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ABSTRACT

Vitamin D is essential for the maintenance of good health. Its sources can be skin production and diet intake. Most humans depend on sunlight exposure (UVB 290–315 nm) to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by the skin, leading to transformation of 7-dehydrocholesterol into vitamin D₃ (cholecalciferol). Season, latitude, time of day, skin pigmentation, aging, sunscreen use, all influence the cutaneous production of vitamin D₃. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risk for other morbidities such as cardiovascular disease, type 1 and type 2 diabetes mellitus and cancer, especially of the colon and prostate. The prevalence of hypovitaminosis D is considerable even in low latitudes and should be taken into account in the evaluation of postmenopausal and male osteoporosis. Although severe vitamin D deficiency leading to rickets or osteomalacia is rare in Brazil, there is accumulating evidence of the frequent occurrence of subclinical vitamin D deficiency, especially in elderly people. (**Arq Bras Endocrinol Metab 2006;50/4:640-646**)

Keywords: Vitamin D; Osteoporosis; Sunlight; Parathyroid hormone; Bone density

RESUMO

Deficiência de Vitamina D: Uma Perspectiva Global.

A vitamina D é essencial para a manutenção da saúde. A sua fonte principal é a pele ou pode ser ingerida com a dieta. A maioria dos seres humanos depende da exposição solar para adquirir quantidades suficientes de vitamina D. A radiação ultravioleta tipo B transforma o 7-deidrocolesterol em vitamina D₃ (colecálciferol). A época do ano, latitude, pigmentação da pele, idade e uso de filtros solares são fatores que influenciam a produção cutânea. Deficiência de vitamina D pode causar raquitismo e osteomalácia, exacerbar a perda óssea na osteoporose, como também pode associar-se a várias morbidades como doenças cardiovasculares, diabetes mellitus tipo 1 e 2, câncer de próstata e de intestino grosso. A prevalência de hipovitaminose D tem sido relatada com grande frequência mesmo em regiões de baixa latitude e deve ser considerada na avaliação da osteoporose. Embora a deficiência severa levando a osteomalácia possa ser vista raramente no Brasil, evidências se acumulam da freqüente ocorrência de deficiência subclínica, especialmente em idosos. (**Arq Bras Endocrinol Metab 2006;50/4:640-646**)

Descritores: Vitamina D; Osteoporose; Luz solar; Paratormônio; Densidade óssea.

VITAMIN D IS ESSENTIAL for the maintenance of good health. Its sources can be skin production and diet intake. Most humans depend on sunlight exposure (UVB 290–315 nm) to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by the skin, leading to transformation of 7-dehydrocholesterol into vitamin D₃ (cholecalciferol). Season, latitude, time of day, skin pigmentation, aging, sunscreen use, all influence the cutaneous production of vitamin D₃. Once formed, vitamin D₃ is metabolized in the liver to 25-hydroxyvitamin D₃ and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D₃. Vitamin D deficiency is an unrecognized worldwide epidemic among both children and adults (1). Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risk for other morbidities such as cardiovascular disease, type 1 and type 2 diabetes mellitus and cancer, especially of the colon and prostate (1,2). Maintaining blood concentrations of 25-hydroxyvitamin D above 80 nmol/L (approximately 30 ng/mL) is not only important for maximizing intestinal calcium absorption but may also be important for providing the extrarenal 1 α -hydroxylase that is present in most tissues for the production of 1,25-dihydroxyvitamin D₃ (3).

SERUM VITAMIN D DETERMINATION

The most important vitamin D metabolite measurable in the serum is the 25-hydroxyvitamin D (25-OHD), which constitutes the major circulating form that can safely be correlated with skin production and dietary intake. Normal serum levels range from 10 to 55 ng/mL according to commercial kits, although these values do not discriminate properly which levels represent deficiency or insufficiency. In elderly subjects these levels should be at least 20 ng/mL as suggested by one study (4). There is no consensus on the ideal serum concentration of 25-OHD and there are many suggested values for setting the lower limit of normality from 20 to as much 37 ng/mL (5-8). Therefore the level of vitamin D should be the one that does not induce a rise in parathyroid hormone (PTH), and the optimal serum 25-OHD concentrations have yet to be established (6,9). The recent report by Binkley et al. (10) highlighted the importance of validation of circulating 25-OHD assays in the user's laboratory, irrespective of the manufacturer's claims, as we did for our

assay. They compared the results of serum 25-OHD measurement from samples of postmenopausal women sent to different laboratories. The DiaSorin RIA, which we use in our laboratory, demonstrated excellent results when compared with the HPLC standard method, and has been very effective in detecting endogenous 25-OHD₂ and 25-OHD₃ in human serum (10,11).

SUNLIGHT EXPOSURE AND VITAMIN D DEFICIENCY

Regular sunlight exposure has been considered an effective prophylaxis against vitamin D deficiency (12). However, studies in other regions of the world located at low latitude, such as the Middle East, have also shown a high prevalence of vitamin D deficiency, ranging from 50 to 97%. These findings have been explained as being mostly due to the customary clothing that covers almost the entire body (13,14). In countries that are exposed to sunlight directly and where the body is not covered entirely, such as the European countries bordering the Mediterranean, the levels of vitamin D can still be low as showed in the Euronut SENECA study (15) carried out among elderly Europeans. Hypovitaminosis D was surprisingly much more common in people living in sunny countries like Italy, Spain, and Greece than among those living in countries in which sunshine exposure is considered insufficient. In that study, up to 83% of elderly Greek women had vitamin D deficiency (levels below 12 ng/ml) compared with only 18% of the elderly population in Norway. Higher fish consumption, vitamin D fortification of food, and a higher percentage of people taking vitamin D supplements could explain this difference.

It has been recognized for some time that at temperate latitudes serum 25-hydroxyvitamin D exhibits an annual cyclic variation, with a peak in late summer and a nadir in late winter. This variation is generally considered to be due to a corresponding variation in the amount of UV-B radiation reaching the skin in the summer and winter months. It is reported that at latitudes above 40° (north or south), photoconversion of 7-dehydrocholesterol to previtamin D does not occur in the winter months, and that as latitude rises, even summer synthesis is blunted (figure 1). What is not known is the quantitative total input of vitamin D from the skin on a daily basis at any time of year, but particularly during the summer. A study conducted in Omaha, Nebraska, USA (16), examined the effects of summer sun exposure on

serum 25-hydroxyvitamin D, calcium absorption fraction, and urinary calcium excretion. The subjects were 30 healthy men who had just completed a summer season of extended outdoor activity (e.g. landscaping, construction work, farming, or recreation). Twenty-six subjects completed both visits: after summer sun exposure and again approximately 175 days later, after winter sun deprivation. The subjects were characterized mainly according to an index in which hours of sun exposure were taken into account in respect to fraction of body surface area exposed to sunlight. At both visits they measured serum 25-OHD, fasting urinary calcium to creatinine ratio, and calcium absorption fraction. Median serum 25-OHD decreased from 49 ng/ml in late summer to 30 ng/ml in late winter. The median seasonal difference of 20 ng/ml (interquartile range, 12–27) was highly significant ($P < 0.0001$). However, they found only a trivial, nonsignificant seasonal difference in calcium absorption fraction and no change in fasting urinary calcium to creatinine ratio (16).

Another study performed in South Florida — a region of year-round sunny weather — determined levels of vitamin D during winter as compared to summer (17). In winter 212 subjects had their 25-OHD measured. The mean winter 25-OHD concentration was 24.9 ± 8.7 ng/ml (62.3 ± 21.8 nmol/liter) in men and 22.4 ± 8.2 ng/ml (56.0 ± 20.5 nmol/liter)

in women. In winter, the prevalence of hypovitaminosis D, defined as 25-OHD less than 20 ng/ml (50 nmol/liter), was 38% and 40% in men and women, respectively. In the 99 subjects who returned for the end of the summer visit, the mean 25-OHD concentration was 31.0 ± 11.0 ng/ml (77.5 ± 27.5 nmol/liter) in men and 25.0 ± 9.4 ng/ml (62.5 ± 23.5 nmol/liter) in women. Seasonal variation represented a 14% summer increase in 25-OHD concentrations in men and a 13% increase in women, both of which were statistically significant. The prevalence of hypovitaminosis D is considerable even in low latitudes and should be taken into account in the evaluation of postmenopausal and male osteoporosis. Although clothing in south Florida commonly leaves arms and legs uncovered, other factors can impair dermal vitamin D production, including age, pigmentation of the skin, and sunscreen use. The higher than expected prevalence of vitamin D deficiency in south Florida might be accounted for avoidance of sun exposure because of the heat and increased awareness of the risk of developing skin cancer. The small seasonal variation in 25-OHD concentrations can be explained by even greater exposure to the sun throughout the year in south Florida, compared with northern regions where sunlight exposure is minimal because of the cold weather and shorter hours of daylight during the winter months.

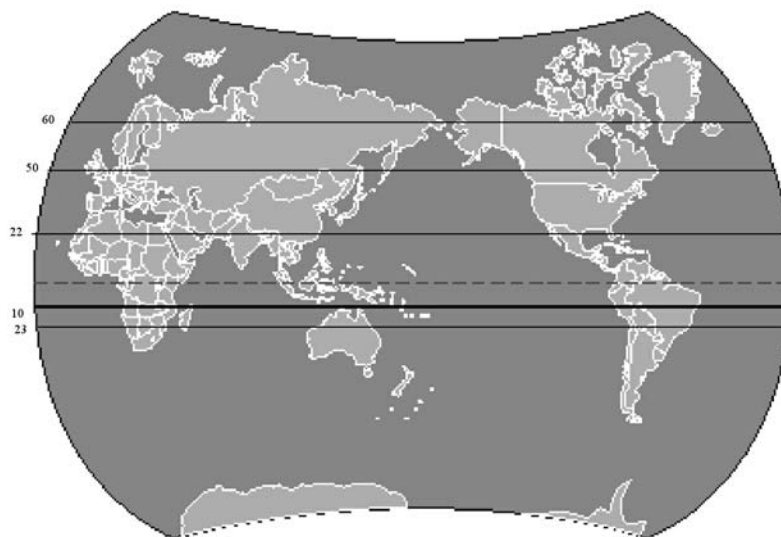


Figure 1. Northern and southern latitudes (in degrees).

- 60° N: Oslo, Norway
- 50° N: Toronto, Canada
- 22° N: Miami, USA
- 10° S: Recife, Brazil
- 23° S: São Paulo, Brazil

In a study performed in Honolulu (latitude 21°) and Madison (latitude 43°) in young men and women of similar age and BMI, serum 25-OHD was determined and correlated with sun exposure. Although it was higher in Honolulu than in Madison (31.4 ± 1.0 vs. 18.3 ± 0.8 ng/ml), the highest serum 25-OHD concentrations were similar in both groups (62 vs. 62.3 ng/ml), as was the range of 25-OHD levels (12 – 62 vs. 5 – 62 ng/ml). Serum 25-OHD was less than 20 ng/ml in 10% of Hawaiian individuals despite sunlight exposure of 23.1 ± 4.9 (range 6–50) hours per week (18).

A new concept is thus being established: people living in high-sun-exposure areas may have a high prevalence of poor vitamin D status, suggesting that living at low latitudes alone does not protect against vitamin D deficiency.

THE WORLD EPIDEMIC OF VITAMIN D DEFICIENCY

Some data from other countries suggest that the occurrence of low 25-OHD levels in the elderly is more common than was thought to be the case, reaching 80% in 80-year-old women living in old people's homes in the Netherlands (19). Even in health adolescents vitamin D deficiency/insufficiency may reach 42% using a cut-off point of 20 ng/ml (50 nmol/L) for serum 25-OHD (20). In Sydney, Australia, a study carried out with men over 60 years of age, including 41 with fractures of the femoral neck, 41 hospitalized for other reasons and 41 outpatients, revealed that the mean serum 25-OHD levels were significantly lower in the patients with fractures of the femoral neck (18.2 ng/ml, or 45.5 nmol/L) than in those hospitalized for other reasons (24.4 ng/ml, or 61 nmol/L) or in the outpatients (25.4 ng/ml, or 63.5 nmol/L). Sub-clinical vitamin D deficiency (defined here as a serum 25-OHD level below 20 ng/ml, or 50 nmol/L) occurred in 63% of the patients with fractures of the femoral neck, compared with 25% of the outpatients (odds ratio= 3.9; CI= 1.74–8.78; $p= 0.0007$). When analyzed in relation to other risk factors for osteoporosis such as age, body weight, concomitant morbid conditions, alcohol intake, smoking and use of corticoids, subclinical vitamin D deficiency was the most important factor in predicting the risk of fractures of the femoral neck (21).

In Wolverhampton, England, a cross-sectional study compared 98 patients from the ethnic Asian community, who were being followed up in rheumatology

clinics, with 36 control individuals. The groups were matched for gender, age and BMI. Most of the patients were vegetarians and had a diet low in calcium. The mean serum 25-OHD was 6.6 ng/ml (16.5 nmol/L) in the study patients and 8.2 ng/ml (20.5 nmol/L) in the controls. The prevalence of severe vitamin D deficiency (25-OHD below 8 ng/ml) was 78% and 58%, respectively in the two groups. The mean serum PTH levels were not significantly different (53 vs. 50 pg/ml), nor was the prevalence of secondary hyperparathyroidism due to severe vitamin D deficiency (22% vs. 33%). The color of the skin, restricting the penetration of sunrays, and typical clothes covering a large part of the body area in a region with a low amount of sunlight, both contribute to the high frequency of severe vitamin D deficiency in these individuals (22).

In a population of noninstitutionalized low-income elderly persons in Boston, USA, aged 64–100 yr, Harris et al. evaluated the serum 25-OHD levels of 308 participants in the Boston Low Income Osteoporosis Study. Twenty-eight black patients (21% of 136) and 12 whites (11% of 110) had levels regarded as very low (< 10 ng/ml). Seventy-three per cent of the black and 35% of the white patients had 25-OHD levels lower than 20 ng/ml (50 nmol/L). In the patients of Asian or Hispanic origin the levels were similar to those of the white patients. The serum PTH levels were considerably higher in the patients with vitamin D deficiency, particularly the blacks (23).

VITAMIN D DEFICIENCY IN BRAZIL

In countries close to the equator the ultraviolet radiation of the sun penetrate the ozone layer of the Earth's stratosphere sufficiently to permit the production of vitamin D by the skin throughout the year. It should be emphasized, however, that the process of ageing by itself leads to a decrease in the skin's ability to produce vitamin D because of the diminution of the amount of 7-dehydrocholesterol. A 70-year-old individual who exposes him or herself to the same amount of ultraviolet sunrays manages to produce only 20% of the amount produced by a young person (24).

Although severe vitamin D deficiency leading to rickets or osteomalacia is rare in Brazil, there is accumulating evidence of the frequent occurrence of sub-clinical vitamin D deficiency in several other populations, especially in the elderly. As a result, there might occur secondary hyperparathyroidism, increased bone remodeling, a decrease in bone mineral density (BMD), particularly in the proximal femur, and an

increased risk of osteoporotic fractures, when compared with individuals considered to have a sufficient supply of vitamin D (25). Likewise, supplementation of adequate amounts of cholecalciferol or ergocalciferol (700 to 800 IU/day) appears to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons (26), and may have a positive impact on musculoskeletal parameters such as lean body mass in children and adolescents (27), who are also prone to vitamin D deficiency especially when sun exposure is limited (28,29).

Some initial data, as stated before, suggested that to satisfactorily meet metabolic requirements, at least 20 ng/ml (50 nmol/L) would be needed, especially in elderly persons, since below this there would be a rise in serum parathyroid hormone (PTH) and increased bone remodeling (4). When these individuals were placed on a vitamin D supplement raising the serum 25-OHD to values above 20 ng/ml, the PTH levels fell by approximately 40% and bone mass increased.

In patients attending an osteoporosis clinic, PTH levels clearly increase when the serum levels of 25-hydroxyvitamin D fall to below 25 ng/ml (62.5 nmol/L) and there is a significant increase in bone remodeling and bone loss with levels even lower than 30 ng/ml (75 nmol/L) (6).

Our data demonstrated that the mean serum 25-OHD levels were similar to that found in our postmenopausal patients who had primary asymptomatic hyperparathyroidism (30) and were also no different from the levels reported in the North American patients in the MORE study (5).

We verified the prevalence of vitamin D deficiency in postmenopausal women using several cutoff points for the serum 25-OHD (31), since there is yet no consensus as to which is the most appropriate. Vitamin D deficiency was found in 8% of the patients considering values below 15 ng/ml (37.5 nmol/L), in 24% of the patients considering values below 20 ng/ml (50 nmol/L) and in 43% considering values below 25 ng/ml (62.5 nmol/L). These data show a prevalence similar to what occurs in the USA, but greater than that of Canada and the Scandinavian countries (5), and reinforce the idea that the abundant presence of sunlight may not prevent vitamin D deficiency in postmenopausal women. Moreover, the Brazilian diet is very poor in vitamin D, the principal source of which is fish with a high fat content found in the cold regions of the northern hemisphere. In Canada and the Scandinavian countries 25-OHD lev-

els are significantly higher than those of the patients in our study. In those countries, despite the lower amount of sunlight, the natural food source is greater and there is also supplementation of milk with vitamin D.

It is also important to bear in mind that in countries with an arid or semi-arid climate (figure 2), with a very low amount of rainfall and therefore sunny weather throughout the year, vitamin D deficiency attains one of the highest rates of prevalence on the whole planet (32,33). Even though the city of Recife (latitude 10°) has a humid tropical climate, these data from arid and semi-arid regions also serve to strengthen the notion that, at least in postmenopausal women, living in areas with abundant sunlight does not prevent vitamin D deficiency.

As vitamin D deficiency may be asymptomatic, albeit predisposing to a greater loss of bone and consequent increased risk of fractures, it is important that each region should attempt to establish the lowest limit of normality for serum 25-OHD, defined as the level at which mean serum PTH levels begin to rise, characterizing secondary hyperparathyroidism (34). We found significant differences in the serum PTH levels up to the 25-ng/ml (62.5 nmol/L) cutoff point for serum 25-OHD. In patients with 25-OHD levels lower than 25 ng/ml, the PTH levels were 52.95 pg/ml in comparison with the patients whose 25-OHD was equal to or greater than 25 ng/ml who presented mean PTH levels of 39.7 pg/ml. Calcium intake was not a contributing factor to the higher PTH values in our patients with 25-OHD below 25 ng/ml (62.5 nmol/L), as the percentage of patients with a low calcium intake was even greater in those patients with higher 25-OHD levels, although the difference was not statistically significant.

The prevalence of vitamin D deficiency increased significantly with age, being found in 30% of the women between 50 and 60 years of age and in even more than 80% of the women over the age of 80 (31).

In a study of 250 elderly individuals from São Paulo (latitude 23°) with a mean age of 79 years, mean serum 25-OHD was 19.8 ng/ml, and overall 57% of them showed values below 20 ng/ml. In the winter and spring months 66 and 69% had 25-OHD concentrations below 20 ng/ml (35).

Finally, functional indices of vitamin D status have been proposed in which serum 25-OHD concentrations above 32 ng/ml (80 nmol/L) are necessary to improve calcium absorption (36).

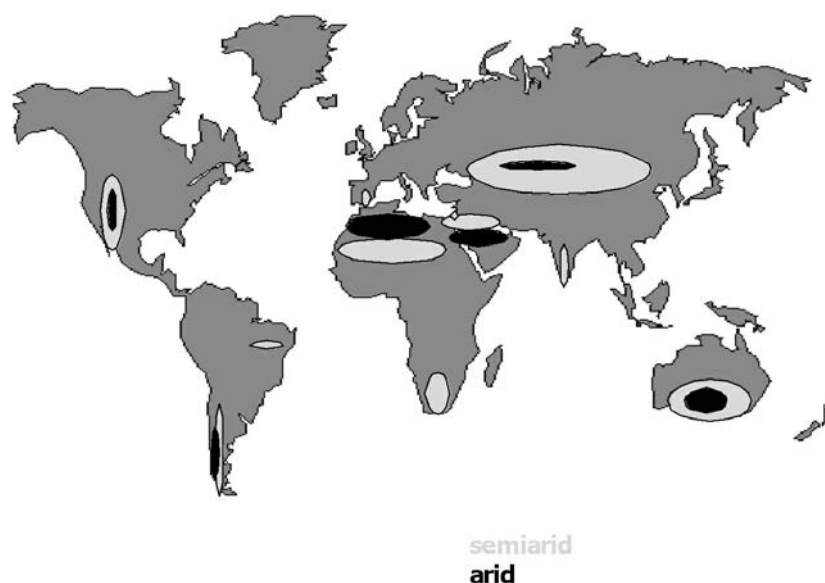


Figure 2. Arid and semiarid regions worldwide.

CONCLUSION

Although vitamin D levels may differ by latitude and skin pigmentation worldwide, there are growing evidences that living in areas with abundant sunlight may not be possible to attain adequate amounts of vitamin D necessary to prevent several chronic diseases.

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