La Prensa Medica Argentina

Review Article

Vitamin D: A Review of Epidemiological Features

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Rec date: Feb 22, 2014 **Acc date:** Sep 9, 2014 **Pub date:** Sep 11, 2014

Abstract

Introduction: Vitamin D disorders have attracted considerable attention in recent decades. This substance plays an important role in human health, including calcium and phosphorous homeostasis, hormone activity, immune responses, protection against tumors, arterial hypertension and type 2 diabetes. Knowledge about physiopathology of the vitamin D serum levels is essential for adequate interpretation of the laboratory data and the clinical investigation findings. This review aims primarily assessing the seasonality of serum vitamin D levels, attributed to the variable intensity of UVB radiation, as well as the general epidemiology of these levels in different geographic regions.

Methods: The relationships between concentrations of 25(OH)D, age, gender and ethnicity, and serum PTH levels of individuals, are also comparatively studied. Bibliographic research was done in MEDLINE and PUBMED, involving the last 12 years, using the terms diet, ethnicity, latitude, UVB radiation, 25(OH)D, and vitamin D. Numerous population studies involving the main factors related to the origin of hypovitaminosis D, in addition to vitamin D insufficiency or deficiency, were analyzed.

Results: There is a lack of consensus regarding the serum levels of 25(OH)D taken as a parameter for establishing the respective diagnoses. There are different methods to determine the serum levels of 25(OH)D, which are affected by seasons of the year, sun exposure and diet. Normal ranges used by different authors must be taken in account when analyzing studies about vitamin D disorders.

Keywords: Diet; Ethnicity; Latitude; UVB radiation; 25(OH)D; Vitamin

Introduction

The high prevalence of hypovitaminosis D has been a major concern of public health in developing countries, including the Latin America, and the Sub-Saharan, Middle East and North Africa. Worth of note, in Brazil as well as in Argentina population studies have addressed to the causative factors both amongst the elderly and young healthy people, focusing the role of diet and the sun exposure [1-3]. Vitamin D is a secosteroid hormone with two forms (D2 and D3), found in diet [4]. Vitamin D3 is also produced in the skin from 7-dehydrocholesterol (7-DHC), after exposure to ultraviolet B radiation (UVB) at wavelengths between 290 and 315 nm. In the bloodstream, vitamin D undergoes two hydroxylations. The first, in the liver, at position 25, and forms 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D, with half-life of two to three weeks. The second, in the kidney, at position 1, gives rise to 1,25-dyhydroxivitamin D [1,25(OH)2D], the active form of vitamin D. The best indicator to determine nutritional status of vitamin D in the human organism is the [25(OH)D] serum level, since this measure reflects vitamin D from total dietary intake and sun exposure, as well as the conversion of this vitamin in the adipose tissue and in the liver. Thus, low levels of 1,25(OH)2D do not necessarily correspond to low concentrations of 25(OH)D, which usually result from kidney failure and less frequently, from oncogenic osteomalacia [5].

The primary role of vitamin D is to maintain the normal serum calcium and phosphorous levels, by stimulating intestinal absorption of these ions, resulting in adequate bone mineralization [4]. Inadequate vitamin D levels, in addition to causing rickets, prevent children from reaching their genetically programmed peak bone mass, contributing to the occurrence of osteoporosis in adults and osteomalacia, in cases of acute deficiency [4]. In recent decades, several authors have investigated mechanisms that associate and confirm the relationship between normal vitamin D levels and overall health, relating this vitamin with at least 2000 genes and distinct actions. Some of these actions are related to adequate muscle and immunological functioning, prevention of type 1 diabetes mellitus, hypertension and certain types of cancer [5]. With base on these data, a number of authors consider that the prevalence of hypovitaminosis D compromises public health, especially in regions where scarce information is available to the population [6].

This review primarily aims to assess the vitamin D levels and its seasonality, attributed to the varying intensity of UVB radiation, as well as the general epidemiology of these levels, in different geographic regions. The relationships between concentrations of 25(OH)D, age, gender and ethnicity of the individuals and the parathormone (PTH) serum levels were also comparatively analyzed.

Hypovitaminosis

Circulating levels of (25(OH)D) may be influenced by factors such as age, gender, ethnicity, dietary intake and sun exposure; and may be related to regional latitude, season of the year and frequency of outdoor activities. Sun exposure is considered to be more important than dietary intake of vitamin D, since extra levels in diet cannot be guaranteed. Few food sources are rich in vitamin D and could ensure a daily balanced diet. In order to classify groups at risk of hypovitaminosis D, according to cutaneous synthesis and sun exposure, a consensus was established in 2010 among the British Association of Dermatologists, Cancer Research UK, Diabetes UK, Multiple Sclerosis Society, National Heart Forum, National Osteoporosis Society and the Primary Care Dermatology Society [7]. These groups include individuals with darker skin, those with clothes

covering their entire body, the elderly, pregnant women, children of mothers with vitamin D deficiency, patients with skin cancer and people confined to their homes or institutions, in addition to those who constantly avoid sun exposure [7].

Since there is no consensus, the parameters are variable to classify hypovitaminosis and vitamin D insufficiency or deficiency, based on circulating levels of 25(OH)D. Thus, current cutoff points are based on population studies that relate 25(OH)D levels with variables associated to their metabolic function. McGrath et al., in a study conducted in Queensland, Australia, a subtropical region situated at a latitude of 27° South, vitamin D deficiency was defined as 25(OH)D levels less than or equal to 15.2 ng/mL and insufficiency as less than or equal to 20 ng/mL [8]. Outila et al., analyzing 178 female teenagers (14 to 16 years) from Helsinki Finland (latitude 60° North), used a cutoff point of 10 ng/mL to define vitamin D deficiency [9]. Looker et al., in a study of subgroups included in the Third National Health and Nutrition Examination Survey (NHANES III), defined vitamin D deficiency as 25(OH)D levels below 7 ng/mL [10]. Bhattoa et al., who investigated 319 Hungarian women in postmenopausal phase, considered hypovitaminosis D as values less than or equal to 20ng/mL [4]. Rahman et al. assumed values between 20 and 40 ng/mL as hypovitaminosis D, and those between 10 and 20 ng/mL as vitamin insufficiency[11]. Meddeb et al. analyzed the prevalence of hypovitaminosis D in 389 Tunisians, establishing 25(OH)D levels of 15 ng/mL as the cutoff point [12]. Levis et al. in Southern Florida [13], Ono et al. in Tokai, Japan [14], Sullivan et al. in Maine [15], Van der Mei et al. in Australia [16], and Sahu et al. in India [17] used 25(OH)D levels < 20 ng/mL to classify hypovitaminosis D. Roth et al., in a study of lactating women in the rural region of Silhet and Gagnon et al., in an analysis of Canadian women at fertile age, defined vitamin D deficiency as 25(OH)D values < 10 ng/mL [18,19].

In summary, most studies consider hypovitaminosis D as 25(OH)D < 20-30ng/mL; vitamin D insufficiency as 25(OH)D < 15-20 ng/mL; and vitamin D deficiency 25(OH)D < 7-10 ng/mL. Accordingly to Unger et al., as vitamin D can be essential for diverse organic systems, maintaining 25(OH)D levels above 40 ng/mL may be an useful tool in preventing diseases and promoting health [3].

Limitations in standardizing the cutoff points of 25(OH)D include the fact that most reference laboratories have raised the lower limit of normality to 30 ng/mL. Moreover, despite of several methods to determine 25(OH)D, the accuracy of non-reference laboratory tests may not be reliable. Another factor that must be considered is that 25(OH)D levels may be altered by seasonal factors, sun exposure, and diet [1-3,20] Thus, parameters used by different researchers must be taken in account when analyzing research data about hypovitaminosis D, vitamin D deficiency or insufficiency.

Prevalence of Hipovitaminosis D

McGrath (25(OH)D < 20 ng/mL) and deficiency (25(OH)D < 15 ng/mL), in the subtropical region of Southeast Queensland, Australia. They studied a total of 222 men and 192 women (+ 42 years), with mean 25(OH)D level of 27.6 ng/mL, and no significant difference in 25(OH)D concentrations between patients with psychoses and normal controls; 23.4% and 8% of individuals exhibited vitamin D insufficiency and deficiency, respectively. There was a positive correlation between vitamin D levels and sunlight [8]. Outila 61.8% of the adolescents studied showed 25(OH)D levels < 16 ng/mL and 13.5% were considered vitamin D deficient (25(OH)D < 10 ng/mL [9]. In another study, the vitamin D dietary intake, supplementation, and sun exposure of healthy Danes (45-58 years) who had recently experienced physiological menopause, was followed for 2.5 years. All of these factors were correlated with 25(OH)D levels, especially sun exposure, with significant seasonal variation. The prevalence of vitamin D deficiency (25(OH)D < 10 ng/mL) was 7%, and 32.8% of individuals with little sun exposure and restricted vitamin D intake were deficient between winter and spring [21]. Looker 25(OH)D levels in two subgroups included in NHANES III; one group from low latitudes, assessed during winter (winter/low latitude group), and the other from high latitudes examined during summer (summer/high latitude group). Less than 1% of the winter/low latitude group exhibited vitamin D deficiency (25(OH)D < 7 ng/mL). However, the prevalence of insufficiency in this group ranged from 1% to 5% (25(OH)D < 10 ng/mL), and from 25% to 57%, with values less than 25 ng/mL; even though the mean latitude for this subgroup (32° North) was considerably lower than that where no vitamin D synthesis was observed during the winter months (42° North). Except for elderly women, lower rates of vitamin D insufficiency (less than 1% to 3% at 25(OH)D concentrations < 10 ng/mL, and between 21% and 49% at less than 25 ng/mL), were observed in the summer/high latitude group [10]. Another study investigated 139 healthy Saudis, participants in a regular blood donor program. All the subjects underwent a complete clinical examination and assessment of calcium and vitamin D intake, as well as the degree of sun exposure. The results show an elevated prevalence of vitamin D deficiency in both sexes [22]. Inderjeeth et al. analyzed 91 patients (66 women + 81.3 years) in order to determine the frequency of vitamin D deficiency (25(OH)D < 11.2 ng/mL) in elderly individuals hospitalized with hip fracture. Vitamin D deficiency occurred in 67% of the cases, without significant seasonal variation, with low levels observed throughout the year; a finding that did not surprise the authors, since it is known that the elderly exhibit a reduction in the cutaneous synthesis of vitamin D [23]. Oliveri et al., in a cross-sectional study of 339 individuals, aged 65 years and older, in seven Argentinean cities, observed lower 25(OH)D levels in the South (latitude between 41° and 55° South) when compared to the North (26° to 27° South); and intermediate values in central regions (33° to 34° South). There was a high prevalence in all regions (87%, 52% and 64%, respectively) of hypovitaminosis D (25(OH)D < 20 ng An analysis of 307 adolescent patients in Boston showed a prevalence of 25(OH)D deficiency (< 15ng/mL) of 24.1%, and insufficiency (< 20 ng/mL) of 42%. Compared to summer, serum 25(OH)D levels were 24% lower in winter [25]. Brustad25(OH)D concentrations in 309 blood samples obtained from women aged 44 to 59 years, from Northern Norway (latitudes between 65° and 71° North. The mean concentration of 25(OH)D was 22 ng/mL, with a variation between 3.2 and 57.2 ng/mL. The prevalence of hypovitaminosis D (25(OH)D < 15 ng/mL) was higher in January and February [26]. In a similar group of healthy postmenopausal women (n=319), Bhattoa (25(OH)D < 20ng/mL) of 56.7%. The prevalence of hypovitaminosis D was associated to mean sun exposure during the three months prior to determination of 25(OH)D levels, corresponding to 71% in spring, 46.3% in summer, 49.4% in autumn and 56.7% in winter [3]. Andersen 25(OH)D levels in winter, in a group of young girls (n=199; +12.6 years) and elderly women (n=211; + 71.8 years). All subjects resided in high-latitude Northern European countries, namely Denmark, Finland, Ireland and Poland [27]. In winter, Levis 25(OH)D (1,25(OH)2D and PTH levels. Mean 25(OH)D concentration in winter was 24.9 ng/mL in men, and 22.4 ng/mL in women, while the prevalence of hypovitaminosis D (25(OH)D < 20 ng/mL) was 38% in men and 40% in women. Ninety-nine of the subjects were reassessed at

the end of summer, showing 25(OH)D increases of 14% and 13% in men and women, respectively [13].

Seasonal Variation of Vitamin D

The seasonal variation of vitamin D has been widely studied and seems to be more important than regional latitude. The question in this context is whether this climatic variation in the cutaneous synthesis of 25(OH)D is a normal physiological state, with programmed physiological adaptations, or if this variation, with alternate vitamin D sufficiency or insufficiency, would promote an imbalance in maintaining body homeostasis. Another relevant finding, given that the seasonal variation of 25(OH)D affects the diagnosis of vitamin D sufficiency, is the plasma half life of vitamin D. Clinicians must consider the sampling month for correct interpretation of 25(OH)D measurements. It is important to remember that these factors represent less than one-fifth of the variation in 25(OH)D, levels, underscoring the role of behavioral factors [16].

In an attempt to assess seasonal variations in vitamin D, Ono et al. performed an observational study with a group of 197 normal individuals of Tokai, Japan, at a latitude of 35.5° North. Mean 25(OH)D levels were lower during winter and higher during summer (15.1 ng/mL in March; 21.5 ng/mL in June vs. 31.6 ng/mL in September; and 23.1 ng/mL in December). The prevalence of hypovitaminosis D (25(OH)D < 20ng/mL) was 86.7%, 33.4%, 1% and 26%, respectively. The results suggest a high prevalence of hypovitaminosis D in Japan during winter, even in sunny regions [14]. Saraiva et al., in a sunny region of Brazil (São Paulo, latitude 23° 34' South), evaluated serum 25(OH)D levels in 250 elderly individuals (+ 79.1 years), according to UVB radiation incidence. Radiation and 25(OH)D levels varied seasonally. The highest and lowest serum 25(OH)D levels found were 26.9 ng/mL and 11.6 ng/mL, respectively, corresponding to the measures obtained in the months following those with the highest and lowest amount of sunlight [28]. Also in São Paulo, Unger et al. demonstrated significant seasonal variation in the 25(OH)D levels of healthy individuals (n=603) after winter and summer [3]. Sullivan et al. followed a group of adolescents in Maine for three years, assessing seasonal variation of 25(OH)D and demonstrated vitamin D insufficiency (25OH)D < 20ng/mL) in 48% of the individuals [15]. Lapatsanis et al. evaluated 178 students (3-18 years) from public schools in Northwest Greece [29]. The children were classified into three age groups and blood samples were collected in summer and winter. There was a high percentage of group III individuals (15-18 years; 47%) with serum 25(OH)D levels below 10 ng/mL in winter, compared with 13-14% at younger age ranges (13 to 14 years); on the other hand, during summer, all subjects exhibited serum 25(OH)D levels above 10 ng/mL. The prevalence was even higher in older girls, coupled with a reduction in phosphorous concentrations in winter [29]. Hill et al. studied 25(OH)D levels in Irish individuals of different age groups, at the end of winter and summer. Among the women, 4-19% showed inadequate serum 25(OH)D levels after summer and 34-85% after winter. During summer, there was a marked absence of severe or moderate vitamin D deficiency in the entire group, and after winter, none of the individuals had severe deficiency [30]. In a cross-sectional study, Chatfield et al., studied 129 inpatients in general clinical units, 65 in winter and 64 in summer. They found lower serum vitamin D levels in winter, compared to summer - 14 ng/mL vs. 17 ng/mL [31]. Hyppönen and Power [32] studied 7437 white individuals (45 years) enrolled in the 1958 British Birth Cohort, observing that the prevalence of hypovitaminosis D was higher in winter and spring; concentrations below 10 ng/mL, 16 ng/mL and 30 ng/mL were found in 15.5%, 46.6% and 87.1% of participants, respectively. During summer and autumn the rates were 3.2%, 15.4% and 60.9%, respectively. Concentrations below 16 ng/mL were twice as frequent in Scottish subjects than in those from other regions of the United Kingdom, such as England and Wales [32]. Van der Mei et al., compared 25(OH)D levels in individuals younger than 60 years residing in three different parts of Australia: Southeastern Queensland - at 27° South (167 M, 211 W), Geelong - at 38° South (561M), and Tasmania - at 43° South (432M, 298H). The prevalence of vitamin D insufficiency (25(OH)D < 20ng/mL) in women during winter and spring was 40.5% , 37.4% and 67.3% in regions from lower to higher latitudes. Although latitude explained only 3.9% of variation, a decrease of 2.498 ng/mL in mean 25(OH)D concentration for each increase in degree of latitude can be clinically relevant [16]. An 18-month cross-sectional study carried out with 121 women, randomly selected in a low-socioeconomic level rural community in India, analyzed serum 25(OH)D and alkaline phosphatase levels, sun exposure and dietary calcium intake. The prevalence of vitamin D deficiency (25(OH)D < 20 ng/mL) was 88.6%. In a group of pregnant women, 74% displayed vitamin D deficiency. Mean serum 25(OH)D level in girls and women was 22.2 ng/mL in summer and 10.9 ng/mL in winter. The seasonal variation of 25(OH)D levels is therefore considerable at a latitude of 26° North [17]. Researchers analyzed 100 women (61 to 83 years), randomly selected from a population-based study (Swedish Mammography Cohort) at a latitude of 60° North. The seasonal rise in 25(OH)D levels was 38% - 28.8 ng/mL in winter vs. 39.6 ng/mL summer [33]. Kull et al., studied 367 Estonians (200M, 167W; + 48.9 years), at a latitude of 59° North, measuring 25(OH)D and PTH concentrations in summer and winter. Mean serum levels of 25(OH)D were 17.5 ng/mL in winter and 23.7 ng/mL in summer. In winter, 73% of patients presented with insufficiency (25(OH)D < 20ng/mL) and 8% deficiency (25(OH)D < 10 ng/mL). The corresponding rates in summer were 29% insufficiency and less than 1% deficiency [34]. Baraké et al., in an analysis of 405 Canadians (65 to 82 years) in Quebec, observed a low prevalence of vitamin D deficiency in both genders, especially in summer. However, more than 50% of participants showed suboptimal vitamin D levels - below 30 ng/mL [35]. According to Burgaz et al., cutaneous synthesis of 25(OH)D is not identifiable during half the year in high-latitudes countries. Thus, the population is dependent on other sources in order to maintain adequate levels of vitamin D. Roth et al. studied 25(OH)D levels in infants from Silhet, Bagladesh at a latitude of 25° North, during the dry season of January and February. The mean 25(OH)D level in 29 infants, aged between one and six months, was 14.7 ng/mL. The proportion of children with vitamin D deficiency (25(OH)D < 10 ng/mL) was 28%. A total of 59% of the children exhibited 25(OH)D concentrations below 16 ng/mL, and levels remained below 32.08 ng/mL in all individuals [18]. Gagnon et al., performed a cross-sectional study involving 153 normal Caucasian Canadian women (18 to 41 years), to determine 25(OH)D and PTH levels. Around 3.9% had serum 25(OH)D levels less than or equal to 10 ng/mL, the deficiency range, while 26.8% were in the insufficiency range, that means, concentrations between 20 and 30 ng/mL. Blood was collected from most women (56.9%) in September, and it was shown that the collection month had a significant effect on 25(OH)D levels. Traveling to sunnier regions during winter or spring was associated to higher levels of 25(OH)D. Therefore, the prevalence of vitamin D insufficiency is relatively high (30%) in Canada during summer in healthy women of reproductive age. Lower 25(OH)D levels in winter indicates high prevalence of vitamin D deficiency or

insufficiency during this season, except for people who travel to areas of sunnier climate [19].

Studies have shown significant seasonal variation in terms of serum 25(OH)D levels, associated to the different incidence of UVB radiation or population habits at each specific time of the year. Non-significant seasonal variations seem to occur only in certain groups of patients, such as those with fractures, who may display chronically reduced 25(OH)D levels, or be subject to different conditions that determine constantly low levels of vitamin D. In addition to seasonality, another important factor in relation to serum 25(OH)D levels involves high-latitude regions, where there is greater tendency to population concentrations with lower D levels. However, this factor is not as important as seasonality.

Heredity

Mean 25(OH)D was 38.4 ng/mL with marked seasonality, and values 6.1 ng/mL lower in winter than in summer. Around 70% of 25(OH)D variations in winter were explained by genetic factors. However, in summer, the 25(OH)D levels displayed no heredity traits [36]. In conclusion, 25(OH)D levels can be highly transmissible during winter, but environmental conditions such as sun exposure in summer prevail over genetic predisposition in determining the serum levels.

Confirming the importance of behavioral factors, Meyer et al., found that vitamin D deficiency is common in individuals from non-occidental countries that immigrate to Western regions. A total of 196 participants (30 to 60 years) in a cross-sectional study conducted in Kandy, Sri Lanka, latitude 7° North, and 242 individuals (31 to 60 years) from Sri Lanka, enrolled in a cross-sectional study performed in Oslo, Norway, latitude 60° North, were included in the analysis. Sinhalese residents of Norway showed significantly lower 25(OH)D levels compared with those who lived in (+ 21.7 ng/mL), and the prevalence of concentrations below 10 ng/mL was 9.3 times higher in Norway than in . In people of this latter group, there was a marked seasonal variation [37]. Bolland et al., measured 25(OH)D levels in 21,987 hospitalized adults in Auckland, New Zealand, from January 2002 to September 2003. A total of 48% of the individuals exhibited 25(OH)D levels below 20 ng/mL in the assessment month, but 63% should display these values in late winter/early spring, based on seasonal variation. The levels of 25(OH)D required to ensure concentrations up to 20 ng/mL throughout the year can range considerably with the season - in summer, from 24 to 30 ng/mL [38].

Effect of Age, Gender, Ethnicity, and Body Mass Index (BMI)

It is known that age can influence vitamin D levels, since elderly individuals show a lower cutaneous concentration of 7-dehydrocholesterol, resulting in less cutaneous synthesis of vitamin D. With respect to age range, McGrath et al., found no correlation between age and 25(OH)D levels [8], but Ono et al. observed a positive association between these data in the individuals that were assessed [14]. In an analysis of 319 postmenopausal women, Bhattoa et al., reported a significant difference in ages between groups with normal and reduced 25(OH)D levels, with respective means of 61.6 and 67.3 years [4]. Meddeb et al., in a population group of 389 Tunisians (aged 20 to 60 years), observed an increase in hypovitaminosis prevalence with advancing age [12]. In a study with 93 mother-child dyads in Jordanian community centers, Gharaibeh and Stoecker reported that children had higher serum 25(OH)D levels than those of their mothers; older women and those with five or more gestations, had significantly lower 25(OH)D levels [39]. Bolland et al., found that the 25(OH)D levels required to ensure concentrations of up to 20 ng/mL throughout the year, in addition to varying with season, declined with increasing age [38]. Atli et al., observed a significant negative correlation between 25(OH)D levels and age, among elderly Turks [40]. Brito et al., in a study of elderly women in Buenos Aires, Argentina, recorded a high prevalence of vitamin D deficiency and inadequate ingestion of calcium and vitamin D; and emphasized the role of nutritional education and vitamin D supplementation in this age group [1]. According to Hill et al., inadequate levels of vitamin D are common among the Irish, especially in young women and elderly men [30]. Roth et al., conducted a study in Bangladesh with infants from one to six months of age and found a positive correlation between age and 25(OH)D levels. In the group of 74 infants and children (one to 17 months), young age was the only risk factor for vitamin D deficiency [18]. Some of the available information on the association between 25(OH)D levels and age is conflicting. Thus, more prospective studies are needed to better understand these findings. The 25(OH)D levels tend to increase in the early stages of life; however, increasing age seems to be a risk factor for reduced vitamin D. These variations could also be related to the habits associated to each age group, such as diet and sun exposure, which are subject to geographic and cultural variations. With respect to gender, 25(OH)D levels generally tend to be higher in men, based on numerous studies [8,13,14,38]. Atli et al, studying a group of elderly Turks, found higher prevalence of vitamin D deficiency among men [40]. Bener et al., observed a high prevalence of vitamin D deficiency in Qatari children (68.8%), predominantly among girls - 51.4% [41]. Hippönen and Power reported higher means during summer and autumn, but not in winter or spring [32]. Sahu et al., found higher mean 25(OH)D levels in boys than in their sisters, at latitude 26° North in winter [17]. Thus, males usually tend to have higher 25(OH)D levels than females, reflected in the higher prevalence of vitamin D deficiency in women compared to men.

With respect to ethnicity as a determining factor of 25(OH)D levels, Looker et al., observed higher levels in non-Hispanic whites, intermediate levels in Mexican Americans, and lower values in non-Hispanic blacks [10]. Rahman et al., determined 25(OH)D levels in 276 postmenopausal women (103 Malaysans and 173 Chinese, aged 50 to 65 years). The levels of 25(OH)D were significantly lower in Malaysan women compared to their Chinese counterparts. Twenty-seven percent of the Malaysians had 25(OH)D levels between 20 and 40 ng/mL, defined as hypovitaminosis D; and 71% were between 10 and 20 ng/mL, defined as vitamin D insufficiency, compared to 87% and 11% of Chinese, respectively. A multivariate analysis revealed a significant association between ethnicity and vitamin D levels [11]. Basile et al., measured 25(OH)D levels in a sample of 100 umbilical cords of newborns in Southeastern USA at latitude 32° 72' North, recording a mean of 13.5 ng/mL. Afro-Americans had lower concentrations than Caucasians [42]. Bolland et al., reported very low mean 25(OH)D values (less than 40 nmol/L) in indigenous peoples, Middle Easterners and Africans. Darker skin tones seem to be associated with lower 25(OH)D levels, possibly due to lower absorption of UVB radiation, necessary for cutaneous vitamin D synthesis. This reduced absorption is related to the presence of melanin (skin color), which competes with 7-dyhydrocholesterol (substrate for vitamin D synthesis [38].

Vitamin D, a liposoluble substance, can be "stored" in fat tissue, and the cholecalciferol produced in the skin or acquired through food is

partially "sequestered" by body fat before being transported to the liver for its first hydroxylation. This stock of cholecalciferol is used during winter, when the sun light is not sufficient to produce this substance. Thus, obese individuals exhibit 50% reduction in the capacity of raising their vitamin D levels when compared to eutrophic subjects. Yanoff et al., in a cross-sectional study of 379 white and black adults, with BMI between 19.9 and 58.2 kg/m^2, observed an increased prevalence of hypovitaminosis D (25(OH)D < 15 ng/mL), with a rise in BMI [43]. Kull et al., also found an inverse association between BMI and 25(OH)D concentration, but with less significance when compared to tanning [34]. Lagunova et al., in an analysis of 2126 patients in Oslo, Norway, observed a higher prevalence of vitamin D deficiency in individuals with BMI greater than or equal to 40 kg/m^2 (32% of the women and 46% of the men). The results of this study suggest that one-third of women and one-half of men with BMI greater than or equal to 40 kg/m^2 are vitamin D deficient. One must emphasize that 25(OH)D levels had a negative correlation with 1,25(OH)2D levels. The seasonal variation in 25(OH)D was more significant in men under 50 years of age and non-obese [44] Jacobs et al., assessed the 25(OH)D levels of 637 individuals in Southern Arizona. Whites were subject to more significant changes with sun exposure, while blacks and Hispanics were more affected by BMI [45]. The literature has shown that an elevated BMI is a risk factor for reduced vitamin D levels, with greater relevance in groups less prone to variation due to factors such as UVB radiation, as evidenced by darker-skinned individuals. However, behavioral factors also influence the role played by BMI.

Parathyroid Hormone (PTH) and Vitamin D Levels

Pasco et al., studying Australian women, observed that decreases in 25(OH)D levels during winter were accompanied by a rise in serum PTH levels, in addition to greater bone resorption and increased number of falls and a corresponding rise in hip and wrist fractures [46] Nashimoto et al., in a study including 133 Japanese (+ 84.6 years), found a prevalence of 57.9% %, respectively, of hypovitaminosis D (iPTH > . There was a negative association between i) levels in individuals aged 80 years and older, but not in younger people [47]. Numerous studies have reported higher serum PTH levels in patients with reduced circulating 25(OH)D [14,25,28,40,48,49] Sullivan et al., associated declines in 25(OH)D levels of 28%, between September and March in 2000, 2001, 2002 and 2003, in 23 girls from Maine, USA, with a 15% rise in PTH levels [14]. Gharaibeh and Stoecker found lower PTH levels in children than in their mothers, when the former exhibited circulating levels above 25(OH)D [39]. Oliveri et al., found an inverse relationship between levels of the central molecular fragment of PTH, or mmPTH, and 25(OH)D, establishing a value of 27 ng/mL for 25(OH)D as the point at which the mmPTH begins to rise [24]. Papapetrou et al., in a comparative study of elder Greeks and young blood donors, observed similar PTH levels between the groups in summer. On the other hand, during winter, the levels obtained in the elderly were two times higher than the levels found in younger people. A rise in PTH levels was also observed when the 25(OH)D level was below 32 ng/mL, followed by secondary hyperparathyroidism [50]. Brot et al., studied 2016 Danish women and found that, although PTH levels were raised in the group with low 25(OH)D levels, the hormone was not a sensitive marker of hypovitaminosis D. Indeed, only 16% of those people presenting with 25(OH)D deficiency showed PTH values above average [21]. Elsammak et al., found no correlation between serum PTH and 25(OH)D levels in a study of 139 healthy Saudis [22]. Rosen observed that the relationship between PTH and 25(OH)D is not curvilinear, exhibiting a significant variation in PTH levels when 25(OH)D level is between 20 and 30 ng/mL. Therefore, the serum 25(OH)D level that represents the specific threshold at which elevated PTH levels would be observed was not established [20]. The present review found a more frequent negative correlation between 25(OH)D concentration and PTH levels, whether intact or fractionated. PTH concentrations are not reliable predictive data to infer vitamin D levels, and no positive correlation was demonstrated between the levels of these substances.

Conclusion

Vitamin D undeniably plays a vital role in bone metabolism as well as in numerous cell and immunological processes. Low vitamin D levels have been associated with several chronic diseases, especially rickets in children and osteoporosis in adults. Adequate vitamin D intake is extremely important in protecting against bone metabolic diseases and preventing complications, such as fractures and bone pain. However, many epidemiological aspects of vitamin D deficiency remain controversial.

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