administration, obviating the need of checking compliance (192, 211, 212). In these studies, hypercalcemia was not observed. However, hypercalcemia has been observed in an older patient with a dose of 2000 IU/d (213) and in one patient receiving a single oral dose of 600,000 IU (214). Although practical, high doses may not be as safe as low doses. In addition, deep intramuscular injections carry some bleeding risk especially in combination with coumarin or acetylsalicylic acid therapy.

Vitamin D supplementation with 400 to 800 IU/d does not influence renal function or serum cholesterol concentration, and hypercalcemia has not been reported (56). High doses when given daily or weekly may cause vitamin D intoxication leading to bone resorption, bone loss, hypercalcemia, hypercalciuria, and renal functional impairment. However, graded oral dosing of vitamin D_3 up to 50,000 IU/d for 8 weeks did not cause hypercalcemia (215). The occurrence of vitamin D intoxication is rather unpredictable, and it may occur even after years. Vitamin D intoxication may also result from over-the-counter dietary supplements which may contain several thousands of units vitamin D per daily dose (216). In vitamin D intoxication, the offending metabolite probably is 25(OH)D, which may bind to the VDR (217, 218). Alternatively, the serum 1,25-$(OH)_2D$ concentration may be increased, causing increased bone resorption that can be blocked by bisphosphonate infusion (219). The free serum 1,25-$(OH)_2D$ may also be increased because the high quantity of 25(OH)D may displace 1,25-$(OH)_2D$ from the vitamin D binding protein, thereby increasing its free concentration (220).

Another rare problem is an increased conversion of 25(OH)D to 1,25-$(OH)_2D$, which may occur in granulomatous diseases such as sarcoidosis, tuberculosis, or malignant lymphoma (221). Vitamin D supplementation might cause an increase of serum 1,25-$(OH)_2D$ and hypercalcemia in these cases.

VII. Public Health Aspects

A. Recommended dietary allowance and adequate intake

The recommended dietary allowance (RDA) is the daily dietary intake sufficient to meet the requirement of 98% of individuals. As most vitamin D in adults originates from cutaneous synthesis under the influence of sunshine, an RDA cannot be determined accurately. Currently, the RDA for vitamin D in the United States has been changed into adequate intake. The RDA for vitamin D in the elderly was 200 IU/d in the United States, and 100 IU/d in other countries such as the United Kingdom and The Netherlands. Recently, adequate intake was defined in the United States to be 200 IU/d in adults until age 50 yr, 400 IU/d in adults from 51 to 70 yr, and 600 IU/d in the elderly over 70 yr based on recent data on vitamin D status in these age groups (222). Similarly, the recommended intake in The Netherlands was increased to 400 IU/d for people 65–75 yr with insufficient exposure to sunshine and for all elderly over 75 yr irrespective of sunshine exposure (223). The European Community has redefined the RDA for vitamin D for

adults from 18–64 yr as 0 to 400 IU/d. The upper end is the recommendation for housebound people, whereas the lower end applies to active people who are able to produce adequate vitamin D in the skin. The RDA for elderly (65 yr and older) is 400 IU/d (224).

When adequate intake is 400 to 600 IU/d, one must consider that these intakes cannot be realized with a usual diet unless it contains fatty fish such as herring or mackerel or fortified products such as vitamin D milk containing 400 IU/liter or quart. In many European countries only margarine is fortified with vitamin D_3 containing 3 IU/g, which is insufficient. This means that most elderly people should either have sufficient exposure to sunshine or rely on vitamin D supplements. Whereas the consumption of a multivitamin tablet may be common in some countries such as the United States, it is not in other regions including most European countries.

B. Risk groups

Public health measures should be directed at persons and groups who accumulate risk factors. Elderly people who are immobile and do not go outdoors will receive insufficient sunshine exposure (37). The same applies to elderly with skin cancer or other skin conditions that cause them to avoid sunshine exposure. Elderly people who underwent gastrectomy or have lactose intolerance will rarely consume dairy products, so that calcium and vitamin D intake are low in these groups (176). These risk factors accumulate in geriatric patients and residents of homes for the elderly and nursing homes. Vitamin D supplementation should be first considered for this group. Immobility may be the strongest risk factor for vitamin D deficiency (41). Vitamin D supplementation should be considered for all immobile elderly.

A low calcium intake causes secondary hyperparathyroidism which increases vitamin D turnover and aggravates vitamin D deficiency (87). This means that calcium supplements should be added when calcium intake is low.

There are striking differences in vitamin D status between countries, and vitamin D status in the elderly is better in the United States than in Europe. Within Europe, vitamin D deficiency is as common in southern as in northern and western European countries (10, 45, 62). Vitamin D deficiency also is common in the Middle-East, which is due to clothing habits (69). On a global scale, more attention should be focused on Southern Europe, the Middle-East, and North Africa (183), although data from these regions are scarce.

C. Prevention strategies

Vitamin D supplementation is an effective way of preventing vitamin D deficiency. Supplementation with a daily dose of 400–800 IU is very effective but may be impractical (56, 187). Independent elderly may take a supplement themselves, but the institutionalized often depend on a distribution system. Distribution of medication in a home for the elderly or nursing home involves between one to six or more different tablets per person, and one more may be a problem. Supplementation once per week or once per month is easier, and some investigators have relied on supplementation once per year either orally (192, 211, 212, 214) or by vitamin D injection (208). Injections carry some risk as many elderly take an anticoagulant such as coumarin or acetylsalicylic acid, which may cause bleeding. An oral supplement once per month may be a practical and safe compromise.

Nutritional supplements may also be considered. Daily consumption of fatty fish (a herring contains 600 IU/d) is impractical. Fortification of milk may be a useful alternative. A controlled study of fortified milk (vitamin D_3, 400 IU/liter) was done in housebound and institutionalized elderly subjects in Ireland (225). Serum 25(OH)D rose from 6 nmol/liter to 37 nmol/liter in elderly subjects who consumed fortified milk, whereas it changed from 8 to 18 nmol/liter in the regular milk group. Vitamin D_3-fortified milk prevented the wintertime decline of serum 25(OH)D in Irish adults (226) and was effective in Irish community-dwelling elderly subjects (227). Fortification of milk with vitamin D_3 is widely practiced in the United States (400 IU/quart) (8), infrequent in Europe (224) but is also done in Beijing, China (228). Consumption of milk fortified with vitamin D_3 (400 IU/quart or 400 IU/liter) should be widely recommended. The vitamin D content of milk may vary (229), and constant supervision is necessary to prevent vitamin D intoxication (218). The dietary intake of calcium and proteins is often low in the elderly, and these nutrients also are abundant in milk (230). However, while milk fortified with vitamin D_3 is widely available in the United States, it cannot be purchased in many European countries. Milk and other foods supplemented with vitamin D_3 should be made available everywhere.

D. Cost-effectiveness

Cost-effectiveness of prevention of fractures in the elderly depends on the effectiveness of therapy, costs of administering the therapy, and the risk of (hip) fracture, which varies with age and sex. The cost-effectiveness of vitamin D by subcutaneous injection and of oral vitamin D and calcium has been studied in detail (231). The costs per averted hip fracture in community-dwelling elderly was £2,317 for parenteral vitamin D and £22,379 for oral vitamin D and calcium. When the treatment was targeted at a high-risk group (frail elderly with BMI < 20 kg/m^2, RR 1.8) the cost per averted hip

TABLE 5. Cost-effectiveness of prevention of hip fractures with either oral vitamin D and calcium or parenteral vitamin D

	Gross cost per averted hip fracture		Net cost per averted hip fracture	
	Oral vitamin D + calcium	Parenteral vitamin D	Oral vitamin D + calcium	Parenteral vitamin D
Independent elderly	22,379	2,317	17,379	−2,683
Independent elderly (low BMI)	6,800	524	1,800	−4,476
Nursing home residents	9,735	323	4,735	−4,677
Nursing home residents (low BMI)	2,779	219	−2,221	−4,781

All costs are in pound sterling (£). Net costs are obtained by deducting the cost of a hip fracture (£ 5,000). Data were taken from Torgerson and Kanis (231). A negative number indicates that the treatment is cost-effective (cost saving).

fracture decreased to £524 for parenteral vitamin D and £6,800 for oral vitamin D and calcium. With a similar high-risk population in a nursing home, the costs further decreased to £219 and £2,779, respectively (Table 5). When the hospital treatment of hip fractures was taken into account, parenteral vitamin D was cost-effective in all groups, whereas oral vitamin D with calcium was cost-effective in nursing home residents with low BMI only. The distribution costs of the oral medication in the nursing home were not taken into account. To be cost-effective, parenteral vitamin D should reduce the cumulative incidence of hip fracture over 4 yr from 6.9 to 6.2%. These calculations, however, are based on the assumption that parenteral vitamin D can prevent hip fracture. This is uncertain, as only one randomized study showed a moderate decrease of upper limb fractures after parenteral vitamin D (208). The data on oral vitamin D and calcium are more solid as they are based on the largest double-blind prevention study with vitamin D and calcium (187). A comparative study showed that vitamin D and calcium treatment is more cost-effective in the prevention of hip fractures than hormone replacement therapy, thiazide diuretics, alendronate, and calcitonin (232).

In conclusion, these data show that treatment with vitamin D without or with calcium for preventing fractures may be cost-effective. They also show that the cost-effectiveness increases when the treatment is targeted at a high-risk group such as nursing home residents.

VIII. Future Prospects

Vitamin D deficiency is one of the risk factors for fractures in the elderly. Treatment with vitamin D (and calcium) may modestly decrease the incidence of hip and other nonvertebral fractures. To diagnose vitamin D deficiency more accurately, the assays for 25(OH)D should be better standardized. Diagnostic criteria for vitamin D deficiency and secondary hyperparathyroidism should be better defined. Regarding prevention, population-based measures include the fortification of milk and other foods. Risk groups such as nursing home residents should be defined, *e.g.*, all institutionalized elderly or all elderly above a certain age (*e.g.*, 80 yr). The effect of a calcium supplement in addition to vitamin D should be studied in more detail; the effects of different combinations on parathyroid function and markers of bone turnover could predict the effects on fracture incidence. A subject of interest is the influence of vitamin D deficiency outside the skeleton, *e.g.*, on muscle strength, the immune response, and cancer. In the near future, strategies for diagnosis and prevention of vitamin D deficiency in the elderly should be further developed.

IX. Conclusion

There is overwhelming evidence that moderate vitamin D deficiency and secondary hyperparathyroidism are common in the elderly, not only in traditional risk groups such as housebound and institutionalized elderly and patients with hip fracture, but also in independent elderly or postmenopausal women in Southern Europe and the Middle East. The high bone turnover due to secondary hyperparathyroidism is accompanied by about 5% (up to 10%) lower bone mass, which is partly reversible (low mineral bone, increased remodeling space) and partly irreversible (cortical thinning). The high turnover may contribute to the pathogenesis of hip fractures and other fractures. Whether moderate vitamin D deficiency decreases muscle strength is less clear. Vitamin D therapy improves vitamin D status, corrects secondary hyperparathyroidism, decreases bone turnover, and increases BMD. The combination of vitamin D and calcium causes a greater decrease of parathyroid function and bone turnover, induces a higher BMD gain, and decreases the incidence of hip fractures and other nonvertebral fractures in a high-risk population.

For prevention, attention should be focused on risk groups, *e.g.*, the institutionalized and some geographical regions, *e.g.*, countries in Southern Europe and the Middle East. Public health measures should include fortification of foods such as milk with vitamin D_3, vitamin D_3 supplementation to high-risk groups, and calcium supplementation when calcium intake is low.

Future studies should investigate the role of moderate vitamin D deficiency in causing falls. The effect of vitamin D and calcium supplementation in preventing fractures should be confirmed by other studies.

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Address all correspondence and requests for reprints to: Paul Lips, M.D., Ph.D., Afdeling Endocrinologie, Vrije Universiteit Medical Center, Postbus 7057, 1007 MB Amsterdam, The Netherlands. E-mail: p.lips@vumc.nl

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