Chapter

Vitamin D Deficiency in Children

Teodoro Durá-Travé, Fidel Gallinas-Victoriano, María Urretavizcaya-Martinez, Lotfi Ahmed-Mohamed, María Malumbres-Chacón and Paula Moreno-González

Abstract

In addition to its contribution to bone metabolism, vitamin D seems to fulfill a broad spectrum of biological functions which justifies the interest in monitoring its body content. The aim of this study is to analyze the prevalence of hypovitaminosis D and associated factors in schoolchildren and adolescents living in a region of northern Spain. A cross-sectional clinical and analytical study (calcium, phosphorus, calcidiol, and parathyroid hormone) was accomplished in a group of 602 Caucasian individuals (aged 3.1–15.4 years). Gender, age, body mass index, residence, and season of the year were recorded, and their association with vitamin D deficiency was analyzed by multiple regression. Vitamin D status was defined according to the US Endocrine Society criteria. The prevalence of hypovitaminosis D was 60.4% (insufficiency: 44.6%; deficiency: 15.8%). The female sex, adolescence, season of blood sample collection (autumn, winter, and spring), an urban residence, and severe obesity showed an association with an increased risk of hypovitaminosis D.

Keywords: associated factors, calcidiol, children, deficiency, insufficiency, prevalence, sufficiency, vitamin D

1. Introduction

Vitamin D (cholecalciferol) is a hormone that is basically synthesized in the skin after exposure to sunlight. This substance undergoes initial hepatic (25-OH-D or calcidiol) and subsequent renal [1, 25-(OH)2-D or calcitriol] hydroxylation before the definitive functional activation. The stimulation of ultraviolet radiation (type B) promotes the endogenous synthesis of vitamin D from epidermal 7-dehydrocholesterol, which is the main source of vitamin D, whereas dietary sources account for less than 10% of the total. The function in bone metabolism and calcium homeostasis has been long considered and known. Vitamin D deficiency causes a reduction in the absorption of dietary calcium and an increase in parathyroid hormone (PTH) secretion with the aim to keep steady levels of serum calcium. A deficiency in vitamin D produces osteoclastic activity and causes loss of bone mineral density [1–6].

Recent studies have shown the presence of vitamin D receptors in the majority of organs (blood vessels, B and T lymphocytes, heart, muscles, skin, brain, mammary gland, colon, prostate, gonads, etc.) and the activity of specific enzymes that are not regulated by PTH and induce calcitriol synthesis. All these findings reveal the biological significance of vitamin D. In fact, several observational studies have suggested that vitamin D deficiency could be related to a higher cardiovascular risk, as well as a risk to present autoimmune, endocrine, infectious, psychiatric, and/or neurological diseases and several types of cancer [1, 4, 7–13]. Additional studies are needed to evaluate the underlying mechanisms.

In other words, in addition to its contribution to bone metabolism, vitamin D seems to fulfill a broad spectrum of biological functions related to cell proliferation, differentiation, and metabolism, which justifies the interest in monitoring its body content. Gender, age, race, season of the year in which serum is collected, sun exposure, and nutritional status have been associated with lower levels of serum calcidiol, but there are disparities among the different authors in the interpretation of these findings [7, 9, 14–20].

The aim of this study is to determine the prevalence of hypovitaminosis D and associated factors among children in northern Spain.

2. Materials and methods

2.1 Participants

The present work is a cross-sectional study conducted in a sample of 602 individuals from ages 3.1 to 15.4 years after the completion of a clinical examination and blood testing in the period January 2014 to December 2014. Tests were carried out in the Pediatric Endocrinology Unit of our hospital. Tanner's criteria were evaluated in every individual and were used in the assignment of individuals in two different groups: school group (Tanner stage I) and adolescent group (Tanner stages II–V). The characteristics of the place of residence were recorded as urban or rural (< or > 10,000 inhabitants, respectively).

All individuals were healthy Caucasian children living in Navarra, Spain. They were selected from the external consultations of the different pediatric subspecialties and were not affected by any chronic pathology with potential interference in growth, body composition, food ingestion, or physical activity. Any participant under treatment with concrete medications (antiepileptic drugs or glucocorticoids), vitamin D, or calcium supplements was put aside from our sample.

2.2 Clinical examination

Body measurements (weight and height) were taken in specific conditions (underwear, barefoot). An Año-Sayol scale (reading interval 0–120 kg and a precision of 100 g) was used for weight registration and a Holtain wall stadiometer (reading interval 60–210 cm, precision 0.1 cm) for height registration. The program Aplicación Nutricional, from the Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition (Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica, available at http://www.gastroinf.es/nutritional/), provided the estimates of the Z-score values of BMI. The reference charts used for comparison were the graphics from Ferrández et al. (Centro Andrea Prader, Zaragoza 2002).

The values of Z-score enabled the assignment of individuals in the following groups:

- Normal: Z-score between −1.0 (15th percentile) and + 1.0 (85th percentile)
- Overweight: Z-score > 1.0 (85th percentile)
- Obesity: Z-score > 2.0 (97th percentile)
- Severe obesity: Z-score > 3.0 (99th percentile)

2.3 Blood testing

The plasma levels of calcium and phosphorous were determined in a fasting sample of blood using colorimetric methods in a cobas 8000 analyzer (Roche Diagnostic, Mannheim, Germany). The determination of calcidiol levels required a high-specific chemiluminescence immunoassay (LIAISON Assay, Diasorin, Dietzenbach, Germany) and the determination of PTH levels a highly specific solid-phase, two-site chemiluminescent enzyme-labeled immunometric assay in an Immulite analyzer (DPC Biermann, Bad Nauheim, Germany).

The distribution of individuals according to Vitamin D plasma levels followed the criteria of the US Endocrine Society [21, 22]. Calcidiol plasma levels lower than 20 ng/ml (<50 nmol/L) corresponded to Vitamin D deficiency, calcidiol levels between 20 and 29 ng/ml (50–75 nmol/L) to Vitamin D insufficiency, and concentrations equal to or higher than 30 ng/ml (>75 nmol/L) to Vitamin D sufficiency. PTH serum levels higher than 65 pg/ml [14, 17] determined secondary hyperparathyroidism.

2.4 Statistical analysis

The figures resulting from the data collection are shown as percentages (%) and means (M) including the respective standard deviations (SD) or confidence intervals (95% CI). The subsequent statistical analysis (descriptive statistics, Student's t-test, analysis of variance, $\chi 2$ test, Pearson's correlation, and multiple logistic regression analysis) was performed using the software package *Statistical Packages for the Social Sciences* version 20.0 (Chicago, IL, USA). A probability value (p-value) <0.05 was established as the level of statistical significance.

Adequate information of the proceedings and potential implications was delivered to the parents and/or legal guardians, and the corresponding consent was required prior to the inclusion in this study in all cases. The study was presented and approved after the evaluation of the Ethics Committee for Human Investigation at our institution (in line with the ethical standards stated in the Declaration of Helsinki, 1964, and later amendments).

3. Results

The average values for calcidiol and PTH plasma levels from the totality of the collections were 27.4 ± 7.7 ng/mL and 33.2 ± 17.3 pg/mL, respectively. Calcidiol levels overtook 30 ng/mL (Vitamin D sufficiency) in 236 individuals (39.6%), oscillated between 20 and 29 ng/mL (Vitamin D insufficiency) in 266 (44.6%), and were lower than 20 ng/mL (Vitamin D deficiency) in 94 (15.8%). The average values for calcium and phosphorus were 9.9 ± 0.5 and 4.6 ± 0.5 mg/dL, respectively. No values for hypo-/hypercalcemia or hypo-/hyperphosphatemia were detected. The frequency of hyperparathyroidism was significantly higher in the deficient vitamin D (11.6%) and insufficient vitamin D (6.6%) groups, whereas the prevalence of hyperparathyroidism was lowest in the sufficient vitamin D (2.3%) group ($p = 0.005$).

Table 1 shows the distribution of the presumed risk factors for hypovitaminosis D (sex, age group, place of residence, season of blood sample collection, and nutrition status).

Table 2 shows and compares the mean values for the clinical characteristics and biochemical determinations according to the risk factors for hypovitaminosis D. Mean PTH values were significantly higher ($p < 0.05$) in females. The average phosphorous values were significantly higher in males ($p < 0.05$). No significant differences were

Item	N (%)
Sex	
Female	340 (43.5%)
Male	262 (56.5%)
Age group	
Child	299 (49.7%)
Adolescent	303 (50.3%)
Residence	
Urban	394 (65.6%)
Rural	207 (34.4%)
Season of study	
Winter	180 (29.9%)
Spring	131 (21.8%)
Summer	106 (17.6%)
Autumn	185 (30.7%)
Nutritional status	
Normal weight	393 (67.3%)
Overweight	69 (11.8%)
Obesity	68 (11.6%)
Severe obesity	54 (9.2%)

Table 1.
Demographics and clinical characteristics of the participants in the study.

detected in age, nutrition situation, calcium, and calcidiol after the comparison between sexes. Calcidiol and phosphorus levels were significantly higher ($p < 0.05$) in the school group, whereas the average values for PTH were significantly higher in adolescents ($p < 0.05$). There were not any significant differences in Calcium levels between the age groups. Those individuals whose residence was in rural areas showed mean values for calcium and calcidiol significantly higher, whereas those individuals living in urban areas had PTH mean values significantly higher. There were no significant differences regarding age, BMI (Z-score), and phosphorous among individuals living in both areas. The lowest calcidiol levels corresponded to spring (26.1 ± 6.2 ng/mL), and they reached a maximum in the summer (34.5 ± 8.0 ng/mL); meanwhile, the lowest parathyroid hormone levels corresponded to summer (26.6 ± 10.1 pg./mL) and reached a maximum value in autumn (37.8 ± 17.2 pg./mL). There were not any significant differences in calcium and phosphorus levels in each season. Mean values of calcidiol and PTH were significantly lower and higher ($p < 0.05$), respectively, in the group of severe obesity than in other groups with different nutritional situations (normal, overweight, and obesity). There were no significant differences in calcidiol and phosphorous mean values among the different groups.

Table 3 exposes and compares the prevalence of the different calcidiol levels in relation to analyzed associated factors in hypovitaminosis D. We did not detect significant differences in the prevalence of the different levels in calcidiol status in relation to sex. However, the prevalence of vitamin D deficiency was significantly higher in the group of adolescents with respect to school children and rural environment. In the same way, individuals with severe obesity showed a prevalence of vitamin D deficiency significantly higher than those in different nutritional situations.

DOI: http://dx.doi.org/10.5772/intechopen.89208

Item	Age (years)	BMI (Z-score)	Calcium (mg/dl)	Phosphorus (mg/dl)	Calcidiol (ng/ml)	PTH (pg/ml)
Sex						
Females	9.88 ± 3.18	0.47 ± 1.69	10.01 ± 0.37	4.52 ± 0.59	26.88 ± 7.75	35.72 ± 18.46
Males	9.98 ± 3.44	0.41 ± 2.10	9.98 ± 0.36	4.71 ± 0.57	27.98 ± 7.69	29.90 ± 15.27
Significance (p)	0.720	0.720	0.348	<0.001	0.083	<0.001
Age group						
School	7.19 ± 2.08	0.17 ± 1.78	10.01 ± 0.38	4.73 ± 0.54	28.50 ± 7.44	30.87 ± 15.42
Adolescent	12.62 ± 1.62	0.71 ± 2.2	9.97 ± 0.34	4.47 ± 0.61	26.22 ± 7.86	35.58 ± 18.91
Significance (p)	<0.001	<0.001	0.157	<0.001	<0.001	<0.001
Residence						
Urban	10.06 ± 3.28	0.44 ± 2.11	9.97 ± 0.35	4.60 ± 0.58	26.46 ± 7.74	34.49 ± 17.64
Rural	9.67 ± 3.31	0.47 ± 1.85	10.05 ± 0.37	4.61 ± 0.60	29.02 ± 7.47	30.89 ± 16.76
Significance (p)	0.171	0.885	0.008	0.807	<0.001	0.019
Season						
Winter	9.78 ± 3.07	0.49 ± 2.5	10.04 ± 0.33	4.57 ± 0.56	26.54 ± 7.39	31.02 ± 18.03
Spring	10.24 ± 3.14	0.55 ± 1.74	10.02 ± 0.37	4.61 ± 0.56	26.11 ± 6.25	32.28 ± 18.05
Summer	10.44 ± 3.28	0.46 ± 2.73	9.97 ± 0.29	4.66 ± 0.64	34.52 ± 8.05	26.65 ± 10.06
Autumn	9.65 ± 3.56	0.33 ± 1.85	9.93 ± 0.40	4.60 ± 0.59	26.26 ± 7.42	37.88 ± 17.21
Significance (p)	0.182	0.806	0.119	0.731	<0.001	<0.001
Nutritional status						
Normal	9.62 ± 3.34	−0.64 ± 0.94	9.98 ± 0.36	4.59 ± 0.57	28.18 ± 7.7	31.11 ± 15.58
Overweight	10.43 ± 2.6	1.37 ± 0.29	10.02 ± 0.38	4.62 ± 0.55	27.65 ± 7.35	33.12 ± 16.25
Obesity	11.09 ± 2.4	2.46 ± 0.28	10.05 ± 0.36	4.66 ± 0.62	26.19 ± 7.01	39.9 ± 20.26
Severe obesity	11.1 ± 3.28	4.66 ± 2.24	9.96 ± 0.36	4.54 ± 0.72	23.09 ± 8.24	45.22 ± 22
Significance (p)	<0.001	<0.001	0.447	0.721	<0.001	<0.001

Table 2.
Clinical and biochemical characteristics according to the presumed risk factors for hypovitaminosis D (M ± DE).

Item	Deficiency N (%)	Insufficiency N (%)	Sufficiency N (%)	Chi² (p)
Sex				
Females	56 (16.7%)	161 (47.9%)	119 (35.4%)	5.65 (0.059)
Males	38 (14.6%)	105 (40.4%)	117 (45%)	
Age group				
School	31 (11.1%)	131 (44.3%)	132 (44.6%)	11.696 (0.003)
Adolescent	61 (20.3%)	135 (45%)	104 (34.7%)	
Residence				
Urban	75 (19.3%)	175 (45%)	139 (35.7%)	12.671 (0.002)
Rural	19 (9.2%)	91 (44.2%)	96 (46.6%)	
Season				
Winter	40 (21.1%)	79 (41.6%)	71 (37.4%)	
Spring	17 (13.3%)	76 (59.4%)	35 (27.3%)	69.12 (<0.001)
Summer	4 (5.3%)	11 (14.7%)	60 (80%)	
Autumn	33 (16.3%)	100 (49.3%)	70 (34.5%)	
Nutritional status				
Normal	46 (11.8%)	176 (45.1%)	168 (43.1%)	
Overweight	11 (15.9%)	27 (39.1%)	31 (44.9%)	30.135 (<0.001)
Obesity	12 (18.2%)	33 (50%)	21 (31.8%)	
Severe obesity	20 (37.7%)	23 (43.4%)	10 (18.9%)	

Table 3.
Prevalence of the different calcidiol levels in relation to the presumed risk factors for hypovitaminosis D.

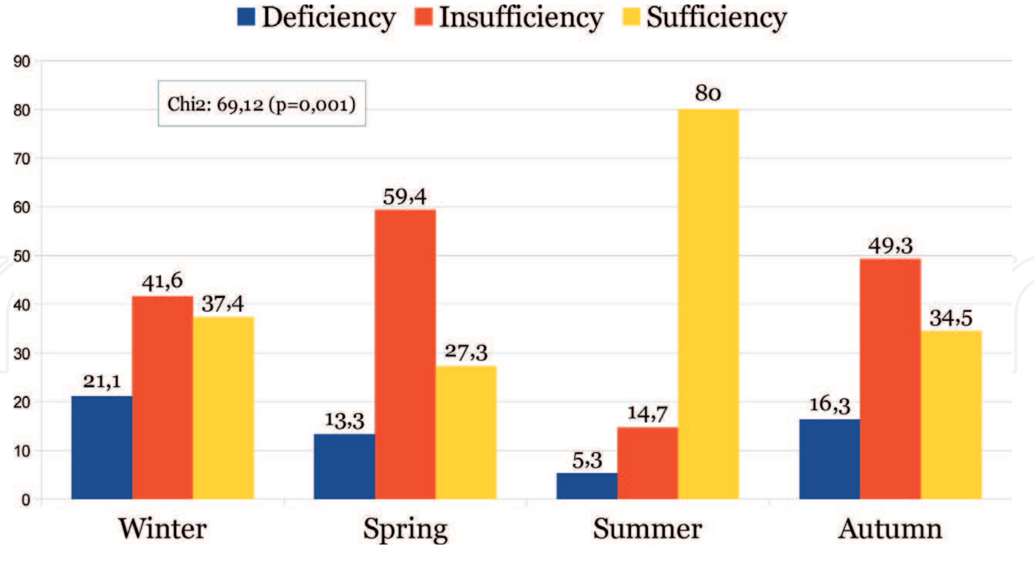

Figure 1.
Prevalence of vitamin D status according to seasons.

Figure 1 presents the prevalence of hypovitaminosis D (deficiency and insufficiency) according to the seasons of the year in healthy pediatric population. The levels of vitamin D during summer was sufficient in 80% of the individuals; this level substantially decreased in autumn and winter (hypovitaminosis was detected in 65.6% and 62.7% during autumn and winter, respectively) and got to the lowest point in spring, a period that revealed a prevalence of hypovitaminosis of 72.7%.

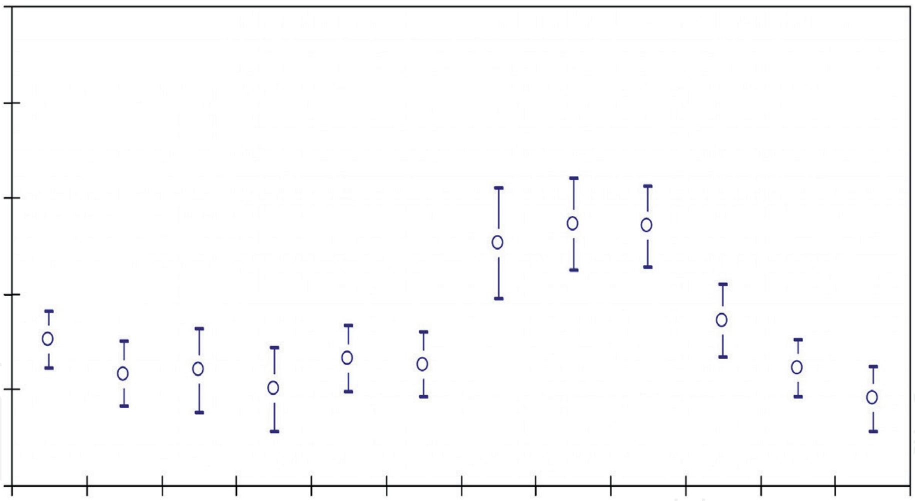

Figure 2.
Calcidiol levels (ng/ml ± CI 95%) throughout the year (ANOVA, p < 0.001).

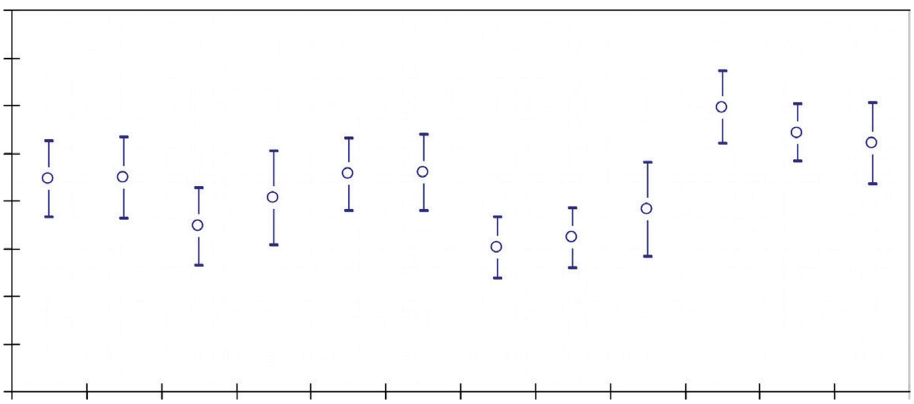

Figure 3.
PTH levels (pg/ml ± CI 95%) in the different months of the year (ANOVA, p < 0.001).

Figure 2 states the average values for calcidiol levels along the months of the year (ANOVA, p < 0.001), showing the highest levels during the summer months (July: 32.6 ng/mL, CI 95%: 29.7–35.5; August: 33.6 ng/mL, CI 95%: 31.2–36; and September: 33.5 ng/mL, CI 95%: 31.4–35.6); in contrast, these levels were lower during the winter and spring months.

Figure 3 presents the PTH levels (average) in the different months of the year (ANOVA, p < 0.001). The autumn months show the highest PTH levels (October: 39.8 pg/mL, CI 95%: 35.4–43.6; November: 37.1 pg/mL, CI 95%: 34.1–34.1; and December: 36.0, CI 95%: 31.7–40.3) and the end of spring (May: 32.8 pg/mL, CI 95%: 29.0–36.6 and June: 33.0 pg/mL, CI 95%: 29.0–37.0); in contrast, these levels were lower in the summer months (July: 25.1 pg/mL, CI 95%: 21.9–28.3 and August: 26.1 pg/mL, CI 95%: 23.0–29.2).

A significant correlation (p < 0.001) between calcidiol and parathyroid hormone levels (r = −0.24) was observed; calcium and PTH plasma levels (r = −0.20) are also correlated. A significant correlation was detected between age and calcidiol levels (r = −0.15) and also between age and PTH levels (r = 0.18).

Table 4 illustrates the multiple logistic regression analysis for the presumed predictors of vitamin D status. The female sex, adolescence, season of blood sample collection (autumn, winter, and spring), an urban residence, and severe obesity showed an association with an increased risk of vitamin D insufficiency. Adolescence, season of blood sample collection (autumn and winter), urban residence, and severe obesity revealed an association with an increased risk of vitamin D deficiency.

Items	Deficiency OR (IC 95%) p	Insufficiency OR (CI 95%) p
Sex		
Males	1 (reference)	1 (reference)
Females	1.1 (0.9–1.8) 0.676	1.6 (1.1–2.3) 0.011
Age group		
School	1 (reference)	1 (reference)
Adolescent	2.0 (1.2–3.4) 0.005	1.8 (1.2–2.6) 0.003
Season		
Summer	1 (reference)	1 (reference)
Autumn	3.8 (1.3–11.5) 0.018	9.5 (4.8–18.7) <0.001
Winter	5.8 (1.9–17.4) 0.002	8.8 (4.5–17.5) <0.001
Spring	3.1 (0.9–9.9) 0.058	13.2 (6.4–27.5) <0.001
Residence		
Rural	1 (reference)	1 (reference)
Urban	2.4 (1.4–4.0) 0.020	1.6 (1.1–2.2) 0.01
Nutritional status		
Normal	1 (reference)	1 (reference)
Overweight	1.3 (0.7–1.8) 0.442	0.8 (0.5–1.4) 0.476
Obesity	1.3 (0.7–2.8) 0.443	1.2 (0.7–2.2) 0.498
Severe obesity	4.4 (2.2–8.6) <0.001	4.4 (1.9–10.3) <0.001

Table 4.
Multiple logistic regression analysis for the presumed risk factor for hypovitaminosis (deficiency and insufficiency).

4. Discussion

There is a high prevalence of hypovitaminosis D in the pediatric population in our environment, which potentially represents a serious public health problem. The criteria from the US Endocrine Society have been used for the comparison of the results with the previous published data. According to these criteria, calcidiol has a long half-life (2 to 3 weeks) and is the best indicator of body vitamin D content; they consider normal serum levels when they reach 30 ng/mL or higher and hypovitaminosis D below this level. In this way, hypovitaminosis is classified into insufficiency (between 21 and 29 ng/mL) and deficiency (lower than 20 ng/mL) [4, 21, 22].

The blood sample analysis shows the following prevalence: vitamin D sufficiency in 39.6% of the individuals, insufficiency 44.6% and deficiency 15.8%, respectively. These results might seem to show a high prevalence of hypovitaminosis for a healthy population, but are indeed relatively moderate in comparison to other studies published in different areas or latitudes of our planet (**Table 5**); this may

Authors	Deficiency	Insufficiency	Sufficiency
Cheng et al., 2003 (Jyväskylä, Finland) [23]	32%	46%	22%
Weng et al., 2007 (Philadelphia, USA) [14]	26%	29%	45%
Gordon et al., 2008 (Boston, USA) [24]	12%	40%	48%
Kelly et al., 2011 (Filadelfia, USA) [25]	47%	27%	26%
Andiran et al., 2012 (Ankara, Turkey) [26]	40%	—	—
Tolppanen et al., 2012 (England, UK) [27]	29%	46%	25%
González-Cross et al., 2012 (Europe) [28]	19%	39%	42%
Vierucci et al., 2013 (Toscana, Italy) [17]	46%	34%	20%
Karagüzel et al., 2014 (Trabzon, Turkey) [29]	71%	23%	6%
Durá-Travé et al., 2015 (Navarra, Spain) [30]	13%	45%	42%
Kaddam et al., 2017 (Saudi Arabia) [31]	49%	46%	5%
Fernández-Bustillo et al., 2018 (Galicia, Spain) [32]	5.9%	60.1%	34%
Guo et al., 2018 (China) [33]	10.8%	39%	50.2%

Table 5.
Prevalence of hypovitaminosis D according to different authors.

be due to the fact that in this study their participants were exclusively of Caucasian origin, since, as is well known, the difference in skin pigmentation in different ethnic groups implies a higher risk of hypovitaminosis D [14, 17, 18, 28, 32, 34–37].

Calcidiol measurements—even though they were not significant—were higher in males, whereas PTH levels were significantly higher in females, but there were no significant differences in the prevalence of hypovitaminosis D among sexes. Previously published data are inconsistent [9, 34, 38, 39]. Nevertheless, the logistic regression analysis revealed that hypovitaminosis D, and more specifically the level of insufficiency, was significantly associated with females. Adolescents (pubertal group) had significantly lower calcidiol levels than school children, but the mean values for PTH and the prevalence of hypovitaminosis D were significantly higher in that group, and these results match those provided by other authors [17, 40]. Furthermore, the logistic regression analysis showed that hypovitaminosis D, as insufficiency and deficiency, was significantly associated to the older group. These findings could be somehow disturbing, since adolescence is a key period for growing, development, and bone formation, when vitamin D requirements are increased and deficiency may affect normal bone mass acquisition. Individuals living in urban areas had calcidiol values significantly lower than those living in rural areas, whereas PTH values and prevalence of vitamin D deficiency were significantly higher in those individuals from urban areas. These findings might be related to the different lifestyles inherent to the different environment, since residents in rural areas are likely to experience longer periods of sun exposure, as several authors have highlighted [17, 19].

The characteristics of sun exposure depend considerably on the location. In this way, it has been found how the axial tilt (obliquity) of our planet in the northern hemisphere (beyond 37th parallel—north), mainly in the colder months of the year, causes a change in the density of incident rays and, therefore, the ultraviolet radiation (type B) decreases up to 80–100%. That is the reason why sun radiation is not able to lead to efficient vitamin D synthesis [14, 17, 29, 41]. Hence the main reasons of vitamin D deficiency are usually in direct relation either to any physical agents that obstruct sun radiation (cutaneous pigmentation, sunscreens, etc.) or to geographical features, such as sunlight exposure, atmospheric pollution, altitude, latitude, and the season of the year [1, 3].

The negative correlation between calcidiol and parathyroid hormone plasma levels has been previously described by different authors [14, 17, 33, 42]; nonetheless, the discussion about the combined oscillations existing among both hormones along a natural year has not been that intense [43, 44]. The analysis of our data has shown simultaneous and asynchronous changes in parathyroid hormone levels with respect to calcidiol, simultaneously with monthly and/or seasonal modifications in calcidiol levels. These adjustments presumably would take place in order to maintain constant calcium levels along the year, as we have noticed in this study. In point of fact, the highest body vitamin D levels are detected in the summer months—there is a more intense sunlight exposure. The levels decrease gradually in the autumn and winter months—except for some biological variability—and they reach the lowest point in springtime. By comparison to the findings of other authors [3, 17, 29], only 18.2% of the 602 individuals classified in the status of vitamin D insufficiency of deficiency presented with PTH levels within the range of hyperparathyroidism; since no diagnosis of hypercalcemia or hypocalcaemia or any bone semiology was previously described, a potential conclusion is that seasonal changes in calcidiol and parathyroid hormone levels would be related to a physiological phenomenon of adaptation to the geographical and climatic conditions endemic to this region. Navarre is a Spanish region located on a high latitude (between 41°55″22 N and 43°16″42 N) with frequent cloudy and rainy days, and this characteristic is important enough to take into consideration that cyclical variation in calcidiol levels in relation to the season of the year could be explained by a possible inefficient vitamin synthesis induced by sun radiation, as several authors have noted [14, 17, 24, 29, 42, 45–47]. Admittedly, the results confirm that vitamin D levels in the summer months were sufficient in 80% of the individuals. They moderately decrease in the months of autumn and winter (the percentage of individual in a situation of hypovitaminosis D gets to 66.6 and 62.7% in autumn and winter, respectively) and fall to the lowest point in spring months, when the prevalence of hypovitaminosis gets to 72.7%.

Because geographical and climatic conditions significantly influence body vitamin D content and, secondarily, PTH plasma levels, a comparison of the different results obtained in the published works from different countries and/or climatic conditions would be unwise and faulty, since the place of residence, latitude, and especially the month of the year when the blood sample is collected always have to be considered. In other words, it is not possible to establish a vitamin D status in a concrete population without considering the seasonal variations because, as this work has shown, a potential condition of hypovitaminosis D is related to the season of the year in which the determination has been made [48, 49].

As BMI (Z-score) increases, calcidiol values decrease and PTH significantly rises, in a way that individuals with severe obesity showed minimum values of calcidiol and maximum values of PTH with respect to the individuals of the remaining nutritional situations. This means, there seems to be a noticeable tendency to present with vitamin D deficiency in the individuals with severe obesity [9, 20, 40, 50]; this eventuality has been outlined as a cardiovascular and/or metabolic risk factor [4, 8–10, 15, 19]. Even though there is not a conclusive explanation in this respect, it has been suggested that this circumstance in obese individuals may be related to environmental factors (decreased sun exposure as a consequence of a sedentary lifestyle, inadequate diet, etc.), although, at present, some authors postulate a hypothetical "sequestration" or excessive accretion of vitamin D in the adipose tissue [2, 4, 7, 8, 16, 18, 21, 42]. Previous reports did not distinguish between obesity and severe obesity, as we did in this work, and this special feature could be of practical relevance, since the logistic regression analysis has verified that hypovitaminosis

D, in levels of insufficiency as well as deficiency, is significantly associated to the nutritional situation of severe obesity.

The development of this study unveiled several limitations. The main weaknesses are the cross-sectional nature of the study and the absence of data on exercise, sun exposure, and the use of sunscreens. There have been some difficulties to get adequate and accurate data, and it restrained us from completing the registration. A nutritional survey (including dietary vitamin D intake, daily supplementation, etc.) was not incorporated in the study. Our experience reflects that dairy product intake in our social context is below the recommended amount and particularly fish intake is quite low in the pediatric population [51]; in this way, only the dietary supplementation of vitamin D could condition the results achieved, but, at present, it is not a widespread practice in our society.

Given the difficulties in maintaining a sufficient body vitamin D content in the pediatric age group throughout the year, the prevention, detection, and, when required, treatment and follow-up of hypovitaminosis should be fully integrated in the programs of health promotion and disease prevention in child and adolescent population corresponding to primary health care. In other words, primary care teams and, more specifically, pediatricians should include a series of preventive measures—in addition to the mandatory vitamin D daily supplementation during the first year of life, 400 UI per day [4, 52, 53], such as promoting adequate sun exposure, in the service portfolio. Around 10–15 minutes of midday sun exposure (between 10 in the morning and 3 in the afternoon) on at least 20% of total body surface (uncovered head and extremities) during spring, summer, and autumn is considered enough to get an adequate vitamin D synthesis [2]. In addition, in case any of the hypovitaminosis D-associated factors is present, especially in those individuals at risk of limited sun exposure (disabled and/or undergoing long stay in the hospital, etc.), the need for additional vitamin D supplementation should be considered, either as pharmacological supplements (600 IU per day), an increase of the ingestion of higher amounts from its natural dietary sources (herring, salmon, sardines, tuna, etc.), or vitamin D fortified foods (dairy products, cereals, etc.) during the months of winter and spring, as several authors have suggested [6, 12, 14, 15, 18, 21, 28, 34, 54].

5. Conclusion

There is a high prevalence of hypovitaminosis D in the pediatric population in our environment, being female sex, pubertal age, the seasons of autumn, winter and spring, living in urban area, and severe obesity considered as associated factors in hypovitaminosis D. Consideration should be given to the administration of vitamin supplements and/or the increase in the ingestion of natural vitamin D dietary sources.

Author details

Teodoro Durá-Travé[1,2,3]*, Fidel Gallinas-Victoriano[2], María Urretavizcaya-Martinez[2], Lotfi Ahmed-Mohamed[2], María Malumbres-Chacón[2] and Paula Moreno-González[2]

1 Department of Pediatrics, School of Medicine, University of Navarra, Pamplona, Spain

2 Department of Pediatrics, Navarra Hospital Complex, Pamplona, Spain

3 Navarra Institute for Health Research (IdisNA), Pamplona, Spain

*Address all correspondence to: tduratra@cfnavarra.es

References

[1] Holick MF. Vitamin D deficiency. The New England Journal of Medicine. 2007;**357**:266-281. DOI: 10.1056/NEJMra070553

[2] Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. Pediatrics. 2008;**122**:398-417. DOI: 10.1542/peds.2007-1894

[3] Hossein-Nezhad AS, Holick MF. Optimize dietary intake of vitamin D: An epigenetic perspective. Current Opinion in Clinical Nutrition and Metabolic Care. 2012;**15**:567-579. DOI: 10.1097/MCO.0b013e3283594978

[4] Palermo NE, Holick MF. Vitamin D, bone health, and other health benefits in pediatric patients. Journal of Pediatric Rehabilitation Medicine. 2014;**7**:179-192. DOI: 10.3233/PRM-140287

[5] Ritu G, Gupta A. Vitamin D deficiency in India: Prevalence, causalities and interventions. Nutrients. 2014;**6**:729-775. DOI: 10.3390/nu6020729

[6] Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Reviews in Endocrine & Metabolic Disorders. 2017;**18**:153-165. DOI: 10.1007/s11154-017-9424-1

[7] Alemzadeh R, Kichler J, Babar G, Calhoun M. Hypovitaminosis D in obese children and adolescents: Relationship with adiposity, insulin sensitivity, ethnicity, and season. Metabolism. 2008;**57**:183-191. DOI: 10.1016/j.metabol.2007.08.023

[8] Roth CL, Elfers C, Kratz M, Hoofnagle AN. Vitamin D deficiency in obese children and its relationship to insulin resistance and adipokines. Journal of Obesity. 2011;**2011**:495101. DOI: 10.1155/2011/495101

[9] Pacifico L, Anania C, Osborn JF, Ferraro F, Bonci E, Olivero E, et al. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. European Journal of Endocrinology. 2011;**165**:603-611. DOI: 10.1530/EJE-11-0545

[10] Olson ML, Maalouf NM, Oden JD, White PC, Hutchison MR. Vitamin D deficiency in obese children and its relationship to glucose homeostasis. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**:279-285. DOI: 10.1210/jc.2011-1507

[11] Mezza T, Muscogiuri G, Sorice GP, Prioletta A, Salomone E, Pontecorvi A, et al. Vitamin D deficiency: A new risk factor for type 2 diabetes. Annals of Nutrition & Metabolism. 2012;**61**:337-348. DOI: 10.1159/000342771

[12] Muscogiuri G, Mitri J, Mathieu C, Badenhoop K, Tamer G, Orio F, et al. Mechanisms in endocrinology: Vitamin D as a potential contributor in endocrine health and disease. European Journal of Endocrinology. 2014;**171**:101-110. DOI: 10.1530/EJE-14-0158

[13] Navarro-Valverde C, Quesada-Gomez JM. Vitamin D, determinant of bone and extrabone health. Importance of vitamin D supplementation in milk and dairy products. Nutrición Hospitalaria. 2015;**31**(Suppl. 2):18-25. DOI: 10.3305/nh.2015.31

[14] Weng FL, Shults J, Leonard MB, Stallings VA, Zemel BS. Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. The American Journal of Clinical Nutrition. 2007;**86**:150-158. DOI: 10.1093/ajcn/86.1.150

[15] Reinehr T, De Sousa G, Alexy U, Kersting M, Andler W. Vitamin D status and parathyroid hormone in obese children before and after weight loss. European Journal of Endocrinology. 2007;**157**:225-232. DOI: 10.1530/eje-07-0188

[16] Pérez-López FR, Pérez-Roncero G, López-Baena MT. Vitamin D and adolescent health. Adolescent Health, Medicine and Therapeutics. 2010;**1**:1-8. DOI: 10.2147/AHMT.S7472

[17] Vierucci F, Del Pistoia M, Fanos M, Gori M, Carlone G, Erba P, et al. Vitamin D status and predictors of hypovitaminosis D in Italian children and adolescents: A cross-sectional study. European Journal of Pediatrics. 2013;**172**:1607-1617. DOI: 10.1007/s00431-013-2119-z

[18] Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. Pediatrics. 2013;**131**:e152-e161. DOI: 10.1542/peds.2012-1711

[19] Bellone S, Esposito S, Giglione E, Genoni G, Fiorito C, Petri A, et al. Vitamin D levels in a paediatric population of normal weight and obese subjects. Journal of Endocrinological Investigation. 2014;**37**:805-809. DOI: 10.1007/s40618-014-0108-3

[20] Radhakishun N, van Vliet M, von Rosenstiel I, Weijer O, Diamant M, Beijnen J, et al. High prevalence of vitamin D insufficiency/deficiency in Dutch multiethnic obese children. European Journal of Pediatrics. 2015;**174**:183-190. DOI: 10.1007/s00431-014-2378-3

[21] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Valuation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism. 2011;**96**:1911-1930. DOI: 10.1210/jc.2011-0385

[22] Holick MF, Binkley NC, Bischoff-Ferrari HA. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**:1153-1158. DOI: 10.1210/jc.2011-2601

[23] Cheng S, Tylavsky F, Kröger H, Kärkkäinen M, Lyytikäinen A, Koistinen A, et al. Association of low 25-hydroxyvitamin D concentrations with elevated parathyroid hormone concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. The American Journal of Clinical Nutrition. 2003;**78**:485-942. DOI: 10.1093/ajcn/78.3.485

[24] Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. Archives of Pediatrics & Adolescent Medicine. 2008;**162**:505-512. DOI: 10.1001/archpedi.162.6.505

[25] Kelly A, Brooks LJ, Dougherty S, Carlow DC, Zemel BS. A cross-sectional study of vitamin D and insulin resistance in children. Archives of Disease in Childhood. 2011;**96**:447-452. DOI: 10.1136/adc.2010.187591

[26] Andıran N, Çelik N, Akça H, Doğan G. Vitamin D deficiency in children and adolescents. Journal of Clinical Research in Pediatric Endocrinology. 2012;**4**:25-29. DOI: 10.4274/jcrpe.574

[27] Tolppanen AM, Fraser A, Fraser WD, Lawlor DA. Risk factors for variation in 25-hydroxyvitamin D_3 and D_2 concentrations and vitamin D deficiency in children. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**:1202-1210. DOI: 10.1210/jc.2011-2516

[28] González-Gross M, Valtueña J, Breidenassel C, Moreno LA, Ferrari M, Kersting M, et al. Vitamin D status among adolescents in Europe: The healthy lifestyle in Europe by nutrition in adolescence study. The British Journal of Nutrition. 2012;**107**:755-764. DOI: 10.1017/S0007114511003527

[29] Karagüzel G, Dilber B, Can G, Ökten A, Değer O, Holick MF. Seasonal vitamin D status of healthy schoolchildren and predictors of low vitamin D status. Journal of Pediatric Gastroenterology and Nutrition. 2014;**58**:654-660. DOI: 10.1097/MPG.0000000000000274

[30] Durá-Travé T, Gallinas-Victoriano F, Chueca Guindulain MJ, Berrade-Zubiri S. Vitamin D deficiency among children and adolescents with normal nutricional status. Nutrición Hospitalaria. 2015;**32**:1061-1066. DOI: 10.3305/nh.2015.32.3.9316

[31] Kaddam IM, Al-Shaikh AM, Abaalkhail BA, Asseri KS, Al-Saleh YM, Al-Qarni AA, et al. Prevalence of vitamin D deficiency and its associated factors in three regions of Saudi Arabia. Medizinhistorisches Journal. 2017;**38**:381-390. DOI: 10.15537/smj.2017.4.18753

[32] Fernández-Bustillo JM, Fernández-Pombo A, Gómez-Bahamonde R, Sanmartín-López GO. Vitamin D levels in a pediatric population of a primary care Centre: A public health problem? BMC Research Notes. 2018;**11**:801. DOI: 10.1186/s13104-018-3903-7

[33] Guo Y, Ke HJ, Liu Y, Fu M, Ning J, Xiao Y, et al. Prevalence of vitamin D insufficiency among children in southern China: A cross-sectional survey. Medicine (Baltimore). 2018;**97**:e11030. DOI: 10.1097/MD.0000000000011030

[34] Harkness L, Cromer B. Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females. Osteoporosis International. 2005;**16**:109-113. DOI: 10.1007/s00198-004-1656-8

[35] Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-1004. Pediatrics. 2009;**124**:362-370. DOI: 10.1542/peds.2009-0051

[36] Bener A, Al-Ali M, Hoffmann GF. Vitamin D deficiency in healthy children in a sunny country: Associated factors. International Journal of Food Sciences and Nutrition. 2009;**60**:60-70. DOI: 10.1080/09637480802400487

[37] Gutiérrez-Medina S, Gavela-Pérez T, Domínguez-Garrido MN, Gutiérrez-Moreno E, Rovira A, Garcés C, et al. The influence of puberty on vitamin D status in obese children and the possible relation between vitamin D deficiency and insulin resistance. Journal of Pediatric Endocrinology & Metabolism. 2015;**28**:105-110. DOI: 10.1515/jpem-2014-0033

[38] Saintonge S, Bang H, Gerber LM. Implications of a new definition of vitamin D deficiency in a multiracial us adolescent population: The National Health and nutrition examination survey III. Pediatrics. 2009;**123**:797-803. DOI: 10.1542/peds.2008-1195

[39] Al-Ghamdi MA, Lanham-New SA, Kahn JA. Differences in vitamin D status and calcium metabolism in Saudi Arabian boys and girls aged 6 to 18 years: Effects of age, gender, extent of veiling and physical activity with concomitant implications for bone health. Public Health Nutrition. 2012;**15**:1845-1853. DOI: 10.1017/S1368980011003612

[40] Rajakumar K, de las Heras J, Chen TC, Lee S, Holick MF, Arslanian SA. Vitamin D status, adiposity, and lipids in

black American and Caucasian children. The Journal of Clinical Endocrinology and Metabolism. 2011;**96**:1560-1567. DOI: 10.1210/jc.2010-2388

[41] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: Exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. The Journal of Clinical Endocrinology and Metabolism. 1988;**67**:373-378. DOI: 10.1210/jcem-67-2-373

[42] Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States a review of the current evidence. Archives of Pediatrics & Adolescent Medicine. 2008;**162**:513-519. DOI: 10.1001/archpedi.162.6.513

[43] Abrams SA, Griffin IJ, Hawthorne KM, Gunn SK, Gundberg CM, Carpenter TO. Relationships among vitamin D levels, parathyroid hormone, and calcium absorption in young adolescents. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**:5576-5581. DOI: 10.1210/jc.2005-1021

[44] Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick MF. Adolescent girls in Maine are at risk for vitamin D insufficiency. Journal of the American Dietetic Association. 2005;**105**:971-974. DOI: 10.1016/j.jada.2005.03.002

[45] El-Hajj Fuleihan G, Nabulsi M, Choucair M, Salamoun M, Hajj Shahine C, Kizirian A, et al. Hypovitaminosis D in healthy schoolchildren. Pediatrics. 2001;**107**:E53. DOI: 10.1542/peds.107.4.e53

[46] Stein EM, Laing EM, Hall DB, Hausman DB, Kimlin MG, Johnson MA, et al. Serum 25-hydroxyvitamin D concentrations in girls aged 4-8 y living in the southeastern United States. The American Journal of Clinical Nutrition. 2006;**83**:75-81. DOI: 10.1093/ajcn/83.1.75

[47] Willis CM, Laing EM, Hall DB, Hausman DB, Lewis RD. A prospective analysis of plasma 25-hydroxyvitamin D concentrations in white and black prepubertal females in the southeastern United States. The American Journal of Clinical Nutrition. 2007;**85**:124-130. DOI: 10.1093/ajcn/85.1.124

[48] Petersen RA, Damsgaard CT, Dalskov SM, Sorensen LB, Hjorth MF, Ritz C, et al. Vitamin D status and its determinants during autumn in children at northern latitudes: A cross-sectional analysis from the optimal well-being, development and health for Danish children through a healthy New Nordic diet (OPUS) school meal study. The British Journal of Nutrition. 2016;**115**:239-250. DOI: 10.1017/S000711451500433X

[49] Hansen L, Tjonneland A, Koster B, Brot C, Andersen R, Cohen AS, et al. Vitamin D status and seasonal variation among Danish children and adults: A descriptive study. Nutrients. 2018;**10**:E1801. DOI: 10.3390/nu10111801

[50] Shapses SA, Lee EJ, Sukumar D, Durazo-Arvizu R, Schneider SH. The effect of obesity on the relationship between serum parathyroid hormone and 25-hydroxyvitamin D in women. The Journal of Clinical Endocrinology and Metabolism. 2013;**98**:E886-E890. DOI: 10.1210/jc.2012-3369

[51] Durá-Travé T, Gallinas-Victoriano F. Dietary pattern among schoolchildren with normal nutritional status in Navarre, Spain. Nutrients. 2014;**6**:1475-1487. DOI: 10.3390/nu6041475

[52] Wagner CL, Greer FD. American Academy of Pediatrics section on breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D

deficiency in infants, children, and adolescents. Pediatrics. 2008;**122**: 1142-1152. DOI: 10.1542/peds.2008-1862

[53] Martínez-Suárez V, Moreno-Villares JM, Dalmau-Serra J. Recomendaciones de ingesta de calcio y vitamina D: Posicionamiento del Comité de Nutrición de la Asociación Española de Pediatría. Anales de Pediatría (Barcelona, Spain). 2012;**77**:e1-e8. DOI: 10.1016/j.anpedi.2011.11.024

[54] Gill TK, Hill CL, Shanahan EM, Taylor AW, Appleton SL, Grant JF, et al. Vitamin D levels in an Australian population. PublicHealth. 2014;**14**:1001. DOI: 10.1186/1471-2458-14-1001