Review

Vitamin D and disease prevention with special reference to cardiovascular disease

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Abstract

Circulating 25-hydroxyvitamin D [25(OH)D] is the hallmark for determining vitamin D status. Serum parathyroid hormone [PTH] increases progressively when 25(OH)D falls below 75 nmol/l. Concentrations of 25(OH)D below 50 nmol/l or even below 25 nmol/l are frequently observed in various population groups throughout the world.

This paper highlights the relationship of vitamin D insufficiency with cardiovascular disease and non-insulin dependent diabetes mellitus, two diseases that account for up to 50% of all deaths in western countries. There is evidence from patients with end-stage renal disease that high PTH concentrations are causally related to cardiovascular morbidity and mortality. Activated vitamin D is able to increase survival in this patient group significantly. Moreover, already slightly enhanced PTH concentrations are associated with ventricular hypertrophy and coronary heart disease in the general population. Experimental studies have demonstrated that a lack of vitamin D action leads to hypertension in mice. Some intervention trials have also shown that vitamin D can reduce blood pressure in hypertensive patients. In young and elderly adults, serum 25(OH)D is inversely correlated with blood glucose concentrations and insulin resistance. Sun-deprived lifestyle, resulting in low cutaneous vitamin D synthesis, is the major factor for an insufficient vitamin D status. Unfortunately, vitamin D content of most foods is negligible. Moreover, fortified foods and over-the-counter supplements usually contain inadequate amounts of vitamin D to increase serum 25(OH)D to 75 nmol/l. As a consequence, legislation has to be changed to allow higher amounts of vitamin D in fortified foods and supplements.

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Keywords: Vitamin D; Parathyroid hormone; Cardiovascular; Hypertension; Diabetes mellitus

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Abbreviation: A, Austria; AL, Albania; B, Belgium; BG, Bulgaria; BY, Belarus; CZ, Czech; D, Germany; DK, Denmark; E, Spain; EST, Estonia; F, France; FIN, Finland; GR, Greece; H, Hungary; I, Italy; L, Luxembourg; LT, Lithuania; LV, Latvia; M, Malta; N, Norway; NL, Netherlands; P, Portugal; PL, Poland; S, Sweden; SLO, Slovenia; RUS, Russia; UKR, Ukraine

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1. Introduction

In the human body, cutaneously synthesized or orally ingested vitamin D is metabolized by a hepatic hydroxylase into 25-hydroxyvitamin D (25(OH)D) and by a renal 1α-hydroxylase into the vitamin D hormone 1,25 dihydroxyvitamin D (calcitriol). This step is under control of parathyroid hormone (PTH). Receptors for the vitamin D hormone (VDR) exist in a large number of different cells among them osteoblasts, myocytes, cardiomyocytes, pancreatic β-cells, vascular endothel cells, neurons, colonocytes, and immune cells. A cytosolic as well as a membrane-bound VDR has been identified. Calcitriol is an important regulator of systemic calcium metabolism, especially of serum calcium homeostasis. In this context, calcitriol is responsible for active calcium transport across the duodenal mucosa, for calcium resorption from bone, and for active calcium reabsorption in the kidney. Moreover, calcitriol is known as a regulator of intracellular calcium metabolism of various tissues and of cellular cytokine secretion. Calcitriol is also produced by local 1α-hydroxylases in various extra-renal tissues. Here, calcitriol plays an important autocrine role which has just been realized during recent years. Local calcitriol production depends on the level of circulating 25(OH)D.

In this article, the different stages of vitamin D status are explained first. Then, data on the vitamin D status of different population groups are presented in order to demonstrate that vitamin D deficiency/insufficiency is indeed a widespread problem. Since the association between vitamin D deficiency/insufficiency and various diseases such as bone diseases, different types of cancer, multiple sclerosis, and diabetes mellitus type I is described in detail in other articles of the issue, this paper has its focus on the relationship between vitamin D insufficiency with cardiovascular disease and non-insulin dependent diabetes mellitus. The two diseases account for up to 50% of all deaths in western countries (Federal Statistical Office, 2003) and mortality rate of these diseases is rapidly increasing in developing countries (Yusuf et al., 2001; Wild et al., 2004). At last, measures to improve vitamin D status are discussed.

2. Stages of vitamin D status

The different stages of vitamin D status can be classified as deficiency, insufficiency, hypovitaminosis, adequacy, and toxicity (Table 1). Vitamin D deficiency is characterized by a lack of the active vitamin D metabolite calcitriol in its target cells. Physiologic circulating 25(OH)D levels are necessary to satisfy the tissue’s requirement to produce an adequate amount of calcitriol. In the case of vitamin D deficiency, severe clinical symptoms such as rickets, osteomalacia, myopathy, severe secondary hyperparathyroidism (SHPT) (serum PTH > 65 pg/ml), and calcium malabsorption are seen. Moreover, renal synthesis of calcitriol becomes

<table>
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<th>Stages of vitamin D status</th>
<th>25(OH)D concentrations (nmol/l)</th>
<th>Biochemical/clinical symptoms</th>
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<tbody>
<tr>
<td>Deficiency</td>
<td>0–25</td>
<td>Severe hyperparathyroidism, calcium malabsorption, rickets, osteomalacia, myopathy</td>
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<tr>
<td>Insufficiency</td>
<td>&gt;25–50.0</td>
<td>Elevated PTH levels, low intestinal calcium absorption rates, reduced bone mineral density, subclinical myopathy</td>
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<tr>
<td>Hypovitaminosis D</td>
<td>&gt;50–70 to 100</td>
<td>Low body stores of vitamin D, slightly elevated PTH levels</td>
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<tr>
<td>Adequacy</td>
<td>70–100 to 250</td>
<td>No disturbances of vitamin D-dependent functions</td>
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<td>Toxicity</td>
<td>&gt;250</td>
<td>Intestinal calcium hyperabsorption, hypercalcemia</td>
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To convert values for 25-hydroxyvitamin D to ng/ml, divide by 2.50.
substrate dependent, i.e. dependent on the circulating 25(OH)D concentration. Based on results obtained in the 8th decade of the 20th century in elderly subjects, it has been hypothesized that a substrate-dependent reduction in serum calcitriol levels may occur if the circulating serum 25(OH)D level falls below 30–40 nmol/l (Lips, 2005). Recently performed studies support this concept also for other age groups. Children and young adults with mean 25(OH)D levels of 30 and 32 nmol/l in winter showed a significant increase in serum calcitriol in summer in parallel with a rise in serum 25(OH)D (Docio et al., 1998; Zittermann et al., 1998). Moreover, vitamin D supplementation resulted in a 25(OH)D rise of 39 nmol/l and a calcitriol increase of 36 pmol/l in women with initial serum 25(OH)D of 26 nmol/l (Pfeifer et al., 2001). On the other hand, serum calcitriol remained constant in subjects with initial serum 25(OH)D of approximately 50 nmol/l, despite a marked rise in serum 25(OH)D following vitamin D supplementation (Vieth et al., 2004).

In the insufficient stage, pathophysiological biochemical alterations such as mild hyperparathyroidism and low intestinal calcium absorption rates are present. However, severe clinical symptoms are usually not observed. The increase in serum PTH will stimulate renal synthesis of calcitriol in order to keep calcium absorption and serum calcium within normal limits (Lips, 2001). Consequently, serum calcitriol is maintained within normal limits at the expense of an increase of serum PTH (Lips et al., 1983). In vitamin D insufficient subjects, even the increase of serum PTH is usually within normal limits. As the maintenance of serum calcitriol and serum calcium is the outcome of a homeostatic control system, the negative relationship is visible between serum PTH and serum 25(OH)D and not serum calcitriol (Lips, 2005). Therefore, circulating 25(OH)D is the hallmark for determining vitamin D status. Hypovitaminosis D characterizes a stage, where the body stores of vitamin D are already un-physiologically low. Only minor functional alterations such as slightly elevated serum PTH levels are seen in this stage. In the stage of adequacy, no disturbances of vitamin D-dependent body functions occur, while toxicity is due to vitamin D-dependent adverse reactions such as calcification disease from the gut and net calcium resorption from bone leading to hypercalcemia.

In line with the above made statements on the different stages of vitamin D status, Thomas et al. (1998) have reported an inverse relationship between serum 25(OH)D and serum PTH in in-hospital patients who had 25(OH) levels in the range of 0–75 nmol/l (0–30 ng/ml) (Fig. 1). Serum PTH showed a progressive increase when serum 25(OH)D was below 27.5–37.5 nmol/l (11–15 ng/ml). Data are supported by several other studies: In 99 of 104 centenarians serum 25(OH)D was undetectable and severe SHPT (mean serum PTH levels: 123 pg/ml) was present (Passeri et al., 2003). It is also noteworthy that no case of SHPT...
(PTH > 65 pg/ml) was seen in elderly subjects with 25(OH)D levels above 100 nmol/l (Gomez-Alonso et al., 2003). Vieth et al. (2003) have demonstrated that no threshold does exist between serum 25(OH)D and serum PTH up to a 25(OH)D level of 150 nmol/l. They have also shown that elderly subjects have higher PTH levels than younger subjects on a given 25(OH)D level. Consequently, higher 25(OH)D levels are necessary in elderly subjects than in younger adults in order to suppress serum PTH levels into the low physiologic range. Supplementation studies demonstrate that even in subjects with initial serum 25(OH)D levels of approximately 70 nmol/l an increase in 25(OH) D to approximately 210 nmol/l still resulted in a decrease in serum PTH levels of 24% (from 29.5 pg/ml; *P* < 0.001) within 4 months of vitamin D supplementation (Heaney et al., 2003). Although the effect of additional vitamin D seems to be highest if serum 25(OH)D is low (see Fig. 1), available data also indicate that serum PTH does obviously not reach a plateau during a wide range of serum 25(OH)D levels (Vieth et al., 2003; Yan et al., 2003). It should also be mentioned that even healthy adolescents have already elevated serum PTH levels if their serum 25(OH)D levels are low (see below) and the various pathophysiological consequences that might occur (see below). People with long lasting vitamin D insufficiency may have the highest risk to develop vitamin D-related chronic diseases.

Serum 25(OH)D is not the only regulator of serum PTH. Dietary calcium intake and renal function are important other factors influencing serum PTH levels. Calcium supplementation of 1000 mg is able to decrease postprandial serum PTH by 50% within 2 h (Karkkainen et al., 2004). The glomerular filtration rate slowly decreases with age from about 125 ml/min at age 20–60 ml/min at age 80. This is accompanied by a gradual increase of serum PTH (Wiske et al., 1979; Marcus et al., 1984). The increase in serum PTH may be caused by slight phosphate retention and lower synthesis of calcitriol. However, low serum 25(OH)D was by far the most common cause of SHPT in a random sample of adults (Karlsson et al., 2005). Even in the above mentioned study in centenarians (Passeri et al., 2003), the calculated levels of creatinine clearance, although quite low, were not correlated with serum PTH, suggesting that SHPT was not due to chronic renal insufficiency. Moreover, serum 25(OH)D is the major factor determining the circulating levels of PTH in normal subjects (Pepe et al., 2004).

### 3. Vitamin D status worldwide

Solar UVB is the major source of vitamin D for humans. McKenna has summarized a large number of studies from North America and Europe on vitamin D status in young adults and elderly subjects until the end of the eight decade of the last century (McKenna, 1992). Healthy elderly subjects had mean 25(OH)D levels in the insufficiency range throughout the year. In institutionalized subjects, most 25(OH)D levels were in the deficiency range. In Europe, young adults often had circulating 25(OH)D levels in the insufficiency range during wintertime. However, earlier studies have also shown that mean summer levels of 25(OH)D can be twice as high as winter levels in European children and young adults. Serum 25(OH)D reached mean concentrations of up to 84 nmol/l (Zittermann, 2003). The SENECA study in Europe supported McKenna’s results. Mean 25(OH)D ranged between 22 nmol/l in elderly Greek people and 46 nmol/l in elderly Scandinavian people (van der Wielen et al., 1995) and were thus consistently in the insufficiency or even deficiency range. In the SENECA study, a positive relationship between serum 25(OH)D and geographic latitude was observed in the elderly subjects. This obvious paradox can probably be explained by different dietary and other lifestyle habits. Elderly people living in Scandinavia and South Europe seem to differ in their fatty fish consumption, the use of vitamin supplements, and the frequency of sun exposure (Lips, 2005). However, if available 25(OH)D data from adolescents and young adults are plotted against the geographic latitude where these studies have been performed, the results differ from those observed in elderly European people (Fig. 2).

Concerning vitamin D status, alarming results have recently been reported in urban dwellers in Europe. In a Hungarian study, middle-aged urban dwellers had only modest seasonal variations in circulating 25(OH)D levels and a high percentage of subjects had a low vitamin D status throughout the year, despite marked
seasonal fluctuations in daily sunshine (Bhattoa et al., 2004). The prevalence of 25(OH)D levels below 50 nmol/l during spring, summer, autumn, and winter was 71.0%, 46.3%, 49.4%, and 56.7%, respectively. Similarly, white British people of an outpatient clinic at a city hospital had mean 25(OH)D levels around 50 nmol/l throughout the year without seasonal fluctuations (Pal et al., 2003). A high prevalence of insufficient or deficient 25(OH)D levels is also reported in dark-skinned people living in Northern latitudes. Mean 25(OH)D levels below 50 nmol/l have been observed in African Americans (Nesby-O’Dell et al., 2002). Moreover, mean 25(OH)D levels below 30 nmol/l in summer and below 15 nmol/l in winter have been reported in South Asian immigrants in Great Britain (Pal et al., 2003).

Even premenopausal women living in a sunny country such as Turkey can have 25(OH)D levels in the deficiency range if they are dressed in traditional Islamic style (Alagol et al., 2000). In Lebanon, another Mediterranean country, 25(OH)D levels below 25 nmol/l were observed in 72.8% of a middle-aged group of adults. In a multiple linear regression analysis, circulating 25(OH)D levels were inversely related to urban dwelling in the group of male adults (−0.57; \( P < 0.001 \)). This association was weaker in female adults (−0.27; \( p = 0.002 \)), whereas inadequate vitamin D intake and the style of clothing was more important than urban or rural dwelling (Gannage-Yared et al., 2000). Very low mean 25(OH)D levels of 8 nmol/l in winter and 18 nmol/l in summer were observed in Indian physicians and nurses who lived in the city of Delhi and had a daily sun exposure of only 25 min. In contrast, Indian soldiers with a daily sun exposure of 370 min had mean 25(OH)D level of 47 nmol/l in winter (Goswami et al., 2000). However, even this concentration is still in the insufficiency range. Beside exposure time, the percentage of the body surface area is possibly another critical factor for the production of adequate amounts of vitamin D. For example, exposure of hands, arms, face and the neck is equivalent to a vitamin D intake of approximately 15 \( \mu \)g/day (Holick, 2002). This is not a sufficient amount to guarantee an adequate vitamin D status (Heaney et al., 2003). In future, more scientific research is necessary to clarify which percentage of body surface area has to be exposed to UVB in order to synthesize adequate amounts of vitamin D.

4. Cardiovascular disease

In humans, strong evidence for a role of vitamin D in the pathogenesis of cardiovascular disease comes from patients with end-stage renal disease (ESRD). In ESRD patients undergoing hemodialysis or peritoneal dialysis, adjusted cardiovascular mortality is 10–20 times higher compared with the general population (Foley
et al., 1998). Moreover, SHPT emerges already in the early stages of the disease and is caused by reduced renal synthesis of calcitriol (Drueke and McCarron, 2003). In ESRD patients, SHPT is regarded an important risk factor in the pathogenesis of cardiovascular disease (Rostand and Drueke, 1999). In patients undergoing hemodialysis, 1α-vitamin D and the vitamin D analogue paricalcitol are very effective drugs in reducing the risk of death from cardiovascular disease (Shoji et al., 2004; Teng et al., 2005). ESRD is also frequently associated with vascular calcification (Rostand and Drueke, 1999). In the general population, the presence of vascular calcification is a predictor of poorer 5-year survival (Margolis et al., 1980). Interestingly, in two human populations at high and moderate risk for ischemic heart disease, serum levels of calcitriol were inversely correlated with the extent of vascular calcification (Watson et al., 1997). It is also well known that excess PTH levels increases blood pressure and cardiac contractility, and leads to cardiomyocyte hypertrophy, and interstitial fibrosis of the heart (Rostand and Drueke, 1999). Thus, excess PTH contributes to cardiovascular disease.

Sambrook et al. (2004) have demonstrated that SHPT was significantly associated with increased mortality in the frail elderly. In that earlier study, serum PTH was also associated with an increased risk of cardiovascular death after stratifying for gender (hazard ratio, 1.88; P = 0.003). Keeping in mind the inverse relationship between 25(OH)D and PTH, it is interesting that in the Tromso study men with left ventricular hypertrophy had PTH levels of 44.1 ± 26.2 pg/ml compared to PTH levels of 29.4 ± 13.9 pg/ml in men without left ventricular hypertrophy (Saleh et al., 2003). Moreover, the rate of coronary heart disease was higher in the subjects with serum PTH > 62 pg/ml than in those with normal or low serum PTH levels [relative risk 1.67, 95% confidence interval (CI) 1.26–2.23 in men and 1.78, 95% CI 1.22–2.57 in women] (Kamycheva et al., 2004). In that study, the highest PTH quartile (> 32 pg/ml in men and > 30 pg/ml in women) predicted coronary heart disease, with odds ratios of 1.70 for men and 1.73 for women, versus the lowest PTH quartile (< 17.3 pg/ml for men and < 16.4 pg/ml for women).

When the mean 25(OH)D concentrations from different studies in children, adolescents, and young adults are plotted against geographic latitude (Fig. 2), an inverse association between 25(OH)D and geographic latitude does exist. The development of cardiovascular disease may last years or even decades. If the hypothesis that vitamin D insufficiency contributes to cardiovascular disease would be correct, cardiovascular mortality should be higher in countries of higher geographic latitude and vice versa. Such a relationship can indeed be found in European countries of different geographic latitudes (Figs. 3A and B).

5. Hypertension

Essential hypertension is a risk factor for cardiovascular disease. Essential hypertension is associated with low blood levels of ionized and ultrafiltrable calcium (McCarron et al., 1987) and elevated PTH levels (Jorde et al., 2005). Although hypocalcemia and/or elevated PTH levels may be causal factors for the development of
hypertension, another plausible mechanism for the association of vitamin D deficiency/insufficiency and hypertension is an activation of the rennin–angiotensin system (RAS). Calcitriol is known to be a negative endocrine regulator of the RAS (Li, 2003). Inappropriate stimulation of the RAS has been associated with hypertension. In several cases, calcitriol treatment was shown to reduce the plasma renin activity, angiotensin II levels, blood pressure, and myocardial hypertrophy (Kimura et al., 1999; Park et al., 1999). In VDR(−/−) mice, hypertension can be corrected by angiotension converting enzyme inhibitors and angiotensin I receptor antagonists (Li, 2003). It has been demonstrated that regular exposure to UVB radiation but not to UVA radiation increases circulating 25(OH)D above a level of 100 nmol/l and also significantly reduces blood pressure by approximately 6 mmHg in hypertensive patients with initial 25(OH)D levels of 26 nmol/l within an intervention period of 6 weeks (Krause et al., 1998). In that earlier study, PTH levels decreased by 15% in UVB-treated subjects and remained unchanged in the UVB-treated group. In another study (Pfeifer et al., 2001), elderly women were supplemented with calcium and 20 μg vitamin D daily or with calcium alone. Initial 25(OH)D levels in the two study groups were 24.6 and 25.7 nmol/l, respectively. Compared with calcium supplementation alone, supplementation with vitamin D and calcium resulted in an increase in serum 25(OH)D of 20 nmol/l (P<0.01), a decrease in serum PTH of 17% (P<0.05), a decrease in systolic blood pressure of 9.3% (P<0.025), and a decrease in heart rate of 5.4% (P<0.025).

6. Non-insulin dependent diabetes mellitus

The prevalence of diabetes mellitus is four- to five-fold higher and serum 25(OH)D is significantly lower in dark-skinned Asian immigrants in the UK than in British Caucasians (McKeigue et al., 1992; Pal et al., 2003). Moreover, serum glucose and the prevalence of diabetes rise (Harris et al., 1998) and serum 25(OH)D falls with age (McKenna, 1992). The dependence of normal insulin secretion in pancreatic β-cells on vitamin D has been known for several decades. Experimental studies have demonstrated that a reduction in vitamin D activity can result in both insulin resistance and reduced insulin secretion (Boucher, 1998). In South Asian immigrants in the UK, serum insulin concentrations measured after a glucose load were twice as high compared to British Caucasians (McKeigue et al., 1988). In multivariate analysis in postmenopausal women, glucose was found to be highly significantly related to body mass index and 25(OH)D but only just significant to age. Higher fasting glucose levels were found in those with serum 25(OH)D up to 40 nmol/l than in those with 25(OH)D above 40 nmol/l. The difference in fasting serum glucose was still significant if those with 25(OH)D below 80 nmol/l were compared with those with 25(OH)D above 80 nmol/l (Need et al., 2005). In another study performed in elderly subjects with insufficient vitamin D status (mean 25(OH)D levels: 42 nmol/l), the subgroup with the lowest tertile of 25(OH)D had a significantly higher blood glucose increase and a higher blood insulin increase after an oral glucose load compared with the subgroup with the highest tertile of 25(OH)D levels (Baynes et al., 1997). Data indicate that low serum 25(OH)D is associated with insulin resistance and that observed differences in glucose tolerance between different population groups may at least in part be explained by differences in serum 25(OH)D. In line with this assumption, a large study with glucose-tolerant young subjects whose 25(OH)D levels ranged between 6 and 200 nmol/l, 25(OH)D showed an independent negative relation with plasma glucose at fasting, 90 and 120 min during an oral-glucose-tolerance-test (Chiu et al., 2004). Moreover, there was also an independent positive correlation between 25(OH)D and insulin sensitivity index (calculated by dividing the average glucose infusion rate during the last hour of each clamp process [(μmol/l)/m²/min] by the average plasma insulin concentration (pmol/l) during the same interval).

7. Preventive strategies

It has recently been emphasized that vitamin D deficiency might become an unnecessary pandemic in the 21st century (Plehwe, 2003). This would have significant health consequences since an insufficient vitamin D status is obviously an important factor in the etiology of various chronic diseases, among them cardiovascular disease and impaired glucose tolerance.

Theoretically, different ways can be used to improve vitamin D status of people at risk. There is no doubt that environmental UVB exposure is the most important natural source of vitamin D. Therefore, strategies to
improve vitamin D status should include regular weekly UVB exposure (e.g. one-quarter of a MED most days of the week). This would mean, for example, that cities and towns have to be turned into safe places for pedestrians, cyclists, and children in order to encourage regular outdoor activities. Nevertheless, it is questionable whether all people who are at risk for low UVB exposure such as indoor workers, veiled women, and elderly people are able to adequately increase their skin synthesis of vitamin D. Moreover, such a measure would not make sense in Europe and North America during winter. The use of lamps with artificial UVB, e.g. in a tanning bed, would offer the opportunity to improve vitamin D status at home. Such a measure also would have the advantage that exact recommendations could be given for UVB exposure times as well as for the percentage of body surface which should be exposed to the UVB lamp.

Dietary advice would not be a good choice. Dietary intakes that are needed to maintain adequate circulating 25(OH)D levels range between 50 and 100 μg daily (Heaney et al., 2003; Vieth et al., 2004). Almost all foods naturally contain less than 10 μg of vitamin D/100 g edible portion. In Europe, only some foods such as margarine, vegetable oil, milk, cereals, breakfast beverages, and breads are fortified with vitamin D. Even these fortified foods are usually enriched with not more than 10 μg vitamin D/100 g edible portion or not more than 10 μg/l. However, a daily vitamin D supplement could be very effective. Unfortunately, in most countries of the world over the counter supplements usually contain not more than 10 μg vitamin D/tablet. Thus, 5–10 tablets have to be taken daily to achieve adequate circulating 25(OH)D levels in the absence of UVB exposure. This would be impossible to realize. An oral bolus containing a high dose of vitamin D several times per year may be equally effective and easier to distribute. Such a measure could be a good choice for elderly subjects who have regular contact to their general practitioner or who are institutionalized.

For disease prevention, 25(OH)D concentrations should at least be higher than 75 nmol/l. Given the high prevalence of insufficient and deficient 25(OH)D concentrations in the general population, an improvement of the population’s vitamin D status must be a major effort for public health service in future. For that reason, in many countries legislation has to be changed in order to allow a vitamin D amount in over-the-counter supplements and vitamin D fortified foods, which is sufficient to increase serum 25(OH)D into the adequate range.

References


