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ORIGINAL ARTICLE

Vitamin D status in children with prolonged hospitalization for chronic respiratory diseases

Estado de vitamina D en pacientes con hospitalización prolongada por enfermedades respiratorias crónicas

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What do we know about the subject matter of this study?

Vitamin D deficiency can aggravate the evolution of children with chronic respiratory diseases, favoring infections and affecting lung development and growth. Around 30-40% of prevalence has been described in children with acute respiratory diseases.

What does this study contribute to what is already known?

We report 39% of vitamin D deficiency/insufficiency in children with chronic respiratory diseases hospitalized for prolonged periods, almost all of them previously supplemented. A lower vitamin D dose was the only associated factor that warranted monitoring of 25OH vitamin D to adjust supplementation.

Abstract

Children with chronic respiratory diseases (CRD) are at high risk of vitamin D deficiency, which can be aggravated in those hospitalized for prolonged periods, a group with unknown prevalence. **Objective:** to determine the vitamin D status and the risk factors in children with CRD hospitalized for prolonged periods. **Patients and Method:** Cross-sectional study carried out at the *Hospital Josefina Martinez* from September to December 2012, in children with CRD. We registered demographic and anthropometry data, hospital length of stay, sun exposure, supplementation, and dietary intake of vitamin D. 25-Hydroxyvitamin D (25(OH)D) was measured in ng/mL, defining as sufficiency (> 30), insufficiency (20-30), and deficiency (< 20). **Results:** 41 patients were studied, 56.1% were boys, with a median age of 31 months (range 5 to 146). 51.2% had a neurological disease, 61.0% were eutrophic, and 58.5% had no sun exposure. Most of the patients (90.2%) received vitamin D supplementation: 65.8% received 400 IU/day and 24.4% received 800. The mean concentration of 25(OH)

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D was 31.02 ± 6.82 ng/mL, therefore, 61% had sufficiency, 34.1% insufficiency, and 4.9% deficiency. Patients receiving 800 IU/day had higher 25(OH)D concentrations than those with lower doses (p = 0.032), showing no association between 25(OH)D and sex, age, nutritional status, motor function, sun exposure, length of stay, or anticonvulsants use. **Conclusion:** This group of children with CRD and prolonged hospitalization had a high prevalence of suboptimal vitamin D status, despite receiving preventive supplementation, thus justifying an adequate monitoring and dosage adjustment.

Abbreviations

25(OH)D:	Plasma 25-Hydroxyvitamin D.
AAP:	American Academy of Pediatrics.
CRD:	Chronic Respiratory Diseases.
GFMCS:	Gross Motor Function Classification System.
WHO:	World Health Organization.
IQR:	Interquartile range.
IU:	International Units.
VitD:	Vitamin D.

Introduction

There is a high prevalence of vitamin D (vitD) deficiency worldwide, affecting 9% of the pediatric population in the United States and 10-30% in European countries[1-3]. In Mexican preschoolers, 24% have vitD insufficiency and, in the southern Chilean zone (southern latitude greater than 40°), it reaches 64% of deficiency[4,5].

VitD status is estimated based on the plasma concentration of 25-Hydroxyvitamin D (25(OH)D), according to which different scientific societies have defined deficiency as 25(OH)D < 20 ng/mL, insufficiency between 21 and 29 ng/mL, and sufficiency ≥ 30 ng/mL[6-8].

Humans obtain vitD from food and supplements, but it is mainly synthesized endogenously, a process that is initiated in the skin by the conversion of 7-dehydrocholesterol to previtamin D3 as a result of sunlight exposure, specifically ultraviolet radiation. Skin pigmentation, use of sunscreen, time of day, season, latitude, and exposed skin area are factors that influence this process. Previtamin D is hydroxylated in the liver (25(OH)D) and later in the kidneys, resulting in the active compound 1.25(OH)vitD[2].

The main function of vitD is to regulate calcium and phosphorus metabolism, which is essential for bone health. However, numerous extraosseous effects have been reported, and its deficiency has been associated with autoimmune, cardiovascular, neurological, and oncological diseases, food allergies[9-12], chronic respiratory diseases (CRD), and bronchial asthma[13-15]. It also participates in innate immunity, has an antimicrobial effect, and regulates inflammatory processes, having reported an inverse relationship between 25(OH)D and upper respiratory infections[16] and a direct relationship with lung function, so that patients with CRD may be more susceptible to damage due to vitD deficiency[17-18]. In mice, it has been demonstrated that this deficiency produces histological damage and smaller lung size and volume, which evidences the direct effect on the development of the respiratory system[19].

In Chile, low concentrations of 25(OH)vitD were reported in 2002, with 22±7 ng/mL in healthy children aged 2 to 18 years with normal bone density. In children with chronic diseases and suspected osteopenia, 32% had 25(OH)vitD less than 14 ng/mL, and 20% effectively presented osteopenia[20,21]. Expert groups recommend supplementation with 400 IU of vitD per day to all infants up to one year of life[6-8] and with 800 to 1,000 IU to at-risk groups[22], considering that excess vitD can cause hypercalcemia, hypercalciuria, and renal lithiasis[23].

In patients with CRD, low sunlight exposure, low vitD intake, insufficient supplementation, malnutrition, and some drugs (anticonvulsants, glucocorticoids) negatively affect vitD status[6,13,21,22]. The *Hospital Josefina Martínez* is a home transition center, where children with CRD are hospitalized to receive comprehensive and interdisciplinary rehabilitation for periods longer than two months[24]. These patients receive supplementation of 400 IU/day of cholecalciferol and, if they additionally present severe limitation of mobility, they receive 800 IU. Although there is information on vitamin D status in asthmatic children or children with acute respiratory infections, the situation in pediatric patients with CRD and prolonged hospitalization is unknown, a situation that can aggravate vitamin D deficiency. The objective of this study was to determine vitamin D status in children with prolonged hospitalization and to explore known risk factors associated with vitamin D deficiency.

Patients and Method

Design

A descriptive, cross-sectional study was conducted at the *Hospital Josefina Martínez* where children with

CRD referred from the neonatology and intensive care units of the public health system hospitals were admitted for their transition to home. Most of these children are vulnerable pediatric populations, who require comprehensive and multidisciplinary rehabilitation. The hospital is located in the southeastern area of Santiago, in central Chile.

Patients

This was a convenience sample, consisting of patients who were hospitalized between September and December 2012, the spring season in the southern hemisphere. Children hospitalized for less than two months, with renal or hepatic insufficiency, intercurrent infections, or malabsorption syndrome were excluded.

Variables analyzed

Age, sex, underlying disease, time of hospitalization at the date of blood sampling, complete physical examination, and anthropometric evaluation were recorded using the 2006 WHO reference curves for children under 5 years of age and the 2007 WHO reference curves for children over 5 years of age (25, 26). In children under 5 years of age, nutritional status was classified according to z-score for weight/height (zW/H) and, in older children, according to z-score for body mass index (zBMI), defined according to these scores: eutrophy (> - 1 and < + 1), excess malnutrition (≥ + 1), and deficit malnutrition (≤ - 1). The Height/Age index expressed as zH/A was calculated.

Sunlight exposure (UVB) was considered present if the child went out for a period longer than 30 minutes from her/his hospital ward to the garden, or playground, or if she/he attended kindergarten or school. No exposure was considered if the child went out for a shorter period or if she/he did not leave the hospital premises. This was recorded on each patient's nursing record sheet.

The supplementation dose and the dietary intake of vitD were recorded, considering the sum of both as the total daily intake of vitD. The use of other supplements and/or medications was also recorded.

The degree of mobility was established according to the gross motor function classification (GMFCS) for children with cerebral palsy[27], adapted as follows: Level I-II: Achieves motor milestones and has a degree of functionality with marked independence; Level III-IV: Achieves motor milestones, but with delayed functionality, and limited mobility; Level V: Completely dependent, with no voluntary functional motor activities, spends most of the day in bed.

Laboratory tests

A fasting blood sample was collected and processed at the Clinical Laboratory of the *Pontificia Universidad Católica de Chile*, accredited by the international standard ISO 15189. The following were measured: 25(OH) D using a competitive chemiluminescent assay (LIAISON® 25 OH Vitamin D Total Assay, DiaSorin), intact parathyroid hormone (PTH) with electrochemiluminescence immunoassay (Molecular Analytics System, Roche), plasma calcium level (colorimetric method), plasma phosphate level (UV Molybdate reaction), and alkaline phosphatases (colorimetric method), the last three with the Cobas® 8000 analyzer (Roche). According to international recommendations, the following 25(OH)D cut-off points were considered to determine vitD status: Deficiency: < 20 ng/mL, Insufficiency: between 21-29 ng/mL, and Sufficiency: ≥ 30 ng/mL[6].

Statistical analysis

A sample size of 41 patients was calculated based on a frequency of vitamin D insufficiency/deficiency of 39%[21,28], with an absolute error of 15%. A database was created in Microsoft Excel 2007 for subsequent analysis with the Minitab 17® software. Descriptive statistics were performed with means or medians according to the distribution of the variables (Anderson-Darling test), as well as comparing subgroups with the Student-t test and ANOVA for 25(OH)VD or non-parametric tests such as Mann-Whitney test and Kruskal-Wallis test for age and length of hospital stay. The proportions were compared using the Chi-square test. Spearman and simple linear regression tests were performed to evaluate the association between 25(OH) VD and the different numerical factors. A $p < 0.05$ was considered significant.

Ethical aspects

International standards for biomedical research in humans were followed. The project was approved by the Scientific Ethics Committee of the Southeast Metropolitan Health Service (resolution no. 2886). Parents or legal guardians signed an informed consent form.

Results

General characteristics

41 patients were recruited, 56% were male, with a median age of 31 months, distributed as 29.3% under 2 years, 36.6% between 2 and 4 years, and 34.1% over 4 years, with no difference by sex. Table 1 describes their characteristics. Among the baseline respiratory diagnoses, chronic post-infectious lung damage predominated and 34.1% required prolonged ventilatory support due to chronic respiratory failure or airway pathology. The median hospitalization stay was 20 months (CI: 11;39).

Nutritional status

In 58.54% of the children, the nutritional status was normal, 31.7% were overweight or obese, and 2.4% were malnourished; 70% of the children were of normal height. The medians of the anthropometric indices were -1.45 (-5.84 to 1.92) for zH/A, 0.25 (-2.7 to 2.86) for zW/H, and 0.41 (-2.83 to 2.35) for zBMI, with no difference according to sex.

Sunlight exposure

24/41 patients (58.5%) had no sunlight exposure and 17 patients (41.5%) had daily exposure longer than 30 minutes.

Supplementation and vitD intake in the diet

37/41 patients (90.4%) received vitD supplementation, of which 27 (73%) received 400 IU/day and 10 (27%) 800 IU/day. Only 4/41 (9.76%) did not receive it because they had normal gait and attended an educational center outside the hospital. Patients with GMFCS V received more vitD supplementation than those with higher gross motor function (Chi2, p = 0.001).

The time of supplementation was equivalent to the time of hospitalization since it had been initiated upon admission to the hospital. There were no differences in 25(OH)D according to length of stay.

Milk formulas were the main source of vitD in the diet, through which patients received a median of 345 IU/day (range: 0 to 1,004 IU/day). When supplementation was added, their total daily intake was 818 ± 258.8 IU/day.

VitD status

Table 2 shows the total daily intake of vitD, 25(OH)D, and the main results of related laboratory tests in the total group, with no differences according to sex. Plasma calcium levels were within the normal range in all patients, 82.93% had normal alkaline phosphatase (AP), and 90.24% had normal PTH. The 2 patients with vitD deficiency had normal plasma calcium, AP, and PTH, although plasma phosphate was low. The percentage distribution according to vitD status was 39% of the patients with suboptimal vitD values (insufficiency or deficiency) (Figure 1). Only two patients had deficiency, one was bedridden, had no sunlight exposure, and received 800 IU/day of vitD supplementation and the other one had normal gait, sunlight exposure, and did not receive vitD supplementation.

Factors associated with vitD status

Figure 2 shows that, among children receiving oral vitD supplementation, those with 800 IU/day had higher 25(OH)D levels than those receiving 400 IU/day (p = 0.032). Of those patients receiving 400 IU/day, 60% had vitD sufficiency and of those receiving 800 IU/day, 80% had sufficiency (Chi2 p = 0.2).

In relation to age, there was a non-significant inverse association trend (p = 0.08) (figure 3).

No association was found between vitD status and sex, respiratory pathology, nutritional status, motor function, sunlight exposure, anticonvulsant use, time of vitD supplementation, or length of hospital stay (table 3).

Discussion

This study describes a high frequency of suboptimal vitD status (39%) in a group of children with prolonged hospitalization due to chronic respiratory diseases, despite that 94% of them were receiving vitD supplementation, which was the only factor associated with 25(OH)D concentration. This is a high-risk group of patients, in whom the low level of vitD may affect the evolution of their disease, given its influence on pulmonary function and the immune response to infections[11,17,19].

VitD insufficiency has been reported in different populations of children with chronic diseases. In a local study, 32% presented vitD insufficiency[21] which is comparable to that found in our work with 34% insufficiency and 5% deficiency, similar to a Swedish

Table 1. Characteristics of 41 children with chronic respiratory disease and prolonged hospitalization

Feature		Result
Age in months, Median (IQR)		31 (18.5; 50)
Male, n (%)		23 (56)
Hospital stay in months, Median (IQR)		20 (11; 39)
Respiratory diagnosis, n (%)	Bronchopulmonary dysplasia	9 (21.9)
	Chronic lung damage	18 (43.9)
	Chronic respiratory failure	12 (29.3)
	Airway pathology	2 (4.9)
Neurological disease, n (%)	Ausente	20 (48.8)
	Enfermedad neuromuscular	15 (36.6)
	Parálisis cerebral	6 (14.6)
Gross motor function*, n (%)	I y II	13 (31.7)
	III_IV	13 (31.7)
	V	15 (36.6)
Anticonvulsant therapy, n (%)		11 (26.8)

IQR: interquartile range. *GMFCS (Gross motor function classification system) adapted: Level I-II: Performs motor milestones and has a degree of functionality with marked independence. Level III-IV: Performs motor milestones, but with delayed functionality and limitation for movement. Level V: Is completely dependent, without performing voluntary functional motor activities, spends most of the day in his wheelchair or bed.

Table 2. Vitamin D intake and main laboratory test results related to vitamin D status in 41 children with chronic respiratory disease and prolonged hospitalization.

	Total	Girls	Boys	P*
n (%)	41 (100)	18 (43.9)	23 (56.1)	-
VitD Supplementation (IU/day)[a]	458.5 ± 229	444.4 ± 233	469.6 ± 230	0.70 [c]
VitD in food (IU/day)[a]	359.6 ± 239	393.6 ± 267	333.0 ± 216	0.44 [c]
Total vitD intake (IU/day)[to]	818.1 ± 259	838.1 ± 300	802.6 ± 227	0.67 [c]
25(OH)D (ng/mL)[a]	31.02 ± 6.8	31.29 ± 7.06	30.8 ± 6.78	0.82 [c]
Plasma calcium (mg/dL)[to]	9.97 ± 0.45	10.08 ± 0.39	9.88 ± 0.48	0.16 [c]
Plasma phosphorus (mg/dL)[b]	4.9 (4.6;5.4)	5.2 (4.6;5.6)	4.9 (4.7;5.3)	0.44
Alkaline phosphatases (mg/dL)[to]	245.7 ± 69.9	246.1 ± 67.6	245.3 ± 73.2	0.93
Parathormone (pg/ml)[b]	24.5 (20.8;31.9)	26.3 (21.7;42.8)	23.1 (20.7;27.7)	0.21

VitD: vitamin D.25(OH)D: plasma 25-hydroxyvitamin D concentration. a: Mean ± standard deviation. b: Median (interquartile range). c: Student's test for independent samples. d: Mann-Whitney test

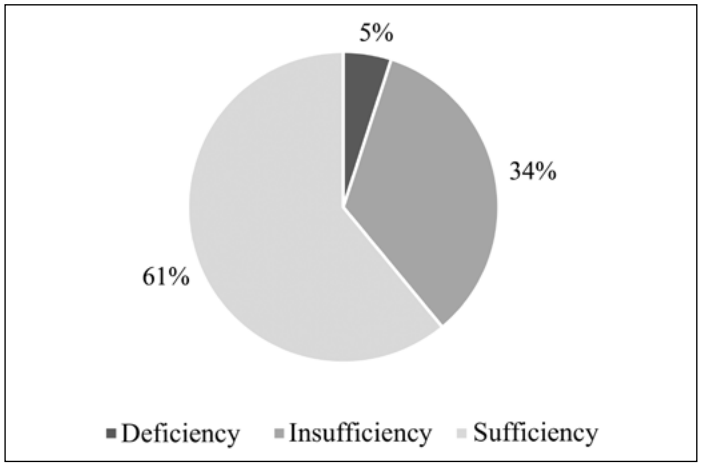

Figure 1. Vitamin D status in 41 children with chronic respiratory diseases and prolonged hospitalization, according to plasma concentration of 25-hydroxyvitamin D

study with 39% and 6%, respectively, in children with wheezing compared with 24% and 3% in healthy controls[28]. On the other hand, other studies have reported no differences in asthmatic preschoolers versus those without asthma[29].

The high frequency found is striking because 94% of the patients were receiving vitD supplementation. We confirmed that the supplementation dose was insufficient since patients receiving 800 IU/day had higher 25(OH)D levels than those supplemented with 400 IU/day. In addition, there was normalization of 25(OH)D in 11 patients with insufficiency who could be controlled after increasing the dose (data not shown), however, it should be noted that 60% of the children receiving 400 IU had vitD sufficiency.

The suboptimal vitD status in this group should be considered in the context of the high prevalence of this deficiency in the pediatric population in Chile, where a

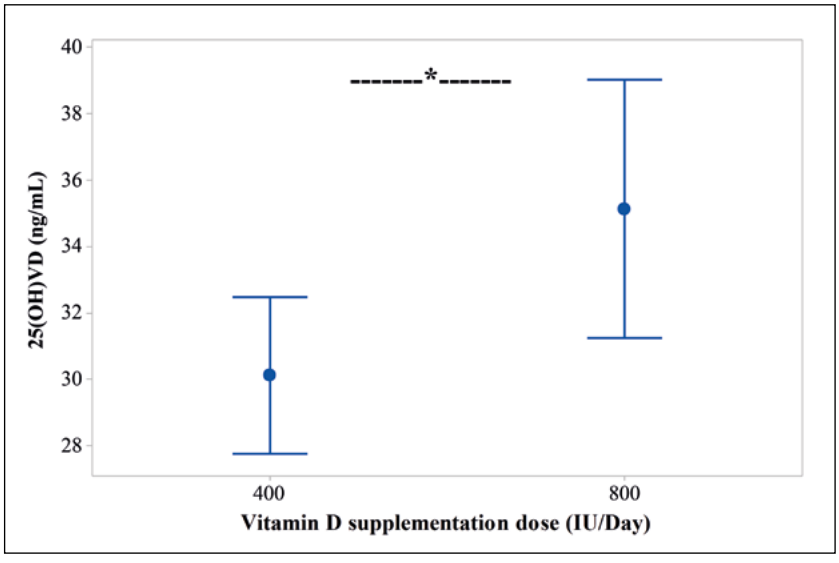

Figure 2. Plasma concentration of 25-hydroxyvitamin D according to the dose of cholecalciferol supplementation, in 41 children with chronic respiratory diseases and prolonged hospitalization.

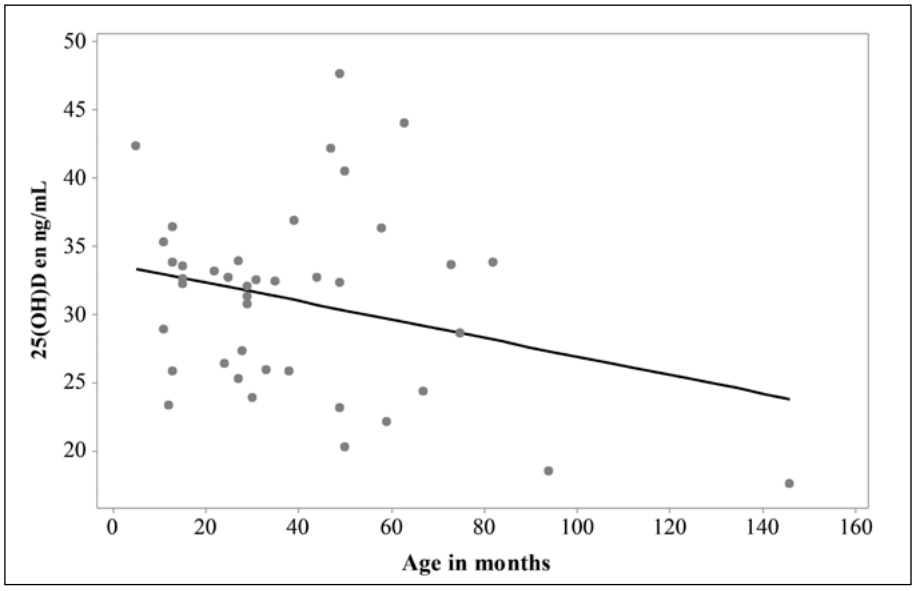

Figure 3. Association between plasma concentration of 25-hydroxyvitamin D and age in 41 pediatric patients with chronic respiratory diseases and prolonged hospitalization.

Table 3. Factors not associated with vitamin D status in 41 children with chronic respiratory disease and prolonged hospitalization

Factor		Deficiency/insufficiency	Sufficiency	p
Age in months, Median (IQR)		35.5 (24.7; 64)	29.0 (15;49)	0.36#
Gender (%)	Girls	38.9	61.1	0.99&
	Boys	39.1	60.9	
Baseline diagnostics	BPD	33.3	66.7	0.13&
	CLD	72.2	27.8	
	CRI	66.7	33.3	
Nutritional status (%)	DM	40	60	0.88&
	Eutrophy	42	58	
	EM	33	67	
GMFCS (%)	I y II	46	54	0.79&
	III y IV	38	62	
	V	33	67	
Sun exposure (%)	Yes	33	66.7	0.37&
	No	47	52.9	
Anticonvulsant use	Yes	36	64	0.8&
	No	40	60	
Hospital stay in months, Median (IQR)		15 (11;63)	24 (6;39)	0.7#

Vitamin D status according to 25(OH)D; deficiency: < 20 ng/mL, insufficiency: between 21-29 ng/mL and sufficiency: ≥ 30 ng/mL.
BPD: bronchopulmonary dysplasia, CPD: chronic lung damage, CRI: chronic respiratory insufficiency. DM: Malnutrition due to deficit (zWeigth/age or zBMI/age ≤ -1), EM: Malnutrition due to excess (zWeigth/age or zBMI/age ≥ +1). GMFCS: Gross Motor Function Classification System. IQR: Interquartile range. #Mann Whitney test. &Chi2 test

minority is derived from patients with chronic diseases such as those studied here. Since the main source of vitD is cutaneous synthesis mediated by sunlight radiation, the deficiency is higher at higher latitudes, both north and south, and varies according to the season of the year[30,31]. Deficiency of up to 96.3% has been reported in the southern zone[5,32]; our study was carried out in central Chile and in the early spring season.

VitD status is very important in these children since it can affect pulmonary function due to their age and general conditions. In children with asthma, it has been suggested that the mechanism would be the induction of resistance to corticoids by vitD, as well as reducing smooth muscle proliferation, inflammatory response, and secretion of remodelers and fibroblast mediators[9,33]. In adults, a significant relationship has

been observed between 25(OH)D levels and pulmonary function tests[17] as well as with a protective effect on immunity, modulating the effects of cytokines through different cells of the immune system[34].

The absence of other markers of vitD deficiency and osteopenia, such as hypocalcemia, hypophosphatemia, and elevated PTH or AP, is striking and is consistent with other studies, but does not help to identify children with vitD deficiency or justify its routine measurement.

The trend found of an inverse association between 25(OH)D and the age of the patients agree with other reports, where it is attributed to the greater requirement of vitD towards puberty due to accelerated growth, especially in males, to the greater adherence to vitD supplementation in minors, or the lower number of consultations and request for 25(OH)D supplementation in older patients[35-37]). In our study, it corresponded to the fact that the latter required higher doses, reinforcing the need for appropriate monitoring and adjustment.

These hospitalized patients did not experience low adherence to long-term supplementation, a serious issue in outpatients[37], and very frequent in the general population. Poor adherence in the context of the high prevalence of deficiency justifies the fortification with vitD of widely consumed foods such as dairy products and flour, a public strategy recently approved in Chile[38].

We did not find a difference by sex in 25(OH)D levels, as other reports that have observed lower values in females than in males[36], nor an association with lower motor function, sunlight exposure, or use of anticonvulsants. Possibly, this occured because most of the patients were previously supplemented and also because of the small size of this sample, which was calculated to detect the prevalence of deficiency and not for differences between these groups.

Although this sample presented 31.7% of overweight or obese children, there was no association of both with 25(OH)D levels. Excess weight is a risk factor for vitD deficiency whose underlying mechanism is unclear. It has been proposed that vitD is deposited and "sequestered" in adipose tissue.

Also, obese children may have less sunlight exposure and low consumption of fortified foods. The relationship between obesity and vitD deficiency has been described in larger and older samples[39-41], which may influence our results. It can also be considered that a significant proportion had neurological damage that can cause lower weight due to a decrease in lean mass due to muscle atrophy. In these patients, a greater fat mass does not determine an increase in W/H or BMI, parameters that define obesity and overweight. The measurement of skinfolds and brachial perimeter allows estimation of fat and lean mass, but these measurements were not included in this study.

The main strength of this study is that it describes vitD status in pediatric patients with severe chronic respiratory disease hospitalized for prolonged periods, which considered total intake and stable and safe vitamin D supplementation, as well as standardized 25(OH) D measurement. However, it is limited by the sample size that, although adequate, has a high absolute error. Other limitations are the use of sunscreen and, more precisely, sunlight exposure was not recorded.

We can conclude that children with chronic respiratory disease with prolonged hospitalization present a high frequency of vitamin D deficiency or insufficiency, even when receiving the supplementation recommended for the general population. In this sample, vitD status was associated only with the dose of supplementation, but not with other known risk factors. We recommend supplementing everyone and monitoring 25(OH)D levels in this at-risk group, at least annually, adjusting supplementation to enable a better vitD status, which may result in a better evolution of their disease and immune response to infections. Prospective studies are required, with a larger sample size, post-supplementation follow-up, and evaluation of its impact on lung function.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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