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Vitamin D and the Elderly

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Summary and Introduction

Summary

This review summarizes current knowledge on vitamin D status in the elderly with special attention to definition and prevalence of vitamin D insufficiency and deficiency, relationships between vitamin D status and various diseases common in the elderly, and the effects of intervention with vitamin D or vitamin D and calcium. Individual vitamin D status is usually estimated by measuring plasma 25-hydroxyvitamin D (25OHD) levels. However, reference values from normal populations are not applicable for the definition of vitamin D insufficiency or deficiency. Instead vitamin D insufficiency is defined as the lowest threshold value for plasma 25OHD (around 50 nmol/l) that prevents secondary hyperparathyroidism, increased bone turnover, bone mineral loss, or seasonal variations in plasma PTH. Vitamin D deficiency is defined as values below 25 nmol/l. Using these definitions vitamin D deficiency is common among community-dwelling elderly in the developed countries at higher latitudes and very common among institutionalized elderly, geriatric patients and patients with hip fractures. Vitamin D deficiency is an established risk factor for osteoporosis, falls and fractures. Clinical trials have demonstrated that 800 IU (20 μg) per day of vitamin D in combination with 1200 mg calcium effectively reduces the risk of falls and fractures in institutionalized patients. Furthermore, 400 IU (10 μg) per day in combination with 1000 mg calcium or 100 000 IU orally every fourth month without calcium reduces fracture risk in individuals over 65 years of age living at home. Yearly injections of vitamin D seem to have no effect on fracture risk probably because of reduced bioavailability. Simulation studies suggest that fortification of food cannot provide sufficient vitamin D to the elderly without exceeding present conventional safety levels for children. A combination of fortification and individual supplementation is proposed. It is argued that all official programs should be evaluated scientifically. Epidemiological studies suggest that vitamin D insufficiency is related to a number of other disorders frequently observed among the elderly, such as breast, prostate and colon cancers, type 2 diabetes, and cardiovascular disorders including hypertension. However, apart from hypertension, causality has not been established through randomized intervention studies. It seems that 800 IU (20 μg) vitamin D per day in combination with calcium reduces systolic blood pressure in elderly women.

Introduction

Strictly speaking, vitamin D is not a vitamin because it is produced in adequate quantities in the skin depending on sufficient sun [ultraviolet B (UVB)] exposure and exposed skin surface.[1] The dermal production is regulated so that inactive metabolites (tachysterol and lumisterol) are produced at times of excess UVB exposure. Vitamin D_3 is, by itself, sensitive to irradiation and is thereby inactivated to suprasterol 1 and 2 and to 5,6-trans-vitamin D_3. Furthermore, vitamin D production depends on skin pigmentation,[2,3] both natural and caused by sunburn, the latter creating a type of negative feedback loop. Hence, vitamin D should probably be considered a hormone produced in the skin and

metabolized to more active compounds in peripheral tissue in the same way as thyroxine is converted to triiodothyronine in liver, kidney and other tissues. In the liver vitamin D is hydroxylated to 25-hydroxyvitamin D (25OHD),[4] which is further 1α-hydroxylated to 1,25(OH)$_2$D in the kidney. 5 Recent studies have disclosed that before the 1-hydroxylation, 25OHD and vitamin D-binding protein (DBP) are filtered in the kidney and reabsorbed in the proximal renal tubules by megalincubilin receptors.[6] The renal hydroxylation is closely regulated, being enhanced by PTH, hypocalcaemia and hypophosphataemia and inhibited by 1,25(OH)$_2$D itself.[4] 1,25(OH)$_7$D regulates gene transcription through a nuclear high-affinity vitamin D receptor (VDR)[8,9] and initiation of rapid cellular responses through a putative plasma membrane-associated receptor membrane.[10] The receptors are located in classical target organs such as the intestine, bone, kidney and parathyroid, as well as in many other tissues and cell types, 7 including the immune system.[11] Vitamin D is deposited in adipose tissue, but the depot is not large enough or sufficiently regulated to prevent seasonal variations in plasma concentrations of 25OHD and PTH (Fig. 1).[12,13]

When vitamin D levels are low, compensatory secondary hyperparathyroidism increases the renal conversion of 25OHD and thereby maintains normal or slightly increased plasma levels of 1,25(OH)$_2$D until the vitamin D deficiency is severe enough (frank osteomalacia) to reduce the level of this metabolite.[14] Low plasma 25OHD and secondary hyperparathyroidism are therefore the biochemical hallmarks for insufficient vitamin D status.[14,15] Furthermore, recent research has demonstrated that various normal human tissues and cell lines possess 25OHD-1β-hydroxylase activity and have the capacity to convert 25OHD directly to 1,25(OH)$_2$D to satisfy local needs in a paracrine way.[16-18] This production probably depends on the availability of circulating 25OHD, indicating the biological importance of sufficient plasma levels of this vitamin D metabolite.

Humans have a considerable ability to adapt to altered living conditions either through a slow genetic selection or faster through altered lifestyle, diet (including food fortification) or pharmacological intervention. The naked ape was probably, like the nonhuman primates, well adapted to its sun-rich tropical environment. 1 Following the exodus from Africa, the northern latitudes were inhabited by fair-skinned people with an increased ability to make use of the limited amount of UVB despite the need for clothing. By contrast, dark-skinned recent immigrants from Palestine, Pakistan and India to Northern Europe may develop severe vitamin D deficiency with proximal myopathy because of the limited effect of sunshine and a low dietary vitamin D intake.[19-20] This problem has triggered pharmacological substitution programs with limited effect.[21-22] By contrast, moderately pigmented Inuits during their migration towards the Polar regions through millenniums have adapted to a life with sparse solar exposure through a diet of fatty fish and blubber with a high content of animal vitamin D. Furthermore, they have genetically developed an enhanced renal conversion of 25OHD to 1,25(OH)$_2$D, improving the use of available vitamin D.[23] By contrast, Asian Indians have developed (or maintained) an increased renal 24,25(OH)$_2$D-hydroxylase activity facilitating the production of the inactive 24,25(OH)$_2$D at the expense of 1,25(OH)$_2$D.[24]

The elderly populations of Europe, the USA and Australia, however, present special problems.[15,25-27] With increasing age, solar exposure is usually limited because of changes in lifestyle factors such as clothing and outdoor activity. Diet may also become less varied, with a lower natural vitamin D content. Most importantly, however, the dermal production of vitamin D following a standard exposure to UVB light decreases with age because of atrophic skin changes with a reduced amount of its precursor.[2,28] Finally, the renal production of 1,25(OH)$_2$D decreases because of diminishing renal function with age.[29] These changes in vitamin D metabolism render the ageing population in general at risk of vitamin D deficiency, especially in winter seasons and when living indoor and at higher latitudes.[15] This deficiency may lead to severe consequences in terms of falls, osteoporosis and fractures.

In this review I describe vitamin D-related problems among the elderly, essentially focusing on the definition and prevalence of vitamin D deficiency and the effects of vitamin D on

risks of falling, osteoporosis and fractures. I have concentrated on randomized controlled studies demonstrating causality between vitamin D and outcome events. However, I have also included epidemiological studies on cancer risk and associations with other common diseases among the elderly, such as type 2 diabetes and cardiovascular disease. I have deliberately excluded the potential favorable influence of UVB radiation and vitamin D status or supplementation on the occurrence of other disorders such as pneumonia,[30] tuberculosis,[31] periodontal disease,[32] type 1 diabetes,[33-36] rheumatoid arthritis,[37] inflammatory bowel disorders[38-40] and multiple sclerosis,[41,42] as these disorders are not specific for the elderly.

For the present narrative review I have searched PubMed 1990-2004 and EMBASE 19902004 using the MESH terms 'calcifediol', 'calcitriol' and 'Vitamin D' in combination with 'osteoporosis', 'fractures', 'falls', 'cancer', 'diabetes', 'hypertension' and 'cardiovascular disease' to July 2004. I have screened all the abstracts and included those of interest. I have also screened reference lists of review papers covering the period 2000-04 for more papers of interest.

Assessment of Vitamin D Status

Individual vitamin D status is usually estimated by measuring plasma 25OHD levels. The biologically most active vitamin D metabolite, 1α,25(OH)$_2$D, is inapplicable to this purpose for several reasons: (a) plasma levels of 1α,25(OH)$_2$D, but not 25OHD, are maintained normal or even elevated in mild to moderate osteomalacia due to secondary hyperparathyroidism;[14,15] (b) plasma levels are more than 100 times higher for 25OHD than for 1α,25(OH)$_2$D; and (c) most peripheral tissues, including bone cells, have the capacity to convert circulating 25OHD to 1α,25(OH)$_2$D and thereby cover local needs.[16-18]

However, several problems are inevitably connected with the use of plasma 25OHD to assess vitamin D status. The first problem is whether we have to define vitamin D deficiency or insufficiency based on a reference range from a normal population or whether a predefined cut-off or threshold value should be used. The use of the lower reference value from a 'normal' population has several unmanageable consequences because plasma 25OHD depends on unchangeable ecological factors (season, local weather conditions and latitude), modifiable individual lifestyle factors (clothing, dietary habits, sunbathing habits, etc.), and unmodifiable individual factors (race, pigmentation, skin thickness and age). Figure 1 illustrates the seasonal variations in sun hours and baseline plasma levels of 25OHD and PTH in around 500 perimenopausal Danish women from the Danish Osteoporosis Prevention Study.[43] A zenith in plasma 25OHD is obvious in late summer around 1 to 2 months after the maximum solar radiation, with a nadir in late winter. Plasma PTH mirrors these changes with peak values in late winter due to secondary hyperparathyroidism and low values in late summer. This secondary hyperparathyroidism during winter is probably a risk factor for bone loss and later fractures.[15] Hence, normal reference values should be based at least on summer values. However, this consideration does not correct for the other reasons leading to low plasma 25OHD mentioned above.

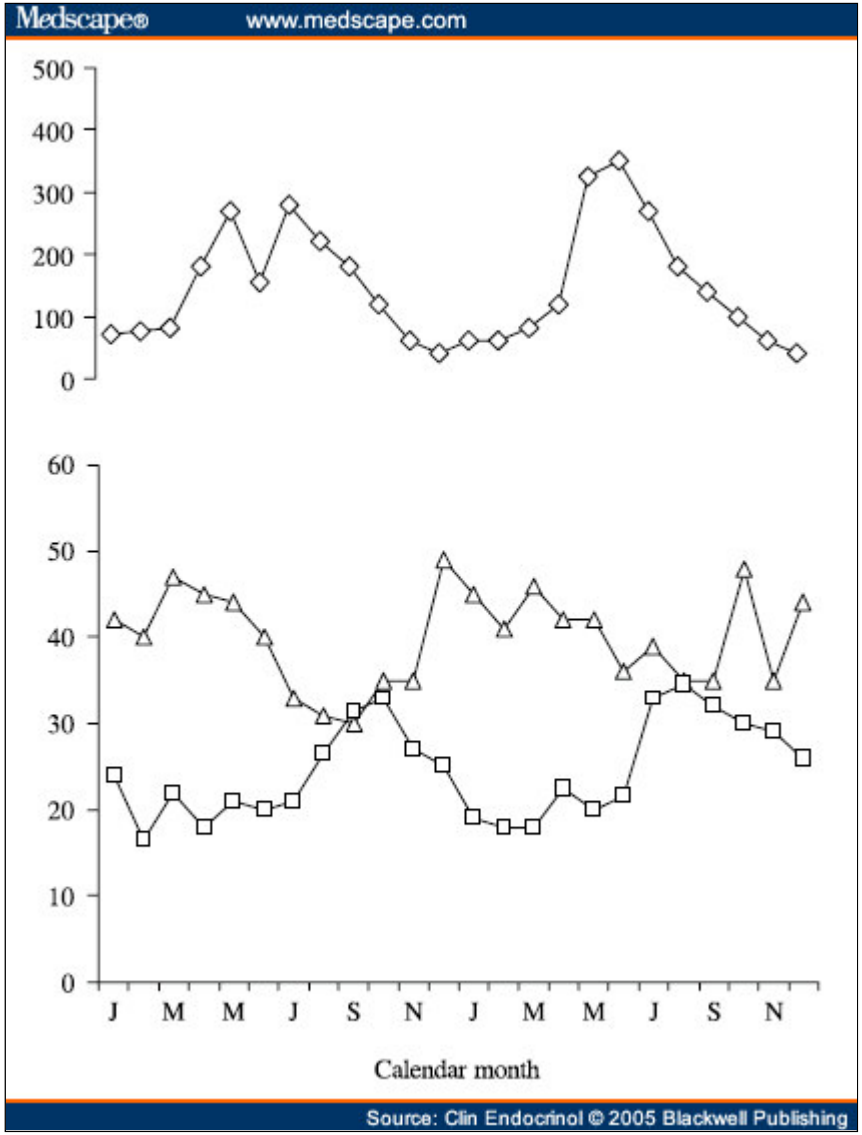
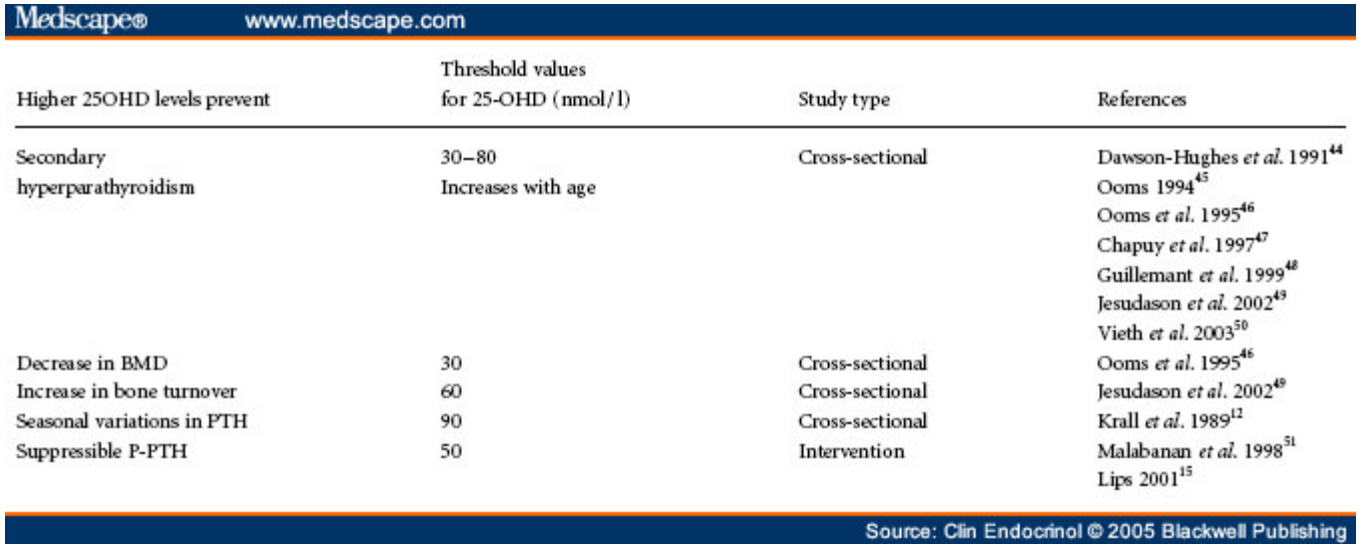


Figure 1. Variations in sun exposure (upper panel: sun hours per month ◇) over 2 years compared with (lower panel) variations in plasma 25OHD (nmol/lY) and plasma PTH (nmol/ l × 10-$^{-1}$1 △) in Danish perimenopausal women. Danish Osteoporosis Prevention Study.[43]

Vitamin D deficiency was defined previously by the occurrence of frank osteomalacia, or rickets, with obvious clinical symptoms. However, at present, the risk of secondary hyperparathyroidism creates the basis for the term vitamin D insufficiency, as this mainly asymptomatic condition enhances the risk of osteoporosis and skeletal fractures. If plasma PTH in the same population is depicted as a function of plasma 25OHD (Fig. 2), it is obvious that elevated PTH occurs with increasing frequency as the plasma 25OHD

falls with a threshold level of around 50 nmol/l. Several cross-sectional studies have been performed to establish this threshold in different populations based on an increased risk of secondary hyperparathyroidism, high bone turnover or low bone mineral density (BMD)[44-50] (Table 1). Studies have also established the lowest plasma 25OHD that ensures that plasma PTH will not be further reduced following a vitamin D and calcium challenge,[51] or that seasonal variations in plasma PTH are abolished[12] (Table 1). Generally, the adverse effects of low plasma 25OHD begin to accumulate at levels below 50 nmol/l, although some studies have suggested higher threshold levels. Based on these findings, Lips[15] has suggested that 25OHD levels between 50 and 25 nmol/l constitute vitamin D insufficiency, whereas levels below 25 nmol/l indicate regular vitamin D deficiency. Levels between 25 and 12 nmol/l may cause proximal myopathy[52] or increased bone turnover estimated by histomorphometry, whereas levels below 10-12 nmol/l are typical findings in frank osteomalacia.[14]

Table 1. Threshold Values for Vitamin D Insufficiency Based on Different Outcomes and Study Types. A Common Threshold Value of 50 nmol/ l Has Been Proposed for Vitamin D Insufficiency, Whereas Vitamin D Deficiency is Characterized by Values < 25 nmol/ l[15]



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Higher 25OHD levels prevent	Threshold values for 25-OHD (nmol/l)	Study type	References
Secondary hyperparathyroidism	30–80 Increases with age	Cross-sectional	Dawson-Hughes *et al.* 1991[44] Ooms 1994[45] Ooms *et al.* 1995[46] Chapuy *et al.* 1997[47] Guillemant *et al.* 1999[48] Jesudason *et al.* 2002[49] Vieth *et al.* 2003[50]
Decrease in BMD	30	Cross-sectional	Ooms *et al.* 1995[46]
Increase in bone turnover	60	Cross-sectional	Jesudason *et al.* 2002[49]
Seasonal variations in PTH	90	Cross-sectional	Krall *et al.* 1989[12]
Suppressible P-PTH	50	Intervention	Malabanan *et al.* 1998[51] Lips 2001[15]

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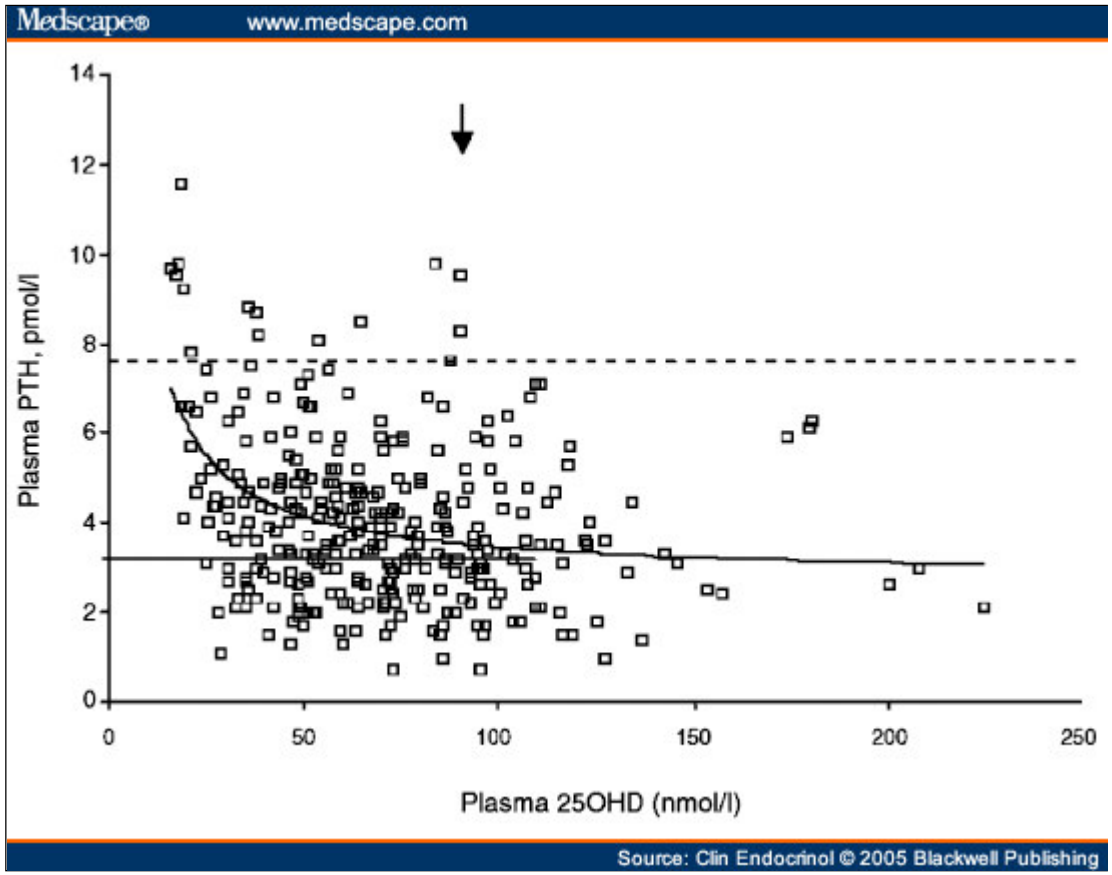

Figure 2. Secondary hyperparathyroidism with declining plasma 25OHD levels in Danishperimenopausal women. Danish Osteoporosis Prevention Study.[43] In this case the threshold value was close to 90 nmol/l (arrow). The broken line indicates the upper normal range for plasma PTH.

A second problem is related to the accuracy of the methods used for determination of plasma 25OHD.[53,54] The analyses need to be cross-calibrated and standardized.[15] Furthermore, the influence of concentrations and phenotypes of vitamin D binding protein (DBP) or group specific component (CG) on plasma 25OHD and biological effects needs to be explored.

A third problem is the predictive value of a point measurement of plasma 25OHD for the previous and future vitamin D status at the individual level. Research on this topic is lacking, but most likely plasma 25OHD levels often reflect recent events such as the effect of the season, indoor/outdoor activities and holidays spent in more sunlit geographical areas than the average vitamin D status for the individual person. However, with increasing age where dermal vitamin D production decreases,[2,28] plasma 25OHD may reflect more stable lifestyle factors such as average vitamin D intake and vitamin D supplementation. These considerations might indicate that plasma 25OHD measurements are suitable for estimating the average vitamin D status in populations or subsets of populations but are less useful at the individual level. However, at the individual level

measurements are well justified to confirm a suspicion of vitamin D-related osteomalacia or proximal myopathy.

As argument for a relatively high threshold level, it can be alleged that plasma 25OHD is generally lower in people who have experienced a fracture than in controls.[55,56] Furthermore, individuals with a 25OHD level less than 68 nmol/l have a four times increased fracture risk over 8 years.[57] This risk is increased 19 times in patients with osteoporosis.[57] Finally, supplementation by 10-20 µg/day of vitamin D reduces the risk of falls and fractures despite only moderate increases in plasma 25OHD from around 30 to 80 nmol/l.

Vitamin D Status Among the Elderly

Despite the described limitations, plasma 25OHD measurements are at present considered the best method for describing vitamin D status in various risk groups, including elderly people living at home and those in sheltered homes for the elderly or nursing homes, in order to establish the need for supplementation or dietary fortification. Lips [15] recently performed a detailed survey of 25OHD levels in various populations in Europe, the USA, Australia and other countries. Different threshold levels used in the referred papers hamper assessment of the prevalence of vitamin D insufficiency and deficiency. However, it seems that vitamin D insufficiency is a frequent finding among community-dwelling elderly, irrespective of latitude, and an almost universal finding among institutionalized elderly. The USA is an exception, probably because of the liberal fortification with vitamin D in that country. However, in patients with hip fracture, vitamin D status was also poor among Americans. Average plasma 25OHD levels varied from 21 to 55 nmol/l in community-dwelling elderly populations from Europe compared with levels between 71 and 86 nmol/l among the elderly from the USA. Patients living in nursing homes and in homes for the elderly had plasma 25OHD levels of 9-37 nmol/l in Europe compared with 53-45 nmol/l in the USA and 26-40 nmol/l in Australia. Geriatric patients had mean levels of 3·3-29 nmol/l in Europe compared with 45-71 nmol/l in the USA. In hip fracture patients, average values varied from 19 to 46 nmol/l in Europe, compared with 32 nmol/l in the USA and 45 nmol/l in Australia. In Denmark, 7% of postmenopausal women have vitamin D deficiency and 40% have insufficiency,[13] 80% of elderly over 65 years have vitamin D insufficiency,[58] 44% of nursing home residents have severe vitamin D deficiency (< 12 nmol/l),[59] 75% of hip fracture cases have vitamin D insufficiency, 25% have vitamin D deficiency and 5% have severe vitamin D deficiency.[60]

Histological and histomorphometric investigations have disclosed that 15-20% of all patients with hip fractures have slight osteomalacia.[61-64] Hip fracture patients also show a higher prevalence of low plasma 25-OHD concentrations than their age-matched controls.[64,65]

Vitamin D, Falls and Fractures

Osteoporotic patients are characterized by reduced muscle mass and muscle strength, indicating that the loss of bone and muscle mass is congruent.[66] Moreover, elderly with low intake of calcium and vitamin D, with reduced cutaneous production of vitamin D or decreased renal production of calcitriol [1,25(OH)2D] may be particularly predisposed to falls due to proximal myopathy caused by vitamin D deficiency and secondary hyperparathyroidism.[15,66,67] Several studies have disclosed a connection between vitamin D status and muscle function in the elderly, among women with postmenopausal osteoporosis and among dark-skinned immigrants with vitamin D deficiency.[19,66,68,69] Some studies have revealed increased sway[69] and affected psychomotor function,[71] with increased risk of falling among vitamin D-deficient elderly. A cross-sectional study[68] has documented that the risk of falls among elderly institutionalized Australian residents depends on vitamin D status and the degree of secondary hyperparathyroidism. Treatment

with 1α-hydroxylated vitamin D metabolites and calcium improved biochemical evidence of osteoporosis-related myopathy in one study,[72] but not muscle strength in another.[73]

Vitamin D exerts a direct action on skeletal muscle function.[74,75] The skeletal muscles express nuclear VDR, which promotes vitamin D-directed protein synthesis.[76,77] Vitamin D stimulates muscle cell uptake of inorganic phosphate, which is important for the production of energy-rich phosphate compounds such as ATP and creatine phosphate, vital for muscle contraction.[78-80] In addition, specific VDRs localized to the cell membrane are essential for the distribution and regulation of intracellular calcium.[10,81] Vitamin D deficiency is followed by secondary hyperparathyroidism, which by itself may exert a negative influence on muscle function.[68,82] In rats, excess PTH increases muscular protein catabolism, and reduces the amount of type 2 muscle fibres, the intracellular energy-rich phosphate compounds, and the mitochondrial oxygen uptake.[83]

It seems that vitamin D deficiency causes impaired muscle function and muscle weakness, which are, however, reversible following vitamin D supplementation.[19] This reduced muscle function is disadvantageous in connection with the skeletal consequences of vitamin D deficiency, leading to an increased risk of falls among the elderly with reduced biomechanical competence of the skeleton.

The Effect of Vitamin D Supplementation on the Risk of Falling

Intervention studies have been performed in institutionalized high-risk patients and in residential elderly populations (Table 2). Vitamin D alone without calcium has no significant effect on the risk of falling (Table 2).[84-86] However, 8 weeks of vitamin D_3 treatment with 800 IU (20 μg) per day combined with 1200 mg calcium is reported to reduce secondary hyperparathyroidism, body sway and number of falls after 1 year in elderly ambulatory women.[87] The number of fallers was not reduced (Table 2). In a double-blind randomized study,[87] 122 otherwise unselected elderly women aged between 63 and 99 years (mean 85 years) in a geriatric department were treated with 800 IU (20 μg) vitamin D_3 + 1200 mg calcium daily (n = 62) or 1200 mg calcium daily (n = 60) and followed for 12 weeks. Plasma 25OHD increased 71% ($P < 0{\cdot}0001$) and plasma PTH decreased 29% (P = 0·002) in the group receiving vitamin D. Muscle function improved significantly in this group ($P < 0{\cdot}01$). The nursing staff registered falls. An intention-to-treat analysis using a Poisson regression model to adjust for baseline covariates disclosed that calcium and vitamin D compared with calcium alone reduced the risk of falling by 49%[95% confidence interval (CI) 14-71%, $P < 0{\cdot}01$]. Individuals with repeated falls had the greatest benefit of the treatment. However, the crude number of fallers was not reduced by the treatment (Table 2).

Table 2. Effect of Vitamin D Alone or in Combination With Oral Calcium on Plasma 25OHD and Risk of Falls. Controlled Clinical Trials (10 μg of Vitamin D Equals 400 IU)

Intervention	N	Females (%)	Age (years)	Duration (years)	P-25OHD (nmol/l) Untreated	Treated	Increase (%)	Risk of falling RR (95% CI)	Reference
Vitamin D alone									
10 µg D_3/day *vs.* placebo	354	85	≥ 70	0·5	–	–	–	0·94 (0·71–1·24)	Graafmans *et al.* 1996[54]
2500 µg D_3/4th month *vs.* placebo	2308	26	≥ 65	1·0	53	74	39	0·96 (0·82–1·11)	Trivedi *et al.* 2003[55]
7500 µg D_3 once *vs.* placebo	222	53	79 (7)	0·5	48	60	26	1·12 (0·79–1·59)	Latham *et al.* 2003[56]
Vitamin D + calcium									
20 µg D_3/day + 1·2 g Ca/day *vs.* 1·2 g Ca/day	148	100	70(1)	1·2	43	66	53	0·55 (0·29–1·06)	Pfeifer *et al.* 2000[57]
10 µg D_3/day + 1 g Ca/day *vs.* no treatment	5771	100	≥ 65	3·5	38	47	23	0·88 (0·79–0·98)	Larsen 2002[58]*
20 µg D_3/day + 1·2 g Ca/day *vs.* 1·2 g Ca/day	122	100	85 (63–99)	0·2	11	26	136	0·75 (0·41–1·37)	Bischoff *et al.* 2003[58]
Inj. 7500 µg D_3 once or Inj. 7500 µg D_3 once + 1 g Ca/day or 20 µg D_3/day + 1 g Ca/day *vs.* placebo	150	100	81 (67–92)	1·0	–	–	–	0·48 (0·26–0·90)	Harwood *et al.* 2004[59]

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In a factorial, pragmatic intervention study,[58] 9605 unselected home-living Danes aged over 65 years in the city of Randers were offered (a) 1000 mg calcium + 400 IU (10 µg) vitamin D, (b) a home visit by a nurse to prevent falls, (c) both interventions, or (d) no interventions. Both intervention programs included general health guidance and revision of medication. A total of 4957 persons were offered calcium and vitamin D, whereas 5063 did not receive this offer. The active participation was 50·3% in the calcium and vitamin D group and 46·4% in the other group. In the following 3·5 years a total of 2770 individuals contacted the casualty ward because of serious falls. An intention-to-prevent analysis disclosed that the offer of calcium and vitamin D reduced the risk of severe falls by 12% (95% CI 2-21%, $P < 0·05$) among the women who had the highest risk of falling (Fig. 3).

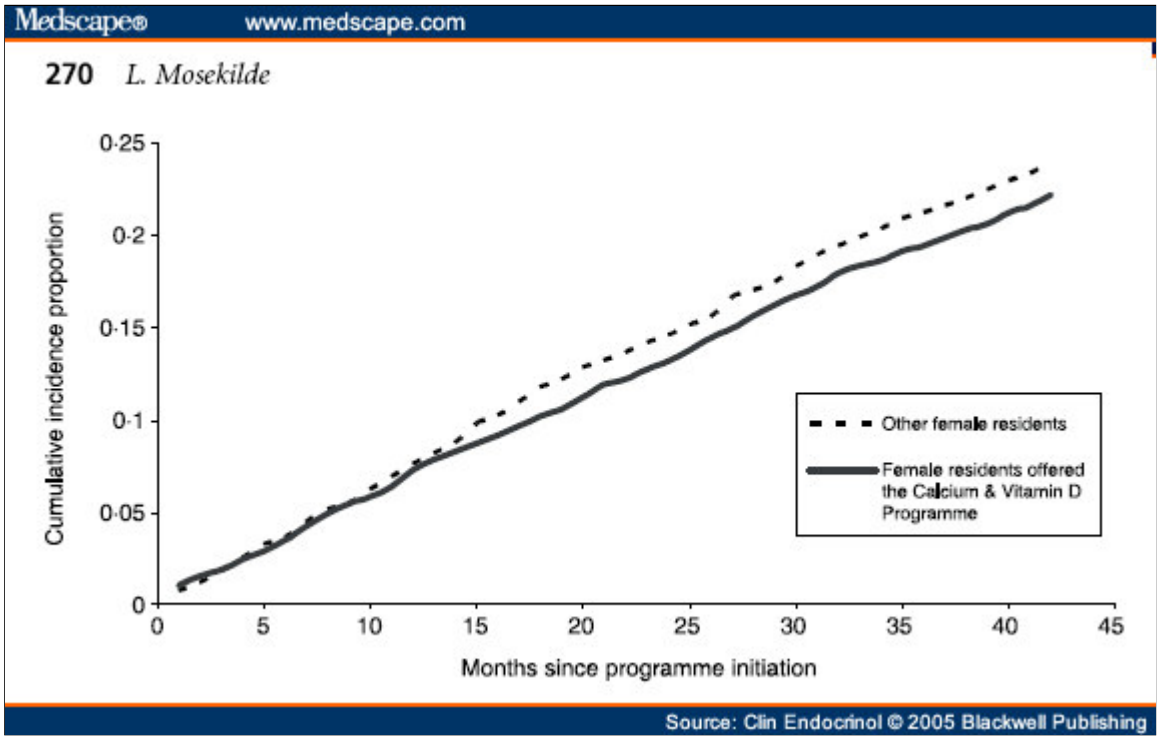

Figure 3. Effect of an offer of 400 IU (10 µg) of vitamin D and 1000 mg of calcium per day to 5771 home-living women aged over 65 years on the occurrence of severe falls leading to hospital contact. Randers City, Denmark, 1995-98.RR = 0·88;& *P* #60; 0·05. Intention-to-prevent analysis (taken from Larsen,[58] with permission).

In a randomized, controlled study,[89] 150 women were recruited following surgery for hip fracture and assigned to a single injection of 300 000 IU (7500 µg) D2, injection of vitamin D_2 + 1000 mg Ca/day, 800 IU (20 µg) oral D_3 plus 1000 mg Ca/day or no treatment and followed for 1 year. The relative risk of falling was reduced by 52% (95% CI 10-74%, $P < 0·05$) in the groups supplemented with vitamin D compared with controls.

A recent meta-analysis on the effect of vitamin D on falls[90] concluded that vitamin D supplementation reduces the risk of falls among ambulatory or institutionalized older individuals with stable health by more than 20% (pooled OR 0·78; 95% CI 0·640·92). However, this analysis also included studies using 1α-hydroxylated vitamin D metabolites.

Vitamin D, Bone Tissue and Fracture Risk

Vitamin D and calcium deficiency results in secondary hyperparathyroidism, increased bone turnover, accelerated bone loss and an increased risk of low-energy fractures due to senile (type 2) osteoporosis.[15,91] In cross-sectional studies bone turnover increases at plasma 25OHD levels below 50 nmol/l[49] and hip BMD decreases at values below 30 nmol/l.[46] The effect of vitamin D supplementation on BMD is reversible and disappears completely after 2 years.[44,92] A large European casecontrol study showed that the risk of hip fractures was associated with reduced sun exposure and decreased calcium intake from milk.[93] Several studies have disclosed moderate to severe vitamin D deficiency

among patients with hip fractures.[56,60,94,95] Even if moderate vitamin D insufficiency can be without short-term clinical symptoms, it could be important to correct it as the skeletal consequences in the long term might be a reduced biomechanical competence with increased fracture risk.

The Effect of Vitamin D and Calcium Supplementation on Fracture Risk

The protective effect may depend on whether vitamin D is given alone or in combination with calcium as suppression of secondary hyperparathyroidism seems to be of major importance for both muscle and skeletal health. The degree of pre-existing vitamin D deficiency may also be of importance. This deficiency seems to be more common among institutionalized individuals than among home-living elderly.[15] Table 3 summarizes the findings in available controlled clinical studies.

Table 3. Effect of Vitamin D Alone or in Combination With Oral Calcium on Plasma 25OHD and Fracture Risk. Controlled Clinical Trials (10 µg of Vitamin D Equals 400 IU)

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Intervention	N	Females (%)	Age (years)	Duration (years)	P-25OHD (nmol/l) Untreated	Treated	Increase (%)	Fracture risk RR (95% CI)	Reference
Vitamin D alone									
10 µg D_3/day *vs.* placebo	2·578	74	80 (6)	3	23	60	160	1·18 (0·81–1·71)	Lips *et al.* 1996[102]
10 µg D_3/day	1·144	75	85 (7)	2	46	84	83	1·09 (0·73–1·63)	Meyer *et al.* 2002[100]
Cod liver oil + vit. D *vs.* cod liver oil – vit. D									
2500 µg D_3/4th month *vs.* placebo	2·686	24	75 (5)	5	53	74	39	0·67 (0·48–0·93)	Trivedi *et al.* 2003[85]
Inj. 7500 µg D_2 once/year *vs.* placebo	9·440	54	≥ 75	3	–	–	–	1·10 (0·94–1·29)	Smith *et al.* 2004[104]
Vitamin D and calcium									
20 µg D_3/day + 1·2 g Ca/day *vs.* placebo	3·270	100	84 (6)	1·5	28	105	275	0·74 (0·56–0,97)*	Chapuy *et al.* 1992[96]
17·5 µg D_3/day + 0·5 g Ca/day	389	55	71 (5)	3	70	112	69	0·46 (0·22–0·91)	Dawson-Hughes *et al.* 1997[25]
20 µg D_3/day + 1·2 g Ca/day *vs.* placebo	583	100	85 (7)	2	20	78	287	0·59 (0·33–1·04)*	Chapuy *et al.* 2002[98]
10 µg D_3/day + 1 g Ca/day *vs.* no treatment	9·605	60	≥ 65	3·5	38	47	23	0·84 (0·72–0·98)	Larsen *et al.* 2004[103]

*Hip fracture risk.

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Institutionalized Elderly

Several studies have shown that vitamin D and calcium supplementation reduces the risk of hip fractures and other peripheral fractures. Chapuy *et al* .[96] observed in a randomized double-blind study that 800 IU (20 µg) of vitamin D per day combined with 1200 mg calcium after 18 months reduced the risk of hip fractures by 26% (RR = 0·74; 95% CI 0·56-0·97) and the risk of peripheral fractures by 25% (RR = 0·75; 95% CI 0·62-0·91) among ambulatory institutionalized elderly. After 3 years of treatment the effect on hip fractures (RR = 0·74; 95% CI 0·60-0·91) and on all peripheral fractures (RR = 0·79; 95% CI 0·69-0·92) was slightly weakened but still significant.[97] A relative low completion rate

may contribute to the modest response. The results were later confirmed in a new double-blind, 2-year, multicentre study including 583 ambulatory institutionalized individuals.[98] The active treatment reduced the risk of hip fractures by 41%, but the result was insignificant (RR = 0·59; 95% CI 0·33-1·04) because of the limited number of participants in the study. Gillespie *et al* .[99] concluded in a Cochrane analysis that treatment with vitamin D_3 and calcium in weak, elderly, institutionalized individuals reduced the risk of fractures.

The effect of vitamin D alone was evaluated in a 2-year, Norwegian, double-blind, randomized study, where residents received either cod liver oil containing 10 µg vitamin D per day or cod liver oil with the vitamin D removed.[100] There was no difference in fracture occurrence between the groups (RR = 1·09, 95% C1 0·73-1·63). By contrast, Heikinheimo *et al* .[101] observed in a quasi-randomized, open study that injection at the start of the winter season of 150 000-300 000 IU of vitamin D in the elderly in Finland reduced the risk of peripheral fractures by 20-30%.

Residents Living at Home

A Dutch study including 2564 individuals followed for 3 years, where the vitamin D group received 10 µg/day without calcium, disclosed no effect on fracture risk.[102] By contrast, a 3·5-year pragmatic intervention study[103] including 9605 home-living Danes aged over 65 years showed that an offer of 10 µg vitamin D per day combined with 1000 mg calcium in an intention-to-prevent analysis reduced the risk of osteoporotic fractures by 16% (RR = 0·84 (0·72-0·98), $P < 0·025$) in both genders (Fig. 4). The reduction was also significant among the females ($P < 0·01$).

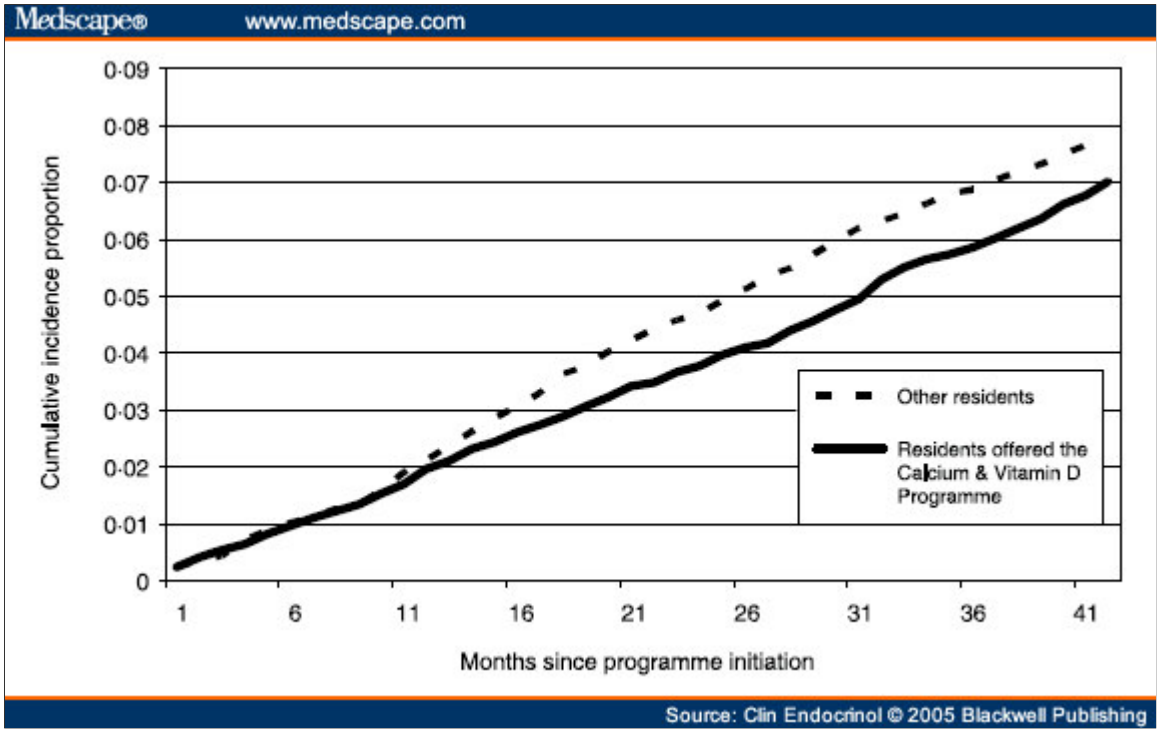

Figure 4. Effect of an offer of 400 IU (10 µg) of vitamin D and 1000 mg of calcium daily to 9505 home-living elderly aged over 65 years on the occurrence of osteoporotic fractures. Randers City, Denmark, 1995-98. RR = 0·8, $P < 0·025$. Intention-to-prevent analysis (taken from Larsen,[58] with permission).

The effect of vitamin D alone without calcium was further evaluated in a randomized, double-blind, 5-year investigation in the UK.[85] The study compared 100 000 IU oral vitamin D (cholecalciferol) given every fourth month [approximately 800 IU (20 µg) per day] with identical placebo. The study included 2689 home-living individuals (2037 males and 649 women) aged between 65 and 85 years. After 5 years the risk among the actively treated of all fractures was reduced by 22% (RR = 0·78, 95% CI 0·61-0·99) and of osteoporotic fractures by 33% (RR = 0·67, 95% CI 0·48-0·93). There was no significant difference in mortality between the groups (RR = 0·88, 95% CI 0·74-1·06).

Preliminary data from another investigation in the UK including more than 7000 home-living elderly aged over 75 years could not document any effect on fracture occurrence of yearly injections of 300 000 IU vitamin D.[104] The lack of effect may be caused by limited bioavailability of vitamin D using this route of administration.

Vitamin D and Cancer

Several different cancer cells including breast, colon and prostate cancer cells and leukaemic cells express VDR and calcitriol [1,25(OH)$_2$D] has an inhibitory effect on these cells.[3] The effect mechanisms have not been fully elucidated but include regulation of the cell cycle, stimulation of differentiation, impairment of growth stimuli, inhibition of angiogenesis and increased apoptosis of malignant cells.[105-107] The use of 1,25(OH)$_2$D as adjuvant treatment for malignant diseases is hampered by the hypercalcaemic effect of the compound when used in higher doses. Vitamin D analogues have recently been developed that conserve the antiproliferative effect with a reduced hypercalcaemic effect.[108] Some of these analogues are being assessed in phase II and phase III clinical studies in various malignant diseases.[105,109]

However, the main effect of vitamin D and its metabolites in relation to malignant disorders may be to prevent the development of malignancy. Epidemiological studies have disclosed that the mortality of a number of malignant diseases is reduced with increasing UVB radiation intensity. The variation in UVB exposure may be related to urbanization or to the latitude of residence.[110-117 The traceable associations are present after adjustment for several other known risk factors[96] and support a protective effect of ,utaneous vitamin D production caused by UVB irradiation. Grant 116 reported considerable premature mortality among white Americans (approximately 157 000/year) related to insufficient UVB irradiation. The increased mortality was caused by an increased occurrence of breast, colon, rectum, prostate, oesophagus, stomach, kidney, bladder and ovarian cancer and lymphoma. Similar results have been observed in Europe,[118] or breast cancer in the USSR[120] and for prostate cancer in several countries mainly inhabited by Caucasians.[120] Table 4 specifies findings in three of the most common cancer forms among the elderly: colon, prostate and breast cancer.

Table 4. Epidemiological Studies Relating Cancer Risk to Vitamin D Status and Sun Exposure (10 µg of Vitamin D Equals 400 IU; 10 ng/ml of 25-OHD Equals 25 nmol/l)

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Design	Total N	Cases N	Controls N	Duration (years)	Outcome incident	Exposure variable	RR or OR (95% CI)	Reference
Colon cancer								
Cohort study	1 954	49	1 905	19	Colorectal cancer	Vitamin D intake > 3·75 µg/day	RR > 0·5 trend over quartiles, $P < 0·05$	Garland *et al.* 1985[125], 1990[111]
Nested case–control study	25 620	34	67	8	Colon cancer	P-25OHD > 67 nmol/l	0·51 (0·22–1·19)	Garland *et al.* 1989[125], 1991[124]
Cohort study	127 749	683	127 006	5	Colorectal cancer	Vitamin intake > 13·13 µg/day *vs.* < 2·75 µg/day	0·80 (0·62–1·02) 0·71 (0·51–0·98)*	McCulough *et al.* 2003[126]
Prostate cancer								
Nested case–control study	19 000	149	596	13	Prostate cancer	P-25OHD < 40 nmol/l *vs.* > 40 nmol/l	1·7 (1·2–2·6)†	Ahonen *et al.* 2000[133]
Nested case–control study	> 200 000	622	1 451	21	Prostate cancer	P-25-OHD < 19 nmol/l *vs.* 40–59 nmol/l P-25-OHD > 80 nmol/l *vs.* 40–59 nmol/l	2·4 (1·1–5·1)‡ 1·7 (1·1–2·4)	Tuohimaa *et al.* 2004[134]
Breast cancer								
Cohort study	5 009	190	4 819	21	Breast cancer	Sun exposure – frequent *vs.* never occasional occupational	0·66 (0·44–0·99) 0·64 (0·41–0·98)	John *et al.* 1995[93]
Cohort study	88 691	3482	85 209	16	Breast cancer	Vitamin D intake > 12·5 µg/day *vs.* < 3·75 µg/day	0·72 (0·55–0·94)§	Shin *et al.* 2002[135]

*Males only, multivariate adjusted, test for trend over quintiles of intake, $P < 0·002$.
†For males < 52 years at entry RR = 3·5 (1·7–7·0).
‡Finland only, not Norway and Sweden.
§Premenopausal women only.

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Colon Cancer

Both normal and malignant colon tissue and cultured transformed colon cells express 1-hydroxylase activity and can thereby transform 25OHD to $1,25(OH)_2D$.[17,121] In patients with an increased risk of colon cancer, 25OHD reduces the proliferation of colon epithelium cells.[122] In a cohort study including 1954 males and with a follow-up time of 19 years,[123] vitamin D intake was reduced ($P < 0·05$) in 49 incident cases of colorectal cancer (1·17 µg/1000 kcal) compared with 1905 controls (1·43 µg/1000 kcal) and the absolute risk of colorectal cancer decreased ($P < 0·05$) from the lowest intake quartile (3·07%) to the highest (1·64%). An intake of more than 3·75 µg/day of vitamin D reduced the risk of colon cancer by more than 50%.[124] In a nested casecontrol study based on a cohort of 25 620 individuals, 125 plasma 25OHD of 67·5-80 nmol/l was associated with a 75% decrease ($P < 0·05$) and values of 82·51-02 nmol/l with a 79% decrease ($P < 0·05$) in risk of colon cancer compared with values < 47·5 nmol/l.[125] However, the risk was only reduced by 27% (NS) at levels > 105 nmol/l. Plasma levels more than 65 nmol/l were associated with a 50% decrease in colon cancer risk.[124] This finding was supported by a large American cohort study that demonstrated that a high intake of vitamin D from diet and multivitamins [i.e. > 525 IU (13·1 µg) per day] was associated with a 19% decrease in risk of colorectal cancer among males compared with 2·75 µg/day.[126]

Prostate Cancer

Both normal and cultured malignant prostate cells express 1-hydroxylase, which facilitates local $1,25(OH)_2D$ production.[127-129] Accordingly, both 25OHD and $1,25(OH)_2D$ inhibit division and growth of prostate cancer cells.[127,130,131] In epidemiological studies, VDR gene polymorphism influences the risk of developing prostate cancer.[132] A Finish nested casecontrol study (cases : controls = 1 : 4) based on a cohort of 19 000 males revealed, after 13 years of observation, 149 patients with prostate cancer. Males with plasma 25OHD at inclusion below 40 nmol/l (median level) had a 70% increased risk of prostate cancer compared with those with higher baseline levels. 133 For younger males (< 52 years) the risk was increased by 250%, in addition to an increased risk of having metastatic disease (OR = 6·3). A subsequent Scandinavian study comparing 622 prostate cancer patients with 1451 controls in a cohort of more than 200 000 males showed that both low (< 19 nmol/l) and high (> 80 nmol/l) plasma 25OHD levels were associated with an increased cancer risk.[134] This interesting observation was tentatively explained by the suggestion that very high 25OHD concentrations locally may accelerate the inactivation of $1,25(OH)_2D$ by tumour-produced 24-hydroxylase.

Breast Cancer

Breast tissue expresses VDR and both vitamin D status and genetic variations in VDR can affect the risk of developing breast cancer.[135] $1,25(OH)_2D$ increases the differentiation of human breast cancer cell lines.[136,137] Furthermore, preclinical studies suggest that vitamin D derivates can reduce breast cancer development in experimental animals.

In a cohort study including 5009 white women, 190 new cases of breast cancer were identified between 1971 and 1992.[138] Several measures of high sun exposure and dietary vitamin D were associated with a 36-15% reduction in breast cancer risk. The effect was most pronounced in areas with high sun exposure. Another large cohort study based on the Nurses Health Study population[139] demonstrated an inverse relationship between a high vitamin D intake (> 500 IU/day or 12·5 µg/day) and a 28% reduced risk of breast cancer among premenopausal women.

Vitamin D and Type 2 Diabetes

Several large-scale cohort and casecontrol studies have shown that vitamin D supplementation during childhood reduced the risk of later type 1 diabetes.[33,35,36] However, a number of studies have also disclosed an association between vitamin D deficiency and type 2 diabetes. The pathogenetic mechanism could be an effect on insulin sensitivity, on β-cell function, or on both. The pancreatic β-cells express VDR.[7] In a cohort of 293 high-risk patients referred for diagnostic coronary angiography, the risk of type 2 diabetes depended on VDR polymorphism being highest in patients with the BB genotype (OR = 3·64; 95% CI 1·53-8·55).[140] Furthermore, vitamin D deficiency inhibits insulin secretion[141,142] and modulates lipolysis.[143] Vitamin D supplementation improves insulin secretion and glucose tolerance in vitamin D-deficient animals[144,145] and in humans.[146] Plasma 25OHD levels are reported to be decreased in type 2 but not in type 1 diabetes.[147,148] In a large cross-sectional study from New Zealand including 5677 individuals aged 40-64 years, $25OHD_3$ levels were decreased in individuals with recently diagnosed impaired glucose tolerance (IGT) and type 2 diabetes after adjustment for obesity, sex, age, ethnicity and season.[149] Glycaemic control in type 2 diabetes depends on the season, with the lowest haemoglobin A_{1c} (HbA_{1c}) levels during summer.[150] In healthy adults UVB irradiation increases plasma $1,25(OH)_2D$ and insulin secretion.[151] In addition, treatment with 1332 IU (33·3 µg) vitamin D_3 daily for 1 month in 10 patients with type 2 diabetes increased plasma 25OHD by 76% and the first phase of the insulin secretion by 34%, evaluated by an intravenous glucose tolerance test (IVGTT).[152] The

decrease in insulin resistance (21·4%) was insignificant. A recent study in glucose-tolerant subjects revealed a positive correlation between plasma 25OHD and insulin sensitivity and a negative effect of hypovitaminosis D on β-cell function as assessed by the hyperglycaemic clamp technique.[153] Hence, it seems that subjects with hypovitaminosis D are at higher risk of insulin resistance and the metabolic syndrome. It is unclear what influence altered vitamin D status may have for the increased fracture risk observed in type 2 and also in type 1 diabetes.[154]

Vitamin D and Cardiovascular Disease

Atherosclerosis and Ischaemic Cardiovascular Disease

VDR has also been demonstrated in heart muscle cells[7] and 1,25(OH)$_2$D may play a role in the maintenance of ventricular pump function.[155] Patients with heart failure have lower plasma levels of 25OHD and 1,25(OH)$_2$D than controls.[156] There is growing evidence that atherosclerosis may be viewed as a chronic inflammatory disease that involves tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). Active vitamin D [1,25(OH)$_2$D] can suppress these cytokines *in vivo* and TNF-α is inversely related to plasma 25OHD *in vivo* .[107] Epidemiological studies indicate an inverse relationship between plasma 25OHD and the occurrence of acute myocardial infarction (AMI),[157] and the risk of coronary heart disease has been associated with VDR polymorphism.[140] In the UK an increased cardiovascular morbidity is associated with low plasma 25OHD concentrations in winter.[158,159]

Essential Hypertension

Mean systolic and diastolic blood pressure (BP) and the prevalence of hypertension vary throughout the world with a linear rise in BP with latitude.[160] Similarly, BP is higher in winter than in summer and varies with skin pigmentation. Exposure to UVB light may contribute to these differences.[160] In essential hypertension, typical changes are observed in calcium homeostasis with decreased intestinal calcium absorption, enhanced renal excretion, reduced plasma concentrations and increased intracellular concentrations of calcium and hyperparathyroidism.[161-164] Some of these alterations depend on intracellular adenyl cyclease, which is influenced by 1,25(OH)$_2$D.[162,165] Diastolic BP is weakly inversely correlated to plasma 25OHD.[166] A daily supplement of 5 µg (200 IU) of vitamin D has no effect on BP in normotensive individuals,[167-168] but 20 µg (800 IU) per day in combination with 1200 mg calcium significantly decreases systolic BP by 9·3% in women aged 70 years or older with vitamin D insufficiency or deficiency.[70] Furthermore, several investigations have demonstrated a BP-lowering effect of 0·751 µg 1,25(OH)$_2$D or UVB (but not UVA) in hypertensive patients.[169-171]

Possibilities for Prevention

There are several ways to improve vitamin D status among the elderly: fortification of food, yearly vitamin D injections and tablets with vitamin D (and calcium). Vigorous exposure to sunshine is controversial because of the risk of skin cancer and is less effective among the elderly[2,28] and during winter at higher latitudes.

Fortification of Food With Vitamin D

Fortification is used in many developed countries.[172] In particular, margarine, vegetable oil and milk are fortified in Europe, whereas enrichment of flour, cornflakes and juice is used in the USA. Fortification of bread, other cereals and margarine is focused on the elderly, whereas fortification of bread and oil is focused on dark-skinned immigrants from,

for example, the Near East, Pakistan or India. Fortification of several types of food ensures a more equal dispersion in the population independent of eating habits. Inadvertent overfortification of milk by a home-delivery dairy from 1985 to 1991 leading to a suspected outbreak of hypervitaminosis D associated with severe illness and death has been described in the USA.[173] However, more detailed studies revealed that the prevalence of increased plasma 25OHD and calcium levels was no greater than expected, and data indicated normal renal function.[174] It was concluded that most people exposed to excess vitamin D exhibited no measurable adverse clinical effects. However, the episode highlights the need for monitoring any fortification process[175] and to spread fortification over a variety of food items.

An adequate fortification program should secure a supply of about 20 µg vitamin D (800 IU) per day to the elderly. Bread and edible fats (butter, oil and margarine) would be obvious food items to enrich to reach this population group. Simulation in Denmark using information on dietary food intake in various Danish populations with an average baseline dietary vitamin D intake of 2·53 µg/day shows that enrichment of edible fat by 35 µg vitamin D/100 g or of bread and cereals by 10 µg vitamin D/100 g will ensure that half of the elderly population gets 20 µg/day from diet and fortification combined.[172] Fortification with a combination of 12 µg vitamin D/100 g fat and 5 µg/100 g cereals will give the same result. This strategy indicates that 10% of the elderly will get 28 µg/day of vitamin D and 5% will get at least 32 µg/day. None of the elderly will get more than 50 µg/day, a level considered safe for this group by the European Commission's Scientific Committee on Food.[176] However, for children between 4 and 10 years old, such a fortification will supply 1418 µg/day of vitamin D, but at the same time 10% will get an oral vitamin D intake close to or above the 25 µg/day that is considered safe.[176] Fortification of bread and cereals by 10 µg/100 g will result in a daily intake above 25 µg/day for 5% of the children and a combination of edible fat with 12 µg/100 g and bread and cereals with 5 µg/100 g will result in an intake of more than 22 µg/day in 5%. These simulations indicate that fortification with vitamin D to ensure an adequate intake by the elderly will result in dietary intakes among children that are considered risky by the authorities. However, these considerations do not exclude a less ambitious fortification programme aimed at meeting the common recommendations of at least 5-10 µg/day among younger adults.

It should be emphasized that there are no controlled intervention studies demonstrating the effect of fortification on falls, low-energy fractures, malignant disorders, infectious and autoimmune disorders or cardiovascular disorders. However, it is known that plasma 25OHD is related to dietary vitamin D[177] and that the risk of hip fractures and reduced muscle function depends on plasma 25OHD.[57]

Yearly Injections With Vitamin D

At higher latitudes yearly injections in late autumn could prevent the fall in plasma 25OHD during winter. From a practical point of view these injections could be given together with the yearly influenza vaccination securing a reasonable compliance. A Finnish investigation among the elderly demonstrated that a yearly injection of 3·75 mg (150 000 IE) of vitamin D could prevent 20-30% of peripheral fractures.[101] However, a recent UK study including more than 7000 elderly participants could not demonstrate any effect on fracture risk of 300 000 IU given once a year.[104] A previous study has demonstrated a greater variability in plasma 25OHD following intramuscular injections compared with oral administration.[178] Hence, lack of bioavailability may explain the negative result of the UK study. Based on these considerations the intramuscular route seems at present to be less attractive for vitamin D administration.

Supplementation With Tablets Containing Vitamin D and Calcium

To prevent falls and fractures among weak, elderly individuals in nursing homes or other geriatric institutions there is good evidence to support a general supplementation with 20

µg (800 IU) of vitamin D in combination with 1000-12 000 mg of calcium based on results from France and Austria.[88,96-98] This will raise plasma 25OHD, suppress plasma PTH, reduce bone turnover, improve muscle force, decrease sway and tendency to fall, improve bone strength and prevent fractures.

In the general population in the UK, supplementation of around 20 µg/day of vitamin D to people aged over 65 years appears to reduce fracture risk if given as 100 000 IU three times a year.[85] Furthermore, 10 µg/day in combination with 1000 mg of calcium reduces low-energy fractures in Denmark.[103] The average participation in such programs varies by 50-66% depending on the delivery methods. There is reasonable evidence to suggest that less vitamin D is needed if given together with calcium as the major muscular and skeletal consequences of vitamin D deficiency are related to secondary hyperparathyroidism. As baseline vitamin D status may vary according to latitude, climate conditions, lifestyle, clothing habits, dietary vitamin D content, and so on, there is at present no evidence that these results can be extrapolated to other regions of the world.

Further Research

Basic research and several epidemiological studies suggest that vitamin D and its metabolites are important for the prevention of a number of frequent and severe infections, diabetes, autoimmune and cardiovascular diseases and for the prevalence and course of several cancers. Besides being considered in the ongoing discussion on vitamin D fortification and supplementation, these observations provide the theoretical basis for large, population-based, long-term randomized intervention studies. Such studies are unlikely to be financed through private medical companies but call for substantial public funding to ensure sufficient infrastructure and personnel. Furthermore, government-implemented fortification and supplementation should, whenever possible, be followed by scientific evaluation of effects and potential disadvantages. Unfortunately, this has not been put into effect until recently. Finally, basic research programs should aim at providing further understanding of the biological effects of vitamin D and its natural or artificial metabolites on the immune system and cancer biology.

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