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ORIGINAL ARTICLE

Vitamin D deficiency in hospitalized adolescents with mental health disorders

Deficiencia de Vitamina D en adolescentes hospitalizados con trastornos de salud mental

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

Vitamin D (VD) has been shown to possess neuroprotective properties and some studies suggest a possible role in neuropsychiatric disorders. In adolescents with mental health disorders (MHD), a deficiency of VD has been reported in approximately 21% of cases.

What does this study contribute to what is already known?

This is among the first studies in Chile to assess VD deficiency in hospitalized adolescents with MHD. The findings revealed a higher prevalence of VD deficiency compared to reports in the international literature, with greater severity than that observed in healthy Chilean adolescents. These differences are especially notable in adolescents with excess malnutrition and during the winter months.

Abstract

Mental health disorders (MHD) are a growing problem in adolescents. There is evidence that vitamin D (VD) deficiency is associated with MHD. **Objective:** To evaluate VD deficiency in adolescents with MHD hospitalized in the Adolescent Hospital Unit (UHA), and to explore associated factors. **Patients and Method:** Observational, analytical, cross-sectional study. All adolescents aged between 10 and 17 years, with MHD, admitted to the UHA, and in whom 25-OH VD measurement was performed were included. The association between serum 25-OH VD concentration and variables of interest (sociodemographic, comorbidity) was evaluated in a multivariate model, including nutritional status (WHO 2007), season, mood disorder, type of diet, age, and sex, among others. **Results:** 164 adolescents were included. VD deficiency was 76.6%, and 44.8% had severe deficiency. The VD deficiency was 90.9% in overweight adolescents and 82.2% in obese adolescents. The adjusted mean

Keywords:
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25-OH VD levels were 23.3 ng/ml (95% confidence interval [CI]: 16.7-30.0) in deficiency malnutrition, and 14.2 ng/ml (95%CI: 10.1-18.3) in overweight ($p< 0.01$); and 21.1 ng/ml (95% CI: 15.7-26.4) in December-February versus 16.2 ng/ml (95% CI: 12.1- 20.2) in June-August ($p= 0.02$). There were no differences according to mood disorder. **Conclusions:** Hospitalized adolescents with MHD have a high VD deficiency. A statistically significant association was found between VD levels and the variables of nutritional status and season.

Introduction

Vitamin D (VD) is currently recognized as a hormone given its multiple functions in the body by acting on different target organs and presenting receptors on almost all cells[1]. It is mainly known for its role in bone health and innate and acquired immunity[2]. However, in recent years, its role in normal brain development has gained importance, having neuroprotective functions due to its involvement in neurotransmitter synthesis, nerve growth factor, and reduction of oxidative stress. The VD receptor and VD metabolizing enzymes are expressed in the human brain, especially in the hypothalamus and in neurons of the *substantia nigra*. Thus, VD potentially regulates calcium transit in the brain and neuronal development and protects against reactive oxygen species[3]. Serum 25-hydroxy-VD (25-OH VD) levels have also been linked to the severity of depressive disorders by proposing the "two-hit hypothesis", which states that VD deficiency predisposes the brain to be more vulnerable to secondary adverse exposures, exacerbating depressive symptoms[4].

Although the etiological relevance of VD in neuropsychiatric disorders is unknown, an association has been established with several of them. Multiple studies link low levels of VD with depression, schizophrenia, obsessive-compulsive disorder, attention deficit hyperactivity disorder, and autism spectrum disorder[5-7]. In adolescents with MHD, the reported VD deficiency is 21%[3]. According to the WHO, globally, 14.3% of young people aged 10-19 years suffer from an MHD, representing 15% of the global burden of disease in this age group[8]. According to the latest prevalence study published in Chile, an estimated 16.5% of adolescents aged 12 to 18 years present some MHD, with the most prevalent diagnoses being disruptive (8%), anxious (7.4%), and affective (7%) disorders[9].

The prevalence of VD deficiency in Chile is 80.4% in the population aged 4 to 14 years from cities in different latitudes of the country[10]. Several factors are associated with VD deficiency, among them are dark skin color, nutritional status, malabsorptive syndromes, insufficient VD intake, extreme latitudes, reduced sun exposure, and increased number of screen hours, among others[11].

Despite the high prevalence of VD deficiency in Chile and the increasing frequency of MHD in adolescents, there are no studies in our country that have described the prevalence of VD deficiency in this specific population. Thus, the objective of our study was to evaluate VD deficiency in adolescents aged 10 to 17 years with MHD hospitalized in the Adolescent Hospital Unit (AHU), *Hospital La Florida* (HLF), between 2019 and 2021, and to explore associated factors.

Patients and Method

Cross-sectional analytical observational study conducted on adolescents aged 10 to 17 years with MHD seen at the AHU-HLF, Metropolitan Region, Chile, between 2019 and 2021. The study was approved by the Ethics Committees of the Faculty of Medicine of the *Pontificia Universidad Católica de Chile* and the Southeast Metropolitan Health Service.

Sampling was performed by convenience, including in the study all adolescents between 10 and 17 years of age, with MHD, admitted for the first time to the AHU-HLF, from March 2019 to December 2021, and in whom 25-OH VD level was measured. We excluded those patients who did not meet the age range ($n = 3$) as well as those who presented more than one measurement of 25-OH VD levels, where we considered only the first measurement ($n = 2$). It is worth mentioning that, in the selected sample, there were no patients with active or recent treatment for VD deficiency (less than 6 months) or with vitamin supplements that included VD.

Since there is little literature that has evaluated VD in adolescents with MHD, we do not have information that would allow us to calculate the sample size for the associations explored in this study. Indirectly, we took as a reference the VD deficit in the adolescent population in Santiago, Chile, by nutritional status, which has been reported to be between 70%-75% in healthy adolescents and 90% in adolescents with obesity. Using the usual parameters (alpha: 0.05, power: 0.8), we obtained a sample size between 120 and 200 subjects in total[10,12].

Sociodemographic and laboratory data (serum 25-OH VD level) were collected. Laboratory data recorded for the first time in patients, at the time of hospital admission, were considered; any repetition of the examination during the observation period was not analyzed. A form was then completed based on the main determinants of VD described in the literature, including personal data such as identification number (associated with the last 4 digits of the patient's RUN[a], to protect confidentiality), date of birth, date of sampling, age, sex, nationality, mental health and other comorbidities, type of diet, use of vitamin supplements (specifying the amount of VD in these), nutritional status, season of the year, presence of disability, and institutionalization.

The comorbidities were grouped based on the multiaxial diagnostic system[11], using four of the five axes presented therein:

- Axis I (clinical syndromes): mood disorders, anxiety disorders, eating disorders (ED), substance use disorders (SUD), adaptive disorders.
- Axis II (developmental and personality disorders): personality disorders, mental retardation.
- Axis III (medical diseases): asthma, allergic rhinitis, constipation, epilepsy, metabolic syndrome.
- Axis IV (psychosocial and environmental problems): family dysfunction, child sexual abuse and/or domestic violence, bullying.

In relation to the dietary pattern, an omnivorous diet was defined as that which included four meals a day, varied, with the inclusion of foods of animal origin; a vegetarian diet as that without meat consumption, with or without the consumption of other animal derivatives; and a vegan diet when there was no consumption of meat or any animal product. The use of dietary supplements during the last year was also specified.

In addition, nutritional status was defined according to WHO 2007 anthropometric standards [12]. Using the WHO 2007 program, AnthroPlus version 1.0.4, the Z-score of body mass index/age (Z-BMI/A) was determined according to sex and age. The nutritional status variable was categorized into 4 groups according to the following diagnostic criteria: deficit malnutrition: Z-BMI/A ≤ -2; normal nutritional status: Z-BMI/A -1.9 to +1; overweight: Z-BMI/A +1 to +1.9; and obesity: Z-BMI/A ≥ +2. Laboratory data were also collected including serum 25-OH VD level during the hospitalization period considered. The classification of VD levels was done using the cut-off points defined in the 2018 "Consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians", according to serum 25-OH VD level[13]. Thus, 25-OH VD sufficiency was defined as serum 25-OH VD levels ≥ 30 ng/mL, insufficiency between 20-29 ng/mL, deficiency < 20 ng/mL, and severe deficiency ≤ 12 ng/mL.

[a]*Rol Único Nacional*: Chilean National ID Number.

Statistical analysis

Continuous variables were described as mean [with standard deviation (SD)] or median [with interquartile range (IQR)] depending on the normality of the data distribution. Categorical variables were described as n and percentage. For comparisons between two variables, Wilcoxon or t-test statistics were used for continuous variables, and Fischer or Chi-square tests for categorical ones. A p-value < 0.05 was considered statistically significant.

The age variable was categorized into two groups, 10–14 years and 15–17 years. The season of the year was categorized into 4 periods of 3 months each: December, January, and February (summer); March, April, and May (fall); June, July, and August (winter); and September, October, and November (spring).

A linear regression model was constructed to explore the association between variables of interest and VD levels, obtaining adjusted means and their respective 95% confidence interval (CI). Variables associated with VD deficits described in the literature (nutritional status, season), predictors in the bivariate comparison, and other variables of interest were included. The model included the following variables: age, sex, type of diet, nutritional status, season of the year, and the following most frequent diagnoses: mood disorder, ED, SUD, adaptive disorders, and constipation.

Statistical analysis was performed using SAS On Demand for Academics (SAS institute, Cary, NC, USA) and GraphPad Prism (LLC, Boston, MA, USA) software.

Results

Study population

Between 2019 and 2021, a total of 169 adolescents with MHD were admitted to the AHU-HLF, and all of them underwent serum 25-OH VD measurement. Three participants were excluded because they were outside the specified age range and 2 because of repeated 25-OH VD sampling, leaving a total of 164 adolescents. Table 1 summarizes the clinical and demographic characteristics of all the adolescents in whom VD values were obtained, and by nutritional status at admission (excess malnutrition).

Of the total group, 81.7% were female, and the age distribution was 51.2% between 10-14 years and 48.8% between 15-17 years. Most of the examinations were performed in the period between September and November (34.8%). The most frequent MHD was mood disorder (78.1%), followed by ED (26.8%). Also, 21.3% had constipation as an associated comorbidity.

Patients with and without excess malnutrition presented a similar distribution of all the variables analyzed (Table 1), except for ED, which was significantly less frequent in the group without excess malnutrition (20.2% vs 35.7%; p-value = 0.03), in patients with and without excess malnutrition, respectively.

The median 25-OH VD level in the total group was 13.0 ng/ml (IQR: 10.0-19.0), and 13.0 ng/ml (IQR: 10.0-17.0) versus 17.0 ng/ml (11.0-22.0) in adolescents with and without excess malnutrition, respectively (p-value < 0.01).

Prevalence of VD deficiency

VD deficiency was 76.6% in this population (44.8% severe deficiency). 16.9% had insufficient levels, and only 6.5% of adolescents had sufficient levels.

Figure 1 shows the prevalence of VD deficiency according to nutritional status. Patients with normal nutritional status or undernutrition had a significantly lower frequency of VD deficiency compared to those with overweight and obesity: 65.5% vs. 90.9% (p < 0.01) in patients with normal weight and those with overweight, respectively; and 42.9% vs. 82.2% (p = 0.046) in patients with undernutrition and those with obesity, respectively.

Table 2 shows the crude and adjusted mean VD levels for the variables of interest (nutritional status, season of the year, mood disorder, type of diet, and age). Patients with deficit malnutrition had significantly higher adjusted mean VD levels than those with excess malnutrition: 23.3 ng/ml (95% CI: 16.7-30.0) vs. 14.2 ng/ml (95% CI: 10.1-18.3) in patients with deficit malnutrition and overweight, respectively (p < 0.01); and 23.3 ng/ml (95% CI: 16.7-30.0) versus 16.3 ng/ml (95% CI: 12.5-20.1) in patients with deficit malnutrition and obesity, respectively (p < 0.05).

During the summer months, adjusted mean VD levels were significantly higher than in the winter months: 21.1 mg/ml (95% CI: 15.7-26.4) versus 16.2 ng/ml (95% CI: 12.1-20.2) in the months of December-February and June-August, respectively (p < 0.05).

Figure 2 shows the adjusted means of VD levels for the variables for which a statistically significant association was obtained: nutritional status and season of the year. Patients with excess malnutrition presented lower VD levels compared to adolescents with deficit malnutrition. Seasonal variation was also observed, with significantly higher VD levels in the summer months compared to the winter months.

Discussion

In Chile, few studies evaluate VD deficiency in the adolescent population and, to date, there are no published studies of VD deficiency in adolescents with MHD.

In this study, VD deficiency was 76.6%, much higher than that described by Föcker M. et al, in their 2017 systematic review, where they reported a deficiency of 21% in adolescents with MHD[3]. This could be because the prevalence of VD deficiency in our country is high, reaching up to 80.4% in the Chilean healthy population aged 4 to 14 years according to the study conducted by Pérez-Bravo, et al in 2022[10]. However, it is striking that in adolescents with MHD, in this study, the severe deficiency was 43.1%, which is much higher than that reported in the study by Pérez-Bravo, et al (26.3%).

Regarding VD deficiency in excess malnutrition, it has been described that, since it is a fat-soluble vitamin, it can be redistributed in adipose tissue, causing its serum level to be associated with body adiposity levels. The greater the fat mass, the lower the VD levels[14]. Concordant with what has been described in the literature, in this study we found a greater deficiency of VD in adolescents with excess malnutrition. This also coincides with the work carried out in prepubertal and pubertal populations in Chile[10,15]. Likewise, these results are similar to those reported in other studies, such as the one from Navarra, Spain, in a population between 9 and 14 years of age, where VD deficiency was 31% in those classified as obese, compared to 14% in those with normal weight[16]. In a recent study by Cárdenas et al (2023), Chilean adolescents with different degrees of obesity attended the nutrition polyclinic of a public hospital in the same city (*Hospital Dr. Sótero del Río*) were analyzed, in which 91% of the total sample presented VD deficiency, being more frequent among adolescents with severe obesity, reaching up to 95%[17].

As previously mentioned, sun exposure is the main source of VD, since dietary intake is low[18,19]. This fact could explain why no significant differences were found in the population studied in relation to dietary patterns (vegetarian versus omnivorous diet). Besides, we did find a seasonal pattern, with significantly higher VD levels in the summer months compared to winter in the population studied.

Finally, our study found no difference in VD levels in adolescents with depression, unlike other studies[6]. It would be interesting to conduct future studies to explore whether there is an association between mood disorders and VD deficits. In our study, only patients with MHD were included, with no information regarding adolescents without this condition.

Table 1. Clinical and Demographic Characteristics of Adolescent Patients (Aged 10–17 Years) Hospitalized for Mental Health Disorders at Hospital La Florida, 2019–2021

Variable		Total	Excess Malnutrition		
		n = 164	Yes (n = 94)	No (n = 70)	p-value
Sex (female), n (%)		134 (81,71)	79 (84,04)	55 (78,57)	0,42
Age group, n (%)	10-14 years	84 (51,22)	53 (56,38)	31 (44,29)	
	15-17 years	80 (48,78)	41 (43,62)	39 (55,71)	0,16
Season:					
December–February		21 (13,04)	12 (13,04)	9 (13,04)	
March–May		41 (25,47)	17 (18,48)	24 (34,78)	
June–August		43 (26,71)	29 (31,52)	14 (20,29)	
September–November		56 (34,78)	34 (36,96)	22 (31,88)	0,1
Nationality (Chilean), n (%)		163 (99,39)	94 (100)	69 (98,57)	0,43
Vegetarian diet, n (%)		24 (14,63)	11 (11,70)	13 (18,57)	0,27
Supplement use, n (%)		3 (1,83)	1 (1,06)	2 (2,86)	0,58
Diagnoses:					
Axis I:					
Mood disorders, n (%)		128 (78,05)	69 (73,40)	59 (84,29)	0,13
Anxiety disorders, n (%)		27 (16,46)	16 (17,02)	11 (15,71)	1,00
ED, n (%)		44 (26,83)	19 (20,21)	25 (35,71)	**0,03**
SUD, n (%)		16 (9,76)	9 (9,57)	7 (10,00)	1,00
Adjustment disorders, n (%)		38 (23,17)	26 (27,66)	12 (17,14)	0,14
Axis II:					
Personality disorders, n (%)		57 (34,76)	37 (39,36)	20 (28,57)	0,19
Intellectual disability, n (%)		8 (4,88)	7 (7,45)	1 (1,43)	0,14
Axis III:					
Constipation, n (%)		35 (21,34)	24 (25,53)	11 (15,71)	0,18
Asthma, n (%)		8 (4,88)	7 (7,45)	1 (1,43)	0,14
Metabolic syndrome, n (%)		5 (3,05)	4 (4,26)	1 (1,43)	0,39
Epilepsy, n (%)		3 (1,83)	2 (2,13)	1 (1,43)	1,00
BMI z-score, mean (SD)		1,13 (1,37)	2.06 (0,77)	-0.12 (0,92)	**< 0,001**
25-OH Vitamin D, median (IQR) (ng/mL)		13,0 (10,0-19,0)	13,0 (10,0-17,0)	17,0 (11,0-22,0)	**0,009**

Abbreviations: SD: standard deviation; IQR: interquartile range; ED: eating disorders; SUD: substance use disorders. Note: Excess malnutrition includes patients with overweight and obesity.

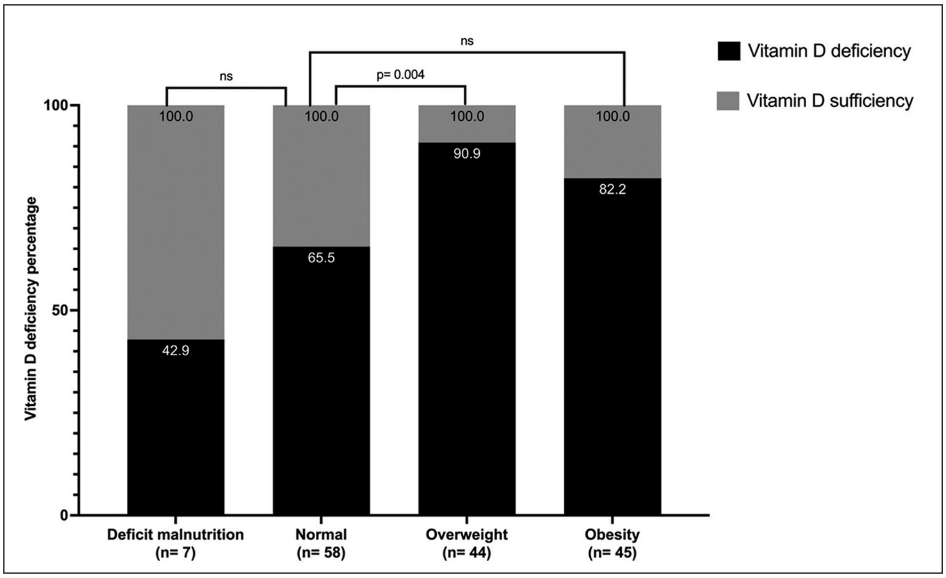

Figure 1. Vitamin D Deficiency by Nutritional Status. Adolescent Health Unit Admissions, Hospital La Florida, 2019–2021.

Table 2. Mean Vitamin D Levels, Crude and Adjusted, in Patients Hospitalized for Mental Health Disorders. Hospital La Florida, 2019–2021

Variable	Mean	SD	Adjusted Mean	95% CI
Nutritional status				
Undernutrition (n =7)	22,29	10,19	23,32	16,67– 29,96
Normal weight (n = 58)	17,45	9,04	18,39	14,54– 22,25
Overweight (n = 44)	13,20	4,68	14,21	10,09– 18,34
Obesity (n = 45)	14,96	6,94	16,28	12,45– 20,10
Pairwise comparisons (p-values):				
Undernutrition vs Overweight: p = 0.005*				
Undernutrition vs Obesity: p = 0.03*				
Normal weight vs Overweight: p = 0.009*				
Overweight vs Obesity: p = 0.22				
Undernutrition vs Normal weight: p = 0.11				
Normal weight vs Obesity: p = 0.18				
Season				
December–February (n = 21)	18,40	6,12	21,06	15,73– 26.38
March–May (n = 41)	16,42	8,06	17,59	13,61– 21,58
June–August (n = 43)	13,88	9,37	16,15	12,07– 20,24
September–November (n = 56)	15,69	6,35	17,40	13,52– 21,28
Pairwise comparisons (p-values):				
Dec–Feb vs Jun–Aug: p = 0.02*				
Dec–Feb vs Sep–Nov: p = 0.08				
Dec–Feb vs Mar–May: p = 0.12				
Mar–May vs Jun–Aug: p = 0.41				
Mar–May vs Sep–Nov: p = 0.91				
Jun–Aug vs Sep–Nov: p = 0.45				
Mood disorders				
Yes (n = 128)	15,60	7,93	17,27	13,15– 21,38
No (n = 36)	16,18	7,01	18,84	14,82– 22,85
p = 0,37				
Vegetarian diet				
Yes (n = 24)	16,60	9,80	18,27	13,43– 23,11
No (n = 140)	15,60	7,40	17,83	14,53– 21,13
p = 0,82				
Age group				
10-14 years (n = 84)	15,13	7,36	17,42	13,44– 21,40
15-17 years (n = 80)	16,32	8,08	18,68	14,87– 22,49
p = 0,33				

Abbreviations: SD: standard deviation; CI: confidence interval. (1) p-values shown are from adjusted comparisons. (2) *p < 0.05. (3) Vitamin D levels were adjusted using a linear regression model that included the following variables: age, sex, depression, eating disorder, substance use disorder, adjustment disorder, constipation, type of diet, season, and nutritional status.

Among the limitations of this study, with respect to the variables collected, although most of those that are relevant to VD deficiency were included, some of them presented a low frequency, such as a vegetarian diet. This could determine a lack of power to find an association between the type of diet and VD deficiency.

Although the regression model included all the variables that we considered important to analyze, it cannot be ruled out that other unmeasured factors influence VD levels.

Conclusion

This study revealed that adolescents aged 10 to 17 years with MHD seen at the AHU-HLF, between 2019 and 2021, present a high VD deficit, higher than reported in the world literature and similar to that reported in the general Chilean population. Moreover, severe deficiency was more frequent than that reported in the Chilean population. The factors associated with this deficit were excess malnutrition and the season of the year, with significantly lower serum VD levels in

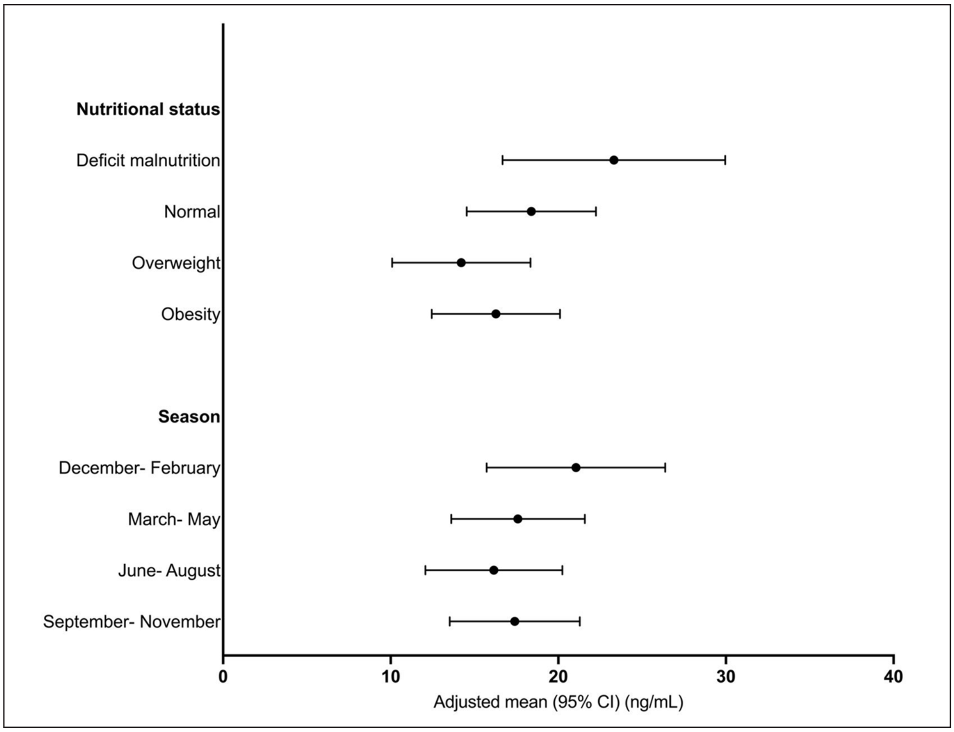

Figure 2. Adjusted Mean Vitamin D Levels for Variables with Statistically Significant Associations: Nutritional Status and Season of the Year. Note: Adjusted using a linear regression model for the following variables: age, sex, depression, eating disorder, substance use disorder, adjustment disorder, constipation, and type of diet.

overweight-obese adolescents and during the winter months.

It is important to measure VD levels in adolescents with MHD due to the high prevalence found in this study conducted in hospitalized adolescents.

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.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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