Vitamin D and living in northern latitudes

REVIEW ARTICLE

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

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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.

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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(OH)D₃ 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 D₃) and ergocalciferol (vitamin D₂), 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 1α,25(OH)₂D₃ is to maintain serum concentrations of calcium and phosphate in the optimal range, supporting cellular processes like neuromuscular function and bone ossification. 1α,25(OH)₂D₃ 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 D₃ 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 D₃ (left) and vitamin D₂ (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)D₃ are very low due to the high binding affinity of DBP (3). 25(OH)D₃ is further hydroxylated to the hormonally active 1α,25-dihydroxyvitamin D₃ (1α,25(OH)₂D₃ or calcitriol) by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) in the kidneys. However, extrarenal hydroxylation to 1α,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 1α,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)D₃-1α-hydroxylase is directly stimulated by PTH and inhibited by calcium or inorganic phosphate (1), while 1α,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. 1α,25(OH)₂D₃ has independent effects on calcium and phosphate levels and participates in feedback loops between 1α,25(OH)₂D₃ and PTH. 1α,25(OH)₂D₃ 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 1α,25(OH)₂D₃.

The vitamin D receptor

The vitamin D receptor (VDR) belongs to the nuclear receptor superfamily. VDR is a 1,25(OH)₂D₃-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 1α,25(OH)₂D₃, including CYP27 and PTH, is presented in Table I.

Analogs of 1α,25(OH)₂D₃ have been developed as potential drugs to treat various diseases, for example, prostate cancer. Currently, more than 2,000 synthetic analogs of vitamin D are known (9). However, the hypercalcemic effect of these analogs 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 |
| β3 integrin | Cell adhesion | CYP27 | Vitamin D synthesis |
| Involucrin | Structural keratinocyte protein | PTH | Metabolism |
| P21 | Cell cycle regulation | PTHrP | Growth and bone formation |
| PLC-γ1 | 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 \( \text{1α,25(OH)}_2\text{D}_3 \) 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 \( \text{25(OH)}_3\text{D} \) 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 \( \text{25(OH)}_3\text{D} \) to \( \text{1α,25(OH)}_2\text{D}_3 \) (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, \( \text{1α,25(OH)}_2\text{D}_3 \) 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 (µg/day) | Calcium (mg/day) | Age (mean) | Baseline and follow-up 25(OH)D Mean (SD) nmol/l | Duration (months) | Assay method | Outcome                                                                 |
|------------|-------------------------------------|-------------------|--------------------|------------------|------------|-----------------------------------------------|-----------------|----------------|------------------------------------------------------------------------|
| Chapuy 1992 (95) | 3,270                               | France            | 20                 | 1,200            | 84         | 40 ± 20.75                                   | 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 ± 37.0                                   | 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 ± 21.1                                   | 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 ± 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 ± 13.6                                   | 2**             | Radioimmuno-assay (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)                                | 36–41           | Competitive protein binding assay | Relative risk effect of vitamin D RR (95% CI) 1.10 (0.87–139) |

*No additional calcium supplementation.
**Months of treatment with 10 months of follow-up.
***IQR interquartile range.
growth. In support of the functional role of 1α,25(OH)₂D₃ in cancer, epidemiological studies have revealed a vitamin D deficiency in patients with prostate (29) and colon cancer (30,31,32). 1α,25(OH)₂D₃ 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(OH)D₃ 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(OH)D₃ 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(OH)D₃ 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 D₃ include fish, offal such as liver and egg yolk. Mushrooms are the only plant food containing small amounts of vitamin D₂ (47). In meat and animal products, vitamin D is present as vitamin D₃. 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 D₃ by 0.5 µg/dl and margarines and butter by 10 µg/100 g, but not yogurts. The effect of these fortifications has been documented in a recent study by Laakski and colleagues in which they documented increased 25(OH)D₃ 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 µg vitamin D₃, which represents 50% to 75% of the recommended dose. In Canada, milk is more strongly fortified and provides 44% of the recommended dose (10 µg) in 250 ml (51). In the U.S., orange juice, cereals, bread and yogurt are allowed to be fortified with
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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 D$_2$ and vitamin D$_3$ are absorbed equally, but vitamin D$_3$ is capable of maintaining higher levels of serum 25(OH)D$_3$ for a longer time due to a more rapid metabolism and clearance of vitamin D$_2$ (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)D$_3$ are the product of dietary intake and exposure to sunlight. 25(OH)D$_3$ 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)D$_3$ and PTH levels. Serum concentrations of 25(OH)D$_3$ 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)D$_3$ 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)D$_3$ 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)D$_3$. During the winter season, levels of the serum 25(OH)D$_3$ 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)D$_3$ 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)D$_3$. 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)D$_3$ (75,76). Surprisingly, in one study, serum 25(OH)D$_3$ 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 (< or= 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 D$_2$ the amount of vitamin D$_3$ was significantly lower in obese compared with non-obese subjects (85).
### Table IV. Current recommended dietary vitamin D intake in different age groups.

| Age                  | Vitamin D intake | Age                  | Vitamin D intake |
|----------------------|------------------|----------------------|------------------|
| 6–23 months          | 10 µg / 400 IU    | 0–13                 | 5 µg / 200 IU    |
| 2–9 years            | 7.5 µg / 300 IU   | 14–18                | 5 µg / 200 IU    |
| 10–60 years          | 7.5 µg / 300 IU   | 19–50                | 5 µg / 200 IU    |
| >60 years            | 10 µg / 400 IU    | 51–70                | 10 µg / 400 IU   |
| Pregnant and lactating women | 10 µg / 400 IU | >70                  | 15 µg / 600 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)D$_3$ 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 |
| 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      | (103)| Greenland| 64          | 36                   | 32±2$^4$                        | n.a.                            | 32  |
| Summer                            |      |         |              |                      | 29±2$^4$                        | n.a.                            |     |
| Winter                            |      |         |              |                      |                                 |                                  |     |

$^1$Mean ± standard deviation.

$^2$Not analysed.

$^3$Mean (95% confidence interval).

$^4$Mean ± 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
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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).

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