

REVIEW ARTICLE

VITAMIN D AND LIVING IN NORTHERN LATITUDES – AN ENDEMIC RISK AREA FOR VITAMIN D DEFICIENCY

Anne Huotari ¹, Karl-Heinz Herzig ^{1,2,3}

¹A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland

²Department of Internal Medicine, Kuopio University Hospital, Kuopio, Finland

³Institute of Biomedicine, Department of Physiology, and Biocenter of Oulu, Oulu University Medical School, Oulu, Finland

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ABSTRACT

Objectives. To review the current literature on the health effects of vitamin D, especially the effects on inhabitants living in the northern latitudes.

Study Design. Literature review.

Methods. The scientific literature concerning health effects of vitamin D was reviewed and the current dietary recommendations for inhabitants living in northern latitudes were discussed.

Results. Vitamin D is a steroid-structured hormone produced in the skin upon exposure to UVB-radiation or obtained from certain food products (for example, liver). Its production is mediated by the vitamin D receptor, which belongs to the nuclear receptor family, and exerts its function as a transcription factor regulating several target genes. Active metabolites of vitamin D play an important role in calcium and phosphate homeostasis. Deficiency of vitamin D results in diminished bone mineralization and an increased risk of fractures. In addition, vitamin D is connected to a variety of other diseases that include different cancer types, muscular weakness, hypertension, autoimmune diseases, multiple sclerosis, type 1 diabetes, schizophrenia and depression.

Conclusions. Vitamin D plays a fundamental role in calcium and phosphate homeostasis. A deficiency of vitamin D has been attributed to several diseases. Since its production in the skin depends on exposure to UVB-radiation via the sunlight, the level of vitamin D is of crucial importance for the health of inhabitants who live in the Nordic latitudes where there is diminished exposure to sunlight during the winter season. Therefore, fortification or supplementation of vitamin D is necessary for most of the people living in the northern latitudes during the winter season to maintain adequate levels of circulating 25(OH)D₃ to maintain optimal body function and prevent diseases. (*Int J Circumpolar Health* 2008; 67(2-3):164-178)

Keywords: Vitamin D, northern latitudes, vitamin D deficiency

INTRODUCTION

Vitamins, organic compounds essential for metabolic reactions in living organisms, cannot be endogenously synthesized and therefore must be obtained from our diets. Among the vitamins, vitamin D is an exception. Vitamin D can be synthesized by the skin when exposed to UVB radiation. Therefore, inhabitants of northern latitudes with a short daylight period during the winter season are at considerable risk of experiencing vitamin D deficiency. Such a deficiency could contribute to numerous diseases and to a deteriorated well-being unless vitamin D is supplemented by nutritional sources. In this review, we focus on vitamin D metabolism, diseases associated with inadequate levels of circulating $25(\text{OH})\text{D}_3$ and the current recommended intake.

The name “vitamin D” refers to the group of compounds possessing antirachitic activity. With relation to its health effects, the most

important forms of vitamin D are cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2), which are formed when our skin is exposed to the sun or obtained from food products. These forms differ in the composition of the side chains (Fig. 1).

The most established physiological function of calcitriol or $1\alpha,25(\text{OH})_2\text{D}_3$ is to maintain serum concentrations of calcium and phosphate in the optimal range, supporting cellular processes like neuromuscular function and bone ossification. $1\alpha,25(\text{OH})_2\text{D}_3$ enhances the efficiency of the intestinal absorption of calcium and phosphate as well as the mobilization of calcium and phosphate stored in the bones (1).

Vitamin D metabolism

Pre-vitamin D_3 is formed in the basal and suprabasal layers of skin epithelial cells from 7-dehydrocholesterol (7-DHC, an immediate precursor of the cholesterol biosynthetic pathway) by a photochemical reaction by UVB

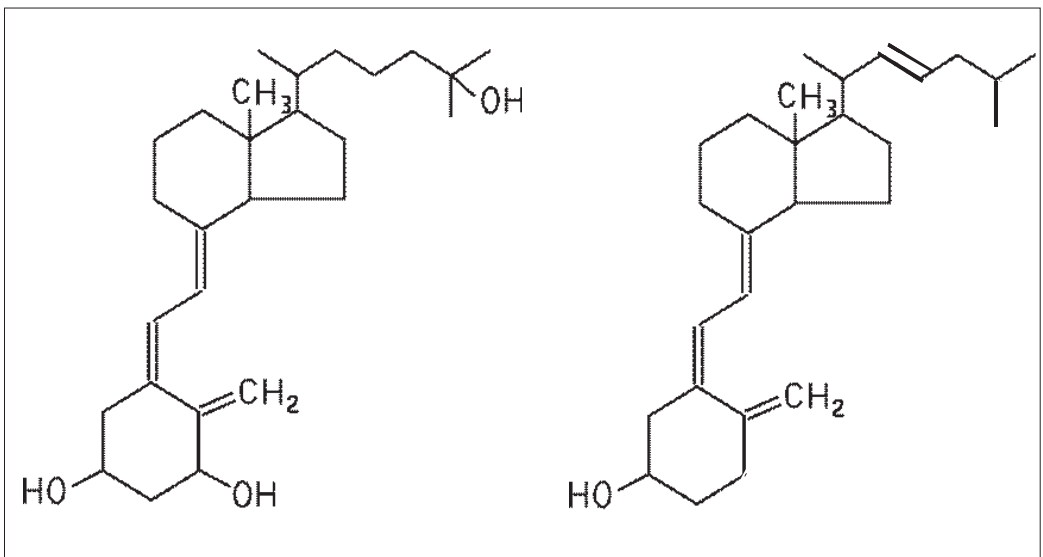


Figure 1. Molecular structures of vitamin D_3 (left) and vitamin D_2 (right).

radiation (wavelength 290–315 nm) (1). The unstable isomers of pre-vitamin D₃ are isomerized to vitamin D₃. However, prolonged exposure does not produce excess amounts of vitamin D₃, since the pre-vitamin is degraded to the biologically inert isomers, lumisterol and tachysterol (1). Vitamin D₃ is then bound to a vitamin D binding protein (DBP) as a carrier protein and transported to the liver, where it is converted into 25-hydroxyvitamin D₃ (calcidiol, 25(OH)D₃) by vitamin D-25-hydroxylase (CYP27A1). Several cytochrome p450 isoforms have been shown to possess vitamin D-25-hydroxylase activity (2). Although 25(OH)D₃ is the major circulating form of vitamin D, it is biologically inert in physiological concentrations (1). Free concentrations of 25(OH)D₃ or 1,25(OH)₂D₃ are very low due to the high binding affinity of DBP (3). 25(OH)D₃ is further hydroxylated to the hormonally active 1 α ,25-dihydroxyvitamin D₃

(1 α ,25(OH)₂D₃ or calcitriol) by 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) in the kidneys. However, extrarenal hydroxylation to 1 α ,25(OH)₂D₃ occurs also in several other tissues including the prostate, colon, lung, pancreatic β -cells, monocytes and parathyroid cells. It is most likely that extrarenal hydroxylation acts primarily as an autocrine/endocrine factor with cell-specific functions (4).

Synthesis and metabolism of 1 α ,25(OH)₂D₃ are tightly regulated. Excess amounts of circulating 25(OH)D₃ can be stored (in adipose tissue), metabolized or activated directly. The regulation involves feedback loops between serum 25(OH)D₃ levels, calcium and parathyroid hormone (PTH) concentrations (Fig. 2). The most crucial step in the metabolism is the activation of 25(OH)D₃ in the kidneys. The 25(OH)D₃-1 α -hydroxylase is directly stimulated by PTH and inhibited by calcium or inorganic phosphate (1), while 1 α ,25(OH)₂D₃

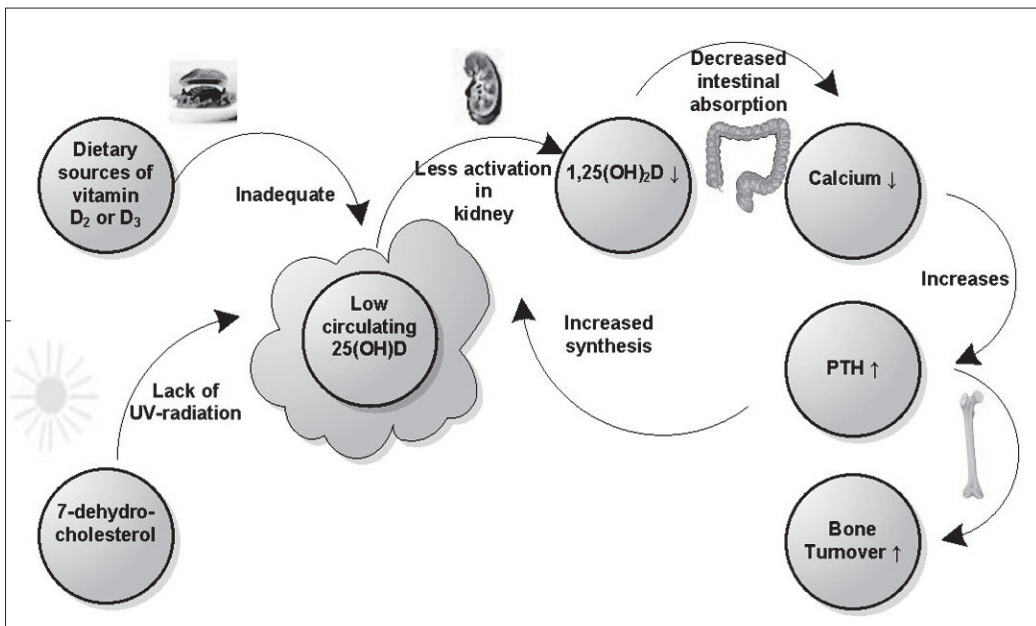


Figure 2. Pathophysiology of low vitamin D metabolites and its consequences on bone metabolism.

decreases PTH mRNA expression (5). Calcium and phosphate regulate synthesis and secretion of PTH, and PTH regulates serum concentration of those ions. $1\alpha,25(\text{OH})_2\text{D}_3$ has independent effects on calcium and phosphate levels and participates in feedback loops between $1\alpha,25(\text{OH})_2\text{D}_3$ and PTH. $1\alpha,25(\text{OH})_2\text{D}_3$ increases blood calcium by increasing the efficiency of intestinal and renal absorption. The promoter region of PTH contains vitamin D binding sites (6), contributing to the negative regulation of the PTH gene by $1\alpha,25(\text{OH})_2\text{D}_3$.

The vitamin D receptor

The vitamin D receptor (VDR) belongs to the nuclear receptor superfamily. VDR is a $1,25(\text{OH})_2\text{D}_3$ -activated transcription factor interacting with coregulators and the transcription the pre-initiation complex to regulate transcription of target genes. Activation of the VDR for gene transcription requires the following

two steps: (1) After ligand binding, the VDR is heterodimerized with a retinoid X receptor (RXR) with subsequent binding to the vitamin D response element (VDRE) in the promoter region of target genes (7). (2) Cofactors function as a bridge between VDR-RXR-complex and basal polymerase machinery in the transcriptional pre-initiation complex, leading to the activation or suppression of target gene expression. A number of coactivators or corepressors have been identified as regulators of gene transcription induced by VDR-RXR (8). A list of target genes of $1\alpha,25(\text{OH})_2\text{D}_3$, including CYP27 and PTH, is presented in Table I.

Analogues of $1\alpha,25(\text{OH})_2\text{D}_3$ have been developed as potential drugs to treat various diseases, for example, prostate cancer. Currently, more than 2,000 synthetic analogues of vitamin D are known (9). However, the hypercalcemic effect of these analogues restricts their therapeutical use (10).

Table I. Vitamin D target genes.

Upregulation	Function	Downregulation	Function
Osteocalcin	Bone formation	IL-1	Cytokine
Osteopontin	Bone metabolism	IL-12	Cytokine
RANKL	Osteoclast development	TNF- α	Cytokine
Calbindin-9k	Cytosolic calcium binding protein	IFN- γ	Cytokine
24-hydroxylase	Vitamin D synthesis	GM-CSF	Cytokine
mCYP3A11	Metabolism	EGF-R	Growth factor receptor
rCYP3A1	Metabolism	c-myc	Oncogene
hCYP3A4	Metabolism	K16	Structural integrity of epithelial cells
β 3 integrin	Cell adhesion	CYP27	Vitamin D synthesis
Involucrin	Structural keratinocyte protein	PTH	Metabolism
P21	Cell cycle regulation	PTHrP	Growth and bone formation
PLC γ 1	Cell proliferation	Rel B	Transcription factor
IGFBP-3	Cell growth regulation		

Note: Upregulated genes contain positive VDRE in the promoter region, whereas downregulation may occur via negative VDRE or by antagonism of transcription factor (e.g., anti-NF-AT and anti-NF- B). (For an additional list, see reference 8).

Vitamin D and bone

Deficiency of vitamin D is known to result in rickets during childhood development and in undermineralized bone or osteomalacia during adulthood. The beneficial effect of sunlight on bone mineralization has been known for centuries, but the biochemical basis for that has not been known for long (8). The optimal vitamin D level is defined as a level of vitamin D intake or synthesis of $1\alpha,25(\text{OH})_2\text{D}_3$ that is high enough to maintain calcium levels and prevent secondary hyperparathyroidism (11).

Osteoporosis is defined as a loss of bone mass and microarchitectural deterioration of the skeleton leading to increased risk of fracture (12). It is at least in part a consequence of a lack of vitamin D in the diet, as the circulating concentrations of $25(\text{OH})\text{D}_3$ above 75 nmol/l have been identified to be effective in the prevention of fractures (13). Osteoporotic fractures result from the combination of reduced bone strength and an increased rate of falls (14). Furthermore, increased age possesses an increased risk of osteoporosis, especially among postmenopausal women due to the additional decrease in estrogen levels (15). It has been estimated that more than 200 million women worldwide have osteoporosis (16), thus creating a major health concern and economical burden and an urgent need for low-cost, effective and well-tolerated therapy.

Epidemiological studies revealed that the prevalence of hip fractures has been the highest in North American and Scandinavian countries (14,16). In Europe, there are huge differences in the prevalence of fractures within different populations, with the highest risks found in Norway and Hungary (16,17). The risk of fractures has been approximately seven times lower in the southern parts of Europe

compared with the Nordic countries (14, 16). The epidemic is also a concern in other parts of world (18).

Vitamin D supplementation (cholecalciferol) might be a promising, effective and well-tolerated therapy with a low toxicity (19). Therefore, several clinical trials have been conducted to assess the efficacy of vitamin D supplementation in the prevention of osteoporosis (reviewed more in detail in 13,19,20). The results of the different trials are summarized in Table II. These studies demonstrate that administration of vitamin D (>20 µg (800 IU) per day) decreased the risk of fractures (13,21,22). In addition, deficiency of vitamin D followed by secondary parathyroidism predisposes an individual to accidents due to proximal myopathy (23,24).

Vitamin D and other diseases

In addition to its importance on bone formation and metabolism, vitamin D deficiency has been associated with a variety of other diseases such as various cancers, muscular weakness, hypertension, autoimmune diseases, multiple sclerosis, type 1 diabetes, schizophrenia and depression. Furthermore, vitamin D has been shown to be involved in the development of Th1-cell driven autoimmune diseases (25) by decreasing the secretion of certain cytokines, including IFN- γ and IL-2.

The connection between vitamin D and cancer is well established. Schwartz et al. demonstrated that prostate cells convert $25(\text{OH})\text{D}_3$ to $1\alpha,25(\text{OH})_2\text{D}_3$ (26). The same activity has been found in a variety of cells, including normal and malignant colon (27) and lung cells (28). In these tissues, $1\alpha,25(\text{OH})_2\text{D}_3$ acts in an autocrine fashion regulating cell

Table II. List of studies indicating a preventive effect of vitamin D (and calcium) supplementation on the incidence of osteoporosis and fractures.

Source	No. of participants (men and women)	Location	Vitamin D ($\mu\text{g/day}$)	Calcium (mg/day)	Age (mean)	Baseline and follow-up -25(OH)D Mean (SD) nmol/l		Duration (months)	Assay method for 25(OH)D	Outcome
Chapuy 1992 (95)	3,270	France	20	1,200	84	40 \pm 20.75	105 \pm 22.5	18	Competitive protein-binding assay	Incidence of fractures decreased from 97 to 66 ($p=0.015$)
Dawson-Hughes 1997 (96)	389	USA	17.5	500	70.5	76.5 \pm 37.0	112 \pm 36.8	36	Competitive protein-binding assay	Incidence of fractures decreased from 12.9% to 5.6% ($p=0.02$)
Trivedi 2003 (97)	2,686	United Kingdom	20	*	76	53.4 \pm 21.1	74.3 \pm 20.7	60	Assay method not mentioned	Relative risk effect of vitamin D RR (95% CI) 0.67 (0.46–0.99)
Meyer 2002 (98)	1,144	Norway	10	*	85	47 \pm 26	64 \pm 21 26	24	High performance liquid chromatography	Relative risk effect of vitamin D RR (95% CI) 0.92 (0.68–1.24)
Pfeifer 2000 (99)	137	Germany	17.5	1,200	71	25.7 \pm 13.6	66.1 \pm 33.1	2**	Radioimmunoassay (Nichols Institute, CA, U.S.A.)	Relative risk effect of vitamin D RR (95% CI) 0.48 (0.13–1.78)
Lips 1996 (100)	2,578	Netherlands	10	*	80	27 (IQR 19–36) ***	62 52-70 (IQR 52-70)	36–41	Competitive protein binding assay	Relative risk effect of vitamin D RR (95% CI) 1.10 (0.87–1.39)

*No additional calcium supplementation.

**Months of treatment with 10 months of follow-up.

***IQR interquartile range.

growth. In support of the functional role of $1\alpha,25(\text{OH})_2\text{D}_3$ in cancer, epidemiological studies have revealed a vitamin D deficiency in patients with prostate (29) and colon cancer (30,31,32). $1\alpha,25(\text{OH})_2\text{D}_3$ causes accumulation of prostate cells in the G1-phase of the cell cycle (33,34) in addition to the induction of apoptosis (35). Surprisingly, Tuohimaa et al. reported in an epidemiological study in Nordic countries that high plasma $25(\text{OH})\text{D}_3$ levels were also associated with an increased risk of prostate cancer (36). However, the study could not define whether the observed higher risk of prostate cancer was due to higher concentrations of circulating $25(\text{OH})\text{D}_3$ or to some other lipid-soluble compounds obtained from a diet rich in vitamin D since, for example, vitamin A has been shown to be associated with an increased risk of prostate cancer.

Supplementation of vitamin D has been shown to inhibit experimentally induced colon cancer in rat models (37,38), and an inverse association between colorectal cancer and vitamin D intake has been described in a multi-ethnic cohort study (39). Induction of detoxifying enzymes for secondary bile acids like lithocholic acid – known colonic carcinogens – are believed to be the molecular mechanism of this inhibitory effect.

The connection between type 1 diabetes and vitamin D intake has remained controversial. Some reports support the finding that adequate supplementation of vitamin D decreases the incidence of type 1 diabetes (40,41). Lower levels of circulating $25(\text{OH})\text{D}_3$ have been found in young patients with type 1 diabetes (42,43). However, in another study, such a correlation could not be shown, suggesting other additional factors are involved in the pathophysiology of type 1 diabetes (44).

An association between UV radiation, vitamin D intake and multiple sclerosis (MS) has been suggested by an epidemiological study (45). Furthermore, Kampman et al. recently demonstrated that outdoor summer activities for children and adolescents living above the Arctic Circle were associated with a decrease in the risk of developing MS (46).

Vitamin D intake and diet

Natural sources of vitamin D_3 include fish, offal such as liver and egg yolk. Mushrooms are the only plant food containing small amounts of vitamin D_2 (47). In meat and animal products, vitamin D is present as vitamin D_3 . Therefore, diet composition affects vitamin D intake. Consequently, vegans and lacto vegetarians have a low vitamin D intake compared with omnivores (48). Food sources containing naturally high amounts of vitamin D are presented in Table III. In 2003, the Finnish Ministry of Social Affairs and Health recommended fortification of milk with vitamin D_3 by $0.5 \mu\text{g}/\text{dl}$ and margarines and butter by $10 \mu\text{g}/100 \text{g}$, but not yogurts. The effect of these fortifications have been documented in a recent study by Laaksi and colleagues in which they documented increased $25(\text{OH})\text{D}_3$ levels in young Finnish men (49) and 4-year-old children (50). In the United Kingdom and Canada, the fortification of margarine is mandatory (51), whereas in Finland, milk and butter/margarines are not required to be fortified (52). In Finland, consumption of a litre of milk contains only $5 \mu\text{g}$ vitamin D_3 , which represents 50% to 75% of the recommended dose. In Canada, milk is more strongly fortified and provides 44% of the recommended dose ($10 \mu\text{g}$) in 250 ml (51). In the U.S., orange juice, cereals, bread and yogurt are allowed to be fortified with

vitamin D, while milk is required to be fortified maximally with 42 IU/ 100 g (1.05 µg/ 100 g) (51,53). The form of dietary vitamin D is important when considering fortification. Both forms of vitamin D₂ and vitamin D₃ are absorbed equally, but vitamin D₃ is capable of maintaining higher levels of serum 25(OH)D₃ for a longer time due to a more rapid metabolism and clearance of vitamin D₂ (54).

The optimal vitamin D dietary intake is discussed widely and controversially in the literature (55–61). Most national recommendations are based on U.S. recommendations (47). Nordic and U.S. recommendations are presented in Table II. However, regardless of the recommendations, vitamin D deficiency remains a common epidemic in many countries because intake of the vitamin and exposure to sunlight are significantly lower than recommended (59,62–66). Furthermore, it seems physicians are not addressing the problem in spite of the overwhelming evidence (67,68). In a recent study, Elina Hyppönen and Chris Power concluded that the “prevalence of hypovitaminosis D in the general population was alarmingly high during the winter and spring, which warrants action at a population

level rather than at a risk group level” (69).

The total intake of vitamin D has been difficult to estimate, since circulating levels of 25(OH)D₃ are the product of dietary intake and exposure to sunlight. 25(OH)D₃ is the major circulating metabolite of vitamin D, and it has been widely used as a marker of endogenous and exogenous intake of vitamin D. However, additional biomarkers for sufficient vitamin D status are available, such as PTH concentration or bone mineral density (55,57). There is an inverse correlation between 25(OH)D₃ and PTH levels. Serum concentrations of 25(OH)D₃ that are lower than 20 nmol/l are considered as vitamin D deficient, levels of 40–80 nmol/l are insufficient and levels of 100–120 nmol/l are optimal (55), while others have claimed that serum levels of 25(OH)D₃ below 80 nmol/l are already deficient (56). If bone mineral density is considered to be a determinant of sufficient levels of vitamin D, then circulating levels of 90–100 nmol/l are considered to be optimal (57). In a recent editorial, it was concluded that in order to maintain optimal health and prevent disease, the circulating levels of 25(OH)D₃ must exceed 75 nmol/l (corresponding to 30 ng/ml) (58).

Table III. Food sources containing the highest natural amounts of vitamin D₃.

Food name	Vitamin D (µg/100 g)	Calcium (mg/100g)	Reference
Haddock liver oil	500	1	(101)
Cod liver oil	250	1	(101)
Cod liver	100	10	(101)
Eel	25.6	19	(102)
Whitefish	22.1	60	(102)
Smoked fatty fish, average	14.0	26.8	(102)
Fish average (baltic herring, vendace, perch, pike)	10.3	96.4	(102)
Salmon fillet	8	16	(102)
Tuna	7.2	16	(102)
Egg yolk, raw	6.5	140	(102)

Note: Data combines the Danish Food Composition Databank (http://www.foodcomp.dk/fcdb_complist.asp) (101) and the Fineli Finnish Food Composition Database (<http://www.fineli.fi/topfoods.php?lang=fi>) (102).

In northern latitudes, seasons strongly affect circulating levels of 25(OH)D₃. During the winter season, levels of the serum 25(OH)D₃ decrease and increase during the summer months (65,70,71). In Finland, one-third of the young adult population was vitamin D deficient during the winter (February to March, latitude 60°) (62). Recently, Andersen et al. investigated vitamin D serum levels in northern Europe (72). They found low levels in young adolescent girls with a median serum value of 25(OH)D₃ of 29.4 nmol/l and in elderly women of 40.7 nmol/l. These low values clearly affect bone health among other possible health related effects (73,74). The latitude of residence seems to be a very strong predictor of seasonal differences in vitamin D status (74,75). At the 61° latitude in Norway, sunlight does not promote vitamin D synthesis during the 6 winter months (75). Interestingly, in some parts of northern Norway (latitude 69°), there are communities consuming high amounts of the traditional Norwegian fish dish “Mølje,” a meal consisting of cod, hard roe, cod liver and fresh cod-liver oil. Even a single meal of “Mølje” increases the levels of plasma 25(OH)D₃. In addition, consumption of cod-liver oil as a supplementary vitamin D source plays a beneficial role by significantly increasing levels of plasma 25(OH)D₃ (75,76). Surprisingly, in one study, serum 25(OH)D₃ concentrations among postmenopausal women in different European countries were higher in northern Europe when compared with countries in southern Europe (77). The authors speculated that Nordic women might have higher rates of

vitamin D production due to their the lighter skin being exposed to the sun and a higher consumption of multivitamin products in the northern European diet.

Several studies indicate that vitamin D deficiency is a very common finding not only in elderly people living in northern latitudes but also in adolescent girls (52,63,72,74,75,78–80). This deficiency has been observed even in spite of a higher nutrient-based intake via traditional food products in the elderly population (52). However, the recommended vitamin D intake for adults 50 years and older is higher (Table IV) and thus the dietary intake remains inadequate, especially among elderly women (64). Elderly people have a higher risk of deficiency due to the decreased capacity of their skin to produce adequate amounts of vitamin D. Atrophic changes in ageing skin reduce the capacity to synthesize vitamin D, combined with a reduced amount of 7-dehydrocholesterol (24,81,82). Furthermore, absorption of vitamin D from food products diminishes with age (81,83).

It has also been shown that obesity correlates with vitamin D deficiency. Carlin and co-workers demonstrated recently in a large group of morbidly obese patients that 166 out of 279 had vitamin D depletion (≤ 20 ng/ml) (84). Furthermore, vitamin D depletion was significantly more prevalent in African-American patients than in white patients, indicating that African-Americans have an additional risk because of their skin pigmentation (84). Wortsman et al. demonstrated that after 24 hours of whole body UV-B exposure or after oral intake of vitamin D₂ the amount of vitamin D₃ was significantly lower in obese compared with non-obese subjects (85).

Table IV. Current recommended dietary vitamin D intake in different age groups.

Nordic recommendations*		U.S. recommendations*	
Age	Vitamin D intake	Age	Vitamin D intake
6–23 months	10 µg / 400 IU		
2–9 years	7.5 µg/ 300 IU	0–13	5 µg/ 200 IU
10–60 years	7.5 µg/ 300 IU	14–18	5 µg/ 200 IU
		19–50	5 µg/ 200 IU
>60 years	10 µg/ 400 IU	51–70	10 µg / 400 IU
		>70	15 µg/ 600 IU
Pregnant and lactating women	10 µg/ 400 IU		

Sources: See references 58, 91, 93, 94.

*Newer studies have clearly indicated that the currently recommended dose of vitamin D is too low when compared with the outcome of recent clinical trials (58). In addition, the margin of safety (hypercalcemia) is several times higher than the intake of any of the current recommendations (91).

Table V. Measured circulating levels of serum 25(OH)D₃ in northern latitudes.

Characteristics of the study group	Ref.	Country	Latitude (°)	Age (years ± SD ¹)	Serum 25(OH)D ₃ (nmol/l ± SD)	Vitamin D intake (µg/day ± SD ¹)	n
Middle-aged women	(75)	Norway	65–71	51.6 ± 4.2	56.9	8.1	300
Postmenopausal women with osteoporosis	(77)	Finland	60–64	65.9 ± 6.0	71.2 ± 26.1	n.a. ²	139
		Norway	59–70	67.3 ± 5.9	89.6 ± 29.3	n.a.	848
		Sweden	57–62	68.2 ± 5.9	86.0 ± 26.8	n.a.	125
		Canada	44–54	65.4 ± 6.9	76.3 ± 30.3	n.a.	425
Healthy adult women	(62)	Finland	~60	38 ± 3	47 ± 34	4.7 ± 2.5	202
Children							
Prior fortification	(50)	Finland	60–70	4	54.7 (51.0–58.4) ³	2.1 (1.9–2.3) ³	82
After fortification					64.9 (59.7–70.1) ³	4.5 (3.8–5.1) ³	36
Healthy men	(49)	Finland	60–70	18–28	33.5 ± 9.2	n.a.	96
Prior fortification							
After fortification					50.2 ± 20.3	7	100
Inuits in Nuuk, Western fare Summer	(103)	Greenland	64	36	32 ± 2 ⁴	n.a.	32
Winter					29 ± 2 ⁴	n.a.	

¹Mean ± standard deviation.

²Not analysed.

³Mean (95% confidence interval).

⁴Mean ± standard error of the mean (SEM).

Vitamin D toxicity

Vitamin D accumulates in the adipose tissue when ingested in excess amounts. The definition for overdosing is based on levels of serum 25(OH)D₃. However, it is currently unclear at which concentration the optimal range is exceeded (86). A Vitamin D overdose causes hypercalcemia, dehydration and tissue calcification (60).

In North America and Europe, the tolerable upper intake dose of vitamin D₃ (cholecalciferol) is defined as 50 µg daily, not including the endogenous production. It has been suggested that circulating levels higher than 200 nmol/l are toxic (86). The accumulated effects of multiple supplements taken together are most often the cause. Adams and Lee (87) investigated 39 upper-middle-class patients in West Los Angeles (34 to 80 years, 37 were white and 32 were women) referred by their primary health care providers for possible osteoporosis or low bone mineral density. Four patients were found to have hypercalciuria and elevated levels of serum 25(OH)D₃. These 4 patients used multiple dietary supplements simultaneously in addition to calcium (mean 4.6 supplements, range 3–8) and possibly fortified food products. Therefore, health care professionals should consider the possibility of overdosing when prescribing or recommending supplements (88).

The optimal circulating levels are considered to be concentrations between 90 and 120 nmol/l (56–58,86,89), creating a narrow therapeutic window. Nevertheless, even prolonged consumption of 100 µg/day for 3 months, which is double the recommended tolerable upper intake and defined as the lowest observed adverse effect level (LOAEL) based on the results by Narang et al. (90), did

not increase the circulating concentrations of 25(OH)D₃ above 96 nmol/l (91). Therefore, it is very unlikely that circulating concentrations of 25(OH)D₃ will reach the toxic range when vitamin D is solely produced by the skin or obtained by nutritional sources, as its production is highly regulated by the degradation of vitamin D and its precursors (86).

Summary

Vitamin D is a steroid-structured hormone obtained from nutritional sources or produced endogenously in the skin when exposed to UVB-radiation. It is essential for health and body maintenance. The active form of vitamin D, 1α,25(OH)₂D₃, is essential for the regulation of calcium and phosphate homeostasis. Deficiency of vitamin D results in several disorders, including osteoporosis, rickets and secondary hyperparathyroidism. Insufficient vitamin D levels have been associated with muscular weakness, autoimmune diseases, type 1 diabetes and various types of cancers. Epidemiological data have clearly shown an epidemic of vitamin D deficiency among clearly defined risk groups: obese, elderly, children and people with dark skin colour.

In the northern latitudes, solar radiation is not sufficient for vitamin D synthesis for nearly half of the year (winter season). Therefore, it must be obtained from nutritional sources. Only animal products contain sufficient vitamin D, yet adequate plasma levels are difficult to obtain from our normal daily “Western style” diet. Therefore, fortification or supplementation of vitamin D is necessary for most people living in the northern latitudes during the winter season in order to maintain adequate levels of circulating 25(OH)D₃ that support optimal body function and prevent

diseases. However, during the summer season, the increased sunlight produces enough vitamin D. Therefore, the amount of fortification or supplementation of vitamin D requires seasonal variation. The current recommendations need reconsideration, as the current recommended intakes (Table IV) are not sufficient to maintain the optimal vitamin D levels in the body (58).

In Finland, general fortification of milk products with vitamin D began in 2003, resulting in a clear improvement of the vitamin D levels among the population. Adequate supplementation of vitamin D together with calcium would be even more economically beneficial in the prevention of fractures. It has been estimated that adequate supplementation of vitamin D would even yield in a financial benefit of 79,000 to 711,000 euros per 1,000 treated women (22).

Furthermore, increased attention to the education of the general population and, in particular, health care professionals on vitamin D intake, metabolism and health effects would improve the quality of life for much of the population and produce a significant reduction in the economic burden of deficiency-related diseases on societies and communities living in the northern latitudes (Table V). Newer studies have clearly indicated that the current recommendations for vitamin D supplementation are too low as demonstrated by the outcome of a recent clinical trial (91). In addition, the margin of safety (hypercalcemia) is several times larger than the intakes of any of the current recommendations (58). Yet caution must be taken when multiple vitamin supplements are taken simultaneously without any further considerations, but even in those cases, documented toxicity is sparse in the scientific literature (87,92).

REFERENCES

1. Feldman D, Pike JW, Glorieux F editors. Vitamin D. 2nd ed. San Diego, CA: Academic Press; 2006. 1952 pp.
2. Prosser DE, Jones G. Enzymes involved in the activation and inactivation of vitamin D. *Trends Biochem Sci* 2004;29:664–673.
3. Vieth R. Simple method for determining specific binding capacity of vitamin D- binding protein and its use to calculate the concentration of “free” 1,25-dihydroxyvitamin D. *Clin Chem* 1994;40:435–441.
4. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol* 2005;289:F8–F28.
5. Silver J, Naveh-Many T, Mayer H, Schmelzer HJ, Popovtzer MM. Regulation by vitamin D metabolites of parathyroid hormone gene transcription in vivo in the rat. *J Clin Invest* 1986;78:1296–1301.
6. Mackey SL, Heymont JL, Kronenberg HM, Demay MB. Vitamin D receptor binding to the negative human parathyroid hormone vitamin D response element does not require the retinoid x receptor. *Mol Endocrinol* 1996;10:298–305.
7. Carlberg C, Seuter S. The Vitamin D Receptor. *Dermatol Clin* 2007;25:515–523.
8. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* 2005;26:662–687.
9. Carlberg C. Molecular basis of the selective activity of vitamin D analogues. *J Cell Biochem* 2003;882:274–281.
10. Masuda S, Jones G. Promise of vitamin D analogues in the treatment of hyperproliferative conditions. *Mol Cancer Ther* 2006;5:797–808.
11. Need AG. Bone resorption markers in vitamin D insufficiency. *Clinica Chimica Acta* 2006;368:48–52.
12. Consensus Development Conference: prophylaxis and treatment of osteoporosis. *Am J Med* 1991;90:107–110.
13. Vieth R. The role of vitamin D in the prevention of osteoporosis. *Ann Med* 2005;37:278–285.
14. Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006;367:2010–2018
15. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts and prospects. *J Clin Invest* 2005;115:3318–3325.
16. Lane NE. Epidemiology, etiology and diagnosis of osteoporosis. *Am J Obstet Gynecol* 2006;194(2 Suppl):S3–S11.
17. Roy DK, Pye SR, Lunt M, O’Neill TW, Todd C, Raspe H et al. Falls explain between-center differences in the incidence of limb fracture across Europe. *Bone* 2002;31:712–717.
18. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726–1733.
19. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005;293:2257–2264.

20. Boonen S, Vanderschueren D, Haentjens P, Lips P. Calcium and vitamin D in the prevention and treatment of osteoporosis – a clinical update. *J Intern Med* 2006; 259:539–552.
21. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res* 2004;19:370–378.
22. Lilliu H, Pamphile R, Chapuy M, Schulten J, Arlot M, Meunier PJ. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. *Maturitas* 2003;44:299–305.
23. Holick MF. Vitamin D: importance in the prevention of cancers, type I diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004;79:362–371.
24. Mosekilde L. Vitamin D and the elderly. *Clin Endocrinol (Oxf)* 2005;62:265–281.
25. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis and inflammatory bowel disease. *Prog Biophys Mol Biol* 2006;92:60–64.
26. Schwartz GG, Whitlatch LV, Chen TC, Lokeshwar BL, Holick MF. Human prostate cells synthesize 1,25-dihydroxyvitamin D3 from 25-hydroxyvitamin D3. *Cancer Epidemiol Biomarkers Prev* 1998;7:391–395.
27. Tangpricha V, Flanagan JN, Whitlatch LV, Tseng CC, Chen TC, Holt PR et al. 25-hydroxyvitamin D-1[alpha]-hydroxylase in normal and malignant colon tissue. *Lancet* 2001;357:1673–1674.
28. Mawer E, Hayes M, Heys S, Davies M, White A, Stewart MF, et al. Constitutive synthesis of 1,25-dihydroxyvitamin D3 by a human small cell lung cancer cell line. *J Clin Endocrinol Metab* 1994;79:554–560.
29. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* 2000;11:847–852.
30. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* 1980;9:227–231.
31. Freedman DM, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. *Occup Environ Med* 2002;59:257–262.
32. Grant WB, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. *Anticancer Res* 2006; 26:2687–2699.
33. Zhuang S, Burnstein KL. Antiproliferative Effect of 1 α ,25-Dihydroxyvitamin D3 in human prostate cancer cell line LNCaP involves reduction of cyclin-dependent kinase 2 activity and persistent G1 accumulation. *Endocrinology* 1998;139:1197–1207.
34. Blutt SE, Allegretto EA, Pike JW, Weigel NL. 1,25-Dihydroxyvitamin D3 and 9-cis-retinoic acid act synergistically to inhibit the growth of LNCaP prostate cells and cause accumulation of cells in G1. *Endocrinology* 1997;138:1491–1497.
35. Blutt SE, McDonnell TJ, Polek TC, Weigel NL. Calcitriol-induced apoptosis in LNCaP cells is blocked by overexpression of Bcl-2. *Endocrinology* 2000;141:10–17.
36. Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int J Cancer* 2004;108:104–108.
37. Pence BC, Buddingh F. Inhibition of dietary fat-promoted colon carcinogenesis in rats by supplemental calcium or vitamin D3. *Carcinogenesis* 1988;9:187–190.
38. Kawaura A, Tanida N, Sawada K, Oda M, Shimoyama T. Supplemental administration of 1 alpha-hydroxyvitamin D3 inhibits promotion by intrarectal instillation of lithocholic acid in N-methyl-N-nitrosourea-induced colonic tumorigenesis in rats. *Carcinogenesis* 1989;10: 647–649.
39. Park S, Murphy S, Wilkens L, Nomura A, Henderson B, Kolonel L. Calcium and vitamin d intake and risk of colorectal cancer: the multiethnic cohort study. *Am J Epidemiol* 2007;165:784–793.
40. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type I diabetes: a birth-cohort study. *Lancet* 2001;358:1500–1503.
41. Vitamin D supplement in early childhood and risk for type I (insulin-dependent) diabetes mellitus. The EU-RODIAB Substudy 2 Study Group. *Diabetologia* 1999; 42:51–54.
42. Pozzilli P, Manfrini S, Crino A, et al. Low levels of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 in patients with newly diagnosed type I diabetes. *Horm Metab Res* 2005;37:680–683.
43. Littorin B, Blom P, Scholin A, Arnqvist HJ, Blohmé G, Bolinder J et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type I diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). *Diabetologia* 2006;49:2847–2852.
44. Viskari H, Kondrashova A, Koskela P, Knip M, Hyöty H. Circulating vitamin D concentrations in two neighboring populations with markedly different incidence of type I diabetes. *Diabetes Care* 2006;29:1458–1459.
45. VanAmerongen BM, Dijkstra CD, Lips P, Polman CH. Multiple sclerosis and vitamin D: an update. *Eur J Clin Nutr* 2004;58:1095–1109.
46. Kampman MT, Wilsgaard T, Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. *J Neurol* 2007; 254: 471–477.
47. Lamberg-Allardt C. Vitamin D in foods and as supplements. *Prog Biophys Mol Biol* 2006;92:33–38.
48. Outila TA, Kärkkäinen MU, Seppänen RH, Lamberg-Allardt CJ. Dietary intake of vitamin D in premenopausal, healthy vegans was insufficient to maintain concentrations of serum 25-hydroxyvitamin D and intact parathyroid hormone within normal ranges during the winter in Finland. *J Am Diet Assoc* 2000;100:434–441.

49. Laaksi IT, Ruohola JP, Ylikomi TJ, Auvinen A, Haataja RI, Pihlajamäki HK, et al. Vitamin D fortification as public health policy: significant improvement in vitamin D status in young Finnish men. *Eur J Clin Nutr* 2006;60:1035–1038.
50. Piirainen T, Laitinen K, Isolauri E. Impact of national fortification of fluid milks and margarines with vitamin D on dietary intake and serum 25-hydroxyvitamin D concentration in 4-year-old children. *Eur J Clin Nutr* 2007;61:123–128.
51. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr* 2004;80:1710S–1716.
52. Lamberg-Allardt CJ, Viljakainen H et al. Follow-up study on the vitamin D status in the Finnish population 2002 and 2004. Helsinki: Ministry of Social Affairs and Health; 2006. 49 pp.
53. Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol* 2006;92:49–59.
54. Armas LA, Hollis BW, Heaney RP. Vitamin D₂ is much less effective than vitamin D₃ in humans. *J Clin Endocrinol Metab* 2004;89:5387–5391.
55. Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr* 2005;135:304–309.
56. Hollis BW. Circulating 25-Hydroxyvitamin D Levels Indicative of Vitamin D Sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr* 2005;135:317–322.
57. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:18–28.
58. Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP et al. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr* 2007;85:649–650.
59. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: A global perspective of current status. *J Nutr* 2005;135:310–316.
60. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? *J Steroid Biochem Mol Biol* 2004;89-90:611–614.
61. Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *J Nutr* 2006;136:1117–1122.
62. Lamberg-Allardt CJ, Outila TA, Kärkkäinen MU, Rita HJ, Valsta LM. Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? *J Bone Miner Res* 2001;16:2066–2073.
63. Samuelson G. Dietary habits and nutritional status in adolescents over Europe. An overview of current studies in the Nordic countries. *Eur J Clin Nutr* 2000;54 Suppl 1:S21–28.
64. Jorde R, Bonaa KH. Calcium from dairy products, vitamin D intake, and blood pressure: the Tromsø Study. *Am J Clin Nutr* 2000;71:1530–1535.
65. Rapuri PB, Kinyamu HK, Gallagher JC, Haynatzka V. Seasonal changes in calciotropic hormones, bone markers, and bone mineral density in elderly women. *J Clin Endocrinol Metab* 2002;87:2024–2032.
66. Calvo MS, Whiting SJ. Prevalence of vitamin D insufficiency in Canada and the United States: importance to health status and efficacy of current food fortification and dietary supplement use. *Nutr Rev* 2003;61:107–113.
67. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;116:2062–2072.
68. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006;81:353–373.
69. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 years: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr* 2007;85:860–868.
70. Harris S, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr* 1998;67:1232–1236.
71. Maxwell JD. Seasonal variation in vitamin D. *Proc Nutr Soc* 1994;53:533–543.
72. Andersen R, Molgaard C, Skovgaard LT, Brot C, Cashman KD, Chabros E, et al. Teenage girls and elderly women living in northern Europe have low winter vitamin D status. *Eur J Clin Nutr* 2005;59:533–541.
73. Outila TA, Kärkkäinen MU, Lamberg-Allardt CJ. Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density. *Am J Clin Nutr* 2001;74:206–210.
74. Gerdhem P, Mallmin H, Akesson K, Obrant KJ. Seasonal variation in bone density in postmenopausal women. *J Clin Densitom* 2004;7:93–100.
75. Brustad M, Alsaker E, Engelsen O, Aksnes L, Lund E. Vitamin D status of middle-aged women at 65–71 degrees N in relation to dietary intake and exposure to ultraviolet radiation. *Public Health Nutr* 2004;7:327–335.
76. Brustad M, Sandanger T, Wilsgaard T, Aksnes L, Lund E. Change in plasma levels of vitamin D after consumption of cod-liver and fresh cod-liver oil as part of the traditional north Norwegian fish dish “Molje.” *Int J Circumpolar Health* 2003;62:40–53.
77. Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, et al. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. *J Clin Endocrinol Metab* 2001;86:1212–1221.
78. Ovesen L, Andersen R, Jakobsen J. Geographical differences in vitamin D status, with particular reference to European countries. *Proc Nutr Soc* 2003;62:813–821.
79. Kauppinen-Mäkelin R, Tähtelä R, Löyttyniemi E, Kärkkäinen J, Välimäki MJ. A high prevalence of hypovitaminosis D in Finnish medical in- and outpatients. *J Intern Med* 2001;249:559–563.

80. Brox J, Bjornstad E, Olausen K. Hemoglobin, iron, nutrition and life-style among adolescents in a coastal and an inland community in northern Norway. *Int J Circumpolar Health* 2003;62:130–141.
81. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* 1985;76:1536–1538.
82. Holick MF, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. *Lancet* 1989;2:1104–1105.
83. Ebeling PR, Sandgren ME, DiMaggio EP, Lane AWW, DeLuca HF, Riggs BL. Evidence of an age-related decrease in intestinal responsiveness to vitamin D: relationship between serum 1,25-dihydroxyvitamin D3 and intestinal vitamin D receptor concentrations in normal women. *J Clin Endocrinol Metab* 1992;75:176–182.
84. Carlin AM, Rao DS, Mesleman AM, Genaw JA, Parikh NJ, Levy S et al. Prevalence of vitamin D depletion among morbidly obese patients seeking gastric bypass surgery. *Surg Obes Relat Dis* 2006;2:98–103.
85. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;72:690–693.
86. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999;69:842–856.
87. Adams JS, Lee G. Gains in bone mineral density with resolution of vitamin D intoxication. *Ann Intern Med* 1997;127:203–206.
88. Marriott BM. Vitamin D supplementation: A word of caution. *Ann Intern Med* 1997;127:231–233.
89. Weaver CM, Fleet JC. Vitamin D requirements: current and future. *Am J Clin Nutr* 2004;80(6 Suppl):1735S–1739S.
90. Narang NK, Gupta RC, Jain MK. Role of vitamin D in pulmonary tuberculosis. *J Assoc Physicians India* 1984;32:185–188.
91. Vieth R, Chan PR, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001;73:288–294.
92. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85:6–18.
93. Nordic Council of Ministers. *Nordic Nutrition Recommendations 2004*. 4th ed. Århus: Nordic Council of Ministers; 2004. 21 pp.
94. Institute of Medicine. *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press; 1997. 448 pp.
95. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992;327:1637–1642.
96. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;337:670–676.
97. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;326:469.
98. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JL. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. *J Bone Miner Res* 2002;17:709–715.
99. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res* 2000;15:1113–1118.
100. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996;124:400–406.
101. Danish Institute for Food and Veterinary Research; 2005 [cited 2007 Jan 2]. Available from: http://www.foodcomp.dk/fcdb_complis.asp.
102. Kansanterveyslaitos; 2007 [cited 2007 Jan 2]. Available from: <http://www.fineli.fi/topfoods.php?lang=fi>.
103. Rejnmark L, Jorgensen ME, Pedersen MB, Hansen JC, Heickendorff L, Lauridsen AL, et al. Vitamin D insufficiency in Greenlanders on a westernized fare: ethnic differences in calcitropic hormones between Greenlanders and Danes. *Calcif Tissue Int* 2004;74:255–263.

*Professor Karl-Heinz Herzig
Institute of Biomedicine
Department of Physiology and Biocenter of Oulu
Oulu University Medical School
Aapistie 7, 90014 Oulu University
FINLAND
Email: karl-heinz.herzig@oulu.fi*