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ORIGINAL ARTICLE

Vitamin D deficiency in adolescents: is there a difference according to the degree of obesity?

Déficit de vitamina D en adolescentes: ¿existe diferencia según el grado de obesidad?

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

Vitamin D has multiple functions in the body and its deficiency is associated with metabolic alterations and negatively impacts bone health. Increased body fat is a risk factor for deficiency.

What does this study contribute to what is already known?

To provide information on the frequency of Vitamin D deficiency in obese adolescents, given the scarcity of data in Chile, in addition to sensitizing health professionals to prevent, detect, and treat this deficiency in order to avoid the deterioration of bone health and prevent cardiometabolic risk.

Abstract

Objective: To analyze the frequency of vitamin D (VD) deficiency in adolescents with different degrees of obesity and its association with alterations in the metabolic profile. **Patients and Method:** Cross-sectional, descriptive, and analytical study in 250 adolescents with different degrees of obesity, treated at the nutrition polyclinic of the *Hospital Dr. Sotero del Río*. Data on age, sex, weight, height, Tanner stage, 25-hydroxyvitamin D levels, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, basal insulin, and glycemia were collected. The following were used for statistical analysis: Student's test, chi-square, multiple linear regression analysis, and Pearson's correlation coefficient. **Results:** 58% of the adolescents presented non-severe obesity and 42% severe obesity, the mean age was 12.4 ± 2.1 years, and 54% were male. 91% of the total sample presented VD deficiency, being more frequent among adolescents with severe obesity, reaching 95%. VD levels were significantly lower in winter. HOMA (homeostatic model assessment) values were higher among patients with severe obesity (6.3/4.2). Low HDL-c was more frequent in adolescents with severe obesity (78%/62%). An inverse correlation was found between VD and triglyceride levels (r = -0.20; p = 0.00) and total cholesterol (r = -0.15; p = 0.03). **Conclusion:** The VD deficiency among obese adolescents is worrying, reaching more than 90% of the study sample. Our results highlight the importance of timely prevention, detection, and treatment of VD deficiency in obese adolescents to prevent bone health deterioration and cardiometabolic risk in adulthood.

Keywords:
Severe Obesity;
Vitamin D;
Adolescents;
Cardiometabolic Risk

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Introduction

Childhood obesity has become a worldwide public health problem that has increased at an alarming rate. According to the World Obesity Federation, in 2020, 158 million children and adolescents are affected by obesity and, if the current growing rate continues, it is estimated that by 2030 this figure will reach 254 million[1]. The global prevalence of severe obesity in adolescents is not well established.

It is known that childhood obesity is an important risk factor for comorbidities and obesity in adulthood, especially when it is severe and the older the child is. 75% of adolescents with severe obesity will maintain this condition into adulthood[2].

One of the most important nutritional deficiencies associated with obesity is vitamin D (VD). International data on overweight and obese children and adolescents report the following prevalences according to the cut-off point used for its definition and the relationship with the season of the year: Germany 96% (< 30 ng/ml) with significantly higher concentrations between summer and autumn, Iran 95.6% (< 30 ng/ml) with samples collected during spring and summer, Spain 81% (< 30 ng/ml) with no significant differences according to season, the United States 78% (< 20 ng/ml) with no differences according to seasonality, Sweden 33% (< 20 ng/ml) with significantly lower levels in winter, the Netherlands 24.5% (< 20 ng/ml) with no differences by season, Malaysia 19% (< 20 ng/ml) which is a country without seasonality, and Denmark 16.5% (< 12 ng/ml) with significantly lower levels in winter[3-10].

In Chile, a recent study of 1,134 children and adolescents aged between 4 and 14 years, from Santiago, Concepción, and Antofagasta, showed that 80.4% of the sample had VD deficiency, with a higher frequency in Antofagasta, despite being the sample with the highest serum levels of 25(OH)D, probably due to its geographical location which could be attributed to the higher frequency of cases of overweight and obesity found in that region[11].

It has been described that the level of 25(OH)D is inversely related to body fat, suggesting that obesity could be a risk factor for its deficiency[12]. Possible mechanisms involved in this relationship are retention and volumetric dilution of VD in increased adipose tissue[13], which reduces its availability to target tissues, decreased outdoor physical activity, reduced sun exposure, and a diet low in vitamin D, especially dairy products.

The association between VD deficiency and obesity has been extensively investigated in adults. The largest meta-analysis published in 2015 which included 15 studies (3,867 obese individuals and 9,342 healthy subjects), evidenced a significant increase in the prevalence of VD deficiency in patients with obesity, with OR (95%) of 3.70 (2.33-5.06), demonstrating that this population is at high risk of developing VD deficiency[14].

VD is a fat-soluble vitamin with multiple functions. 80% of vitamin D levels in the human body come from photosynthesis, specifically from cutaneous bioconversion by ultraviolet B (UVB) light of 7-dehydrocholesterol[15], and the remaining 20% from the diet. The time of sun exposure necessary to maintain healthy vitamin D levels in healthy individuals varies according to skin phototype, the season of the year, and the time of day. In the case of phototype I, for example, 6 minutes of exposure to the sun at midday in summer and 17 minutes in winter would be sufficient, exposing some areas of the body such as the face, arms, and hands[16].

VD plays an important role in bone mineralization, it regulates ~3% of the human genome, modulates immune function[17], anti-inflammatory activity, suppression of the renin-angiotensin system, and reduces insulin resistance[18]. Appendix 1 summarizes the scientific evidence supporting the functions of vitamin D and its association with metabolic alterations.

The impact of VD deficiency has been underestimated despite the importance of this vitamin for health. It has been described that its deficiency is associated with bone pathologies and serious conditions such as cancer, autoimmune diseases, cognitive deficiencies, and abnormal immune system response to viruses[31]. It has also been suggested that its deficiency is associated with cardiovascular disease and cardiometabolic risk factors such as diabetes, metabolic syndrome, high blood pressure, and dyslipidemia, the latter through mechanisms that are not completely known[13]. Despite the above, VD status is not routinely studied in the obese population.

Given the increase in severe obesity recorded in recent years in our country, the impact of VD deficiency on health, and the scarcity of national data on VD status in obese adolescents, the objective of this study was to correlate the frequency of VD deficiency in adolescents with different degrees of obesity and to determine whether this condition could be related to alterations in the metabolic profile.

Patients and Method

Study design

Cross-sectional, descriptive, and analytical study of the frequency of VD deficiency in adolescents with obesity. The sample size was determined using the Cleveland Clinic Risk Calculator library (RiskCalc) of the University of Cleveland[32]. For an estimated preva-

lence of VD deficiency of 45% in severely obese adolescents, statistical power of 80%, and significance level of 5%, the inclusion of a minimum of 96 severely obese adolescents and 134 non-severe obese adolescents was required.

We recruited a group of 250 individuals with different degrees of obesity, aged between 10 and 19 years, seen between January 2017 and June 2021 at the nutrition polyclinic of the *Hospital Dr. Sotero del Río*, in the commune of Puente Alto. The electronic medical records of the patients were reviewed, selecting those who had the following data on admission: weight, height, Tanner stage, concomitant serum measurement of 25(OH)D, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), basal insulin, and glycemia. Patients excluded were those with incomplete data on the variables under study, those undergoing bariatric surgery, or with a history of malabsorption syndrome, cancer, diabetes mellitus, nephrotic syndrome, genopathies, or the use of drugs that could alter lipid, glycemic, and VD metabolism or who had received vitamin supplements 3 months before recruitment.

The following variables were collected: age, sex, weight (kg), and height (cm) using a mechanical scale with stadiometer (Seca®), with an accuracy of 0.1 kg and 1 cm, respectively. Pubertal development was evaluated by physical examination according to Tanner›s stage. Lifestyle data were collected, such as daily screen time exposure and hours of physical activity per week, obtained from the anamnesis performed by the pediatric nutritionist at admission.

Nutritional evaluation

With the variables weight (kg) and height (cm), the body mass index (BMI = Weight in kg/Height^2 in m) was calculated using the AntroPlus software, expressing the results in absolute value and z-score (z = actual value-median/1SD) for age and sex according to WHO 2007. The nutritional classification was performed according to the definitions established by the Ministry of Health of Chile[33].

Biochemical determinations

All biochemical samples were collected and analyzed in the laboratory of the *Hospital Dr. Sotero del Río* using standardized protocols: fasting for 8 hours, serum sample transported in a container with vertical slits at room temperature, and processing of the sample within 4 hours of collection. 25(OH)D was determined in serum samples by the chemiluminescent microparticle immunoassay (method standardized by the U.S. National Institute of Standards of Technology)[34]. Additionally, the season of the year in which samples were collected was recorded.

VD deficiency has been defined as 25(OH)D values below 20 ng/ml and insufficiency as 21-29 ng/ml (18). Therefore, we consider deficient values below 30 ng/ml.

TC, HDL-c, and TG levels were determined by enzymatic colorimetric method and LDL-c was calculated with the Friedewald formula [LDL-c (mg/dL) = TC - (TG/5 + HDL-c)], which is valid as long as the triglyceride concentration does not exceed 400 mg/dl. To consider levels altered, the risk cut-off point of the recommendations of the Nutrition Branch of the Chilean Pediatric Society[35] was used. For glucose determination, the hexokinase method was used and its alteration was defined as fasting glucose values ≥ 100 mg/dl, insulin was determined by chemiluminescent microparticle immunoassay, and the insulin resistance index (HOMA-IR) was calculated with the Matthews formula $HOMA_{IR}$ = (Fasting insulin µUI/ml x Fasting glucose mmol/L) / 22.5. IR was defined as values ≥ the 90th percentile of HOMA-IR, according to sex and pubertal development of the distribution of a Chilean cohort of adolescents[36].

Statistical analysis

Statistical Product and Service Solutions (SPSS) version 18.0 software (SPSS Inc., Chicago, IL, USA) was used. Descriptive characteristics were presented as means, continuous variables as standard deviation, and nominal variables as percentages. The normal distribution of the sample was determined with the Kolmogorov-Smirnov test. The groups were compared with the Student's t-test and chi-square test. Multiple linear regression analysis was performed to estimate associations between serum 25(OH)D concentration and serum lipids, glycemia, and HOMA. Effect modification by body mass index (BMI) was assessed by Pearson's correlation coefficient. All $p < 0.05$ values were considered statistically significant.

Ethics Statement/Declaration

The protocol of this study was approved by the Scientific-Ethical Committee of the Southeast Metropolitan Health Service and the *CEC-Salud UC* (ID 211014008) and was conducted according to the principles of the Declaration of Helsinki.

Results

General characteristics of the sample

The sample consisted of 250 adolescents, 54% were male. The group with non-severe obesity accounts for 58% (n = 144) and those with severe obesity 42% (n = 106). The average age was 12.4 ± 2.1 years with

no differences between groups. Within the anthropometric variables, weight, height, and z-BMI means were significantly higher in the severely obese group ($p < 0.05$). The pubertal stage did not show significant differences between groups, with Tanner stage IV as the most frequent (37%). In the mean daily screen time exposure, no statistically significant difference was found according to the type of obesity. The time dedicated to physical activity was reported in 173 adolescents (69%) with a mean of 1.9 ± 1.2 hours per week, being significantly lower in the group of severely obese adolescents. Of the remaining 77 adolescents (31%) who reported no physical activity, 48% corresponded to the severely obese group. There were no significant differences between the groups. Table 1 shows the general characteristics of the sample.

Alterations in the metabolic profile according to obesity level

When comparing the metabolic profile variables of the adolescents according to the degree of obesity, we observed that serum insulin and HOMA were significantly higher in the severely obese group. The frequency of IR in the adolescents of the total sample was 47%, being more frequent in the severely obese group (68%). A low level of HDL-c was present in 69% of the total sample and was significantly higher in adolescents with severe obesity representing 78% of this group. No significant differences were found in the rest of the values analyzed (table 2).

Vitamin D deficiency in obese adolescents

In the sample, the 25(OH)D value reached a mean of 19.3 ± 7.0 ng/ml, with a minimum value of 6.1 ng/ml and a maximum of 46.8 ng/ml. Of the total sample, 91% of the adolescents presented VD deficiency. No statistically significant association was found by age or sex. Significant differences in 25(OH)D levels were observed in the different seasons of the year, with the lowest levels observed during winter (Figure 1A). No significant differences were found according to the year of sample recruitment (Figure 1B).

Regarding serum 25(OH)D levels according to the obesity degree, we observed a mean value of 18.66 ± 1.20 ng/ml in adolescents with severe obesity and 19.77 ± 1.24 ng/ml in those with non-severe obesity, with no significant differences between groups (Figure 1C). Additionally, when analyzing the VD status according to the obesity degree, we see that deficiency was more frequent among adolescents with severe obesity, representing 95% of this group (101/106), that is, only 5% of adolescents with severe obesity had sufficient VD

Table 1. General characteristics of adolescents according to obesity degree.

Variable	Non severe obesity n = 144 (58%)	Severe obesity n = 106 (42%)	Total n = 250	Valor - p
Age a years	12.3 ± 2.0	12.5 ± 2.1	12.4 ± 2.0	0.31
Sex[a]				
Masculine %	49	61	54	0.06
Anthropometry[b]				
Weight kg	67.3 ± 14.2	86.8 ± 19.9	75.6 ± 19.4	0.00*
Height cm	154.0 ± 12.4	157.1 ± 10.7	155.3 ± 11.8	0.04*
zBMI	2.5 ± 0.2	3.4 ± 0.4	2.9 ± 0.5	0.00*
Tanner[a] %				
I	19	17	18	0.71
II	31	37	34	
III	8	10	8	
IV	40	34	37	
V	2	2	3	
Habits[b]				
Screen time hours/day	4.5 ± 1.6	4.8 ± 1.5	4.6 ± 1.6	0.10
Physical activity hours/week	1.5 ± 1.4	0.9 ± 0.9	1.9 ± 1.2	0.0008*

Abbreviations: zBMI: Body mass index z score. [a]Chi square (χ^2), [b] T-test.

levels, while in the group with non-severe obesity, 89% presented deficiency. No statistically significant difference was found between the obesity degree and VD deficiency (Figure 1D).

Vitamin D deficiency and metabolic profile alterations

When VD status was compared with alterations in the metabolic profile, statistical significance was only found between VD deficiency and triglyceride level ($p = 0.0062$). There was no significant association between VD deficiency and serum levels of TC, LDL-c, HDL-c, glycemia, and HOMA (table 3).

Subsequently, VD deficiency and the serum parameters of the metabolic profile were correlated by multiple linear regression (table 4). The coefficients described show the direction and level of correlation. The p-value indicates whether the correlation is significant or not. In the second column, we can see the values of the coefficients described for this correction together with the p values. The correlations of the metabolic variables with the VD deficiency (rxy) were mostly inverse, with TC and triglycerides as the only statistically significant ones.

Given that there is a correlation between the metabolic profile alterations in people with obesity, we adjusted our linear regression using obesity (z-BMI) as a confounding factor. When controlling for the effect of the BMI variable, and after calculating the partial correlation coefficient ($r_{12.3}$), there was no significant difference between the two coefficients, so it is estimated that BMI did not influence the correlations obtained by Pearson's coefficient.

Discussion

In our study, VD deficiency was highly frequent, reaching 91% of adolescents which is similar to those figures reported in the international literature on overweight and obese children and adolescents[3-6]. Numerous studies have shown that 25(OH)D concentrations are lower in obese individuals[3,4,5,6,10,12]. A study in obese adolescents showed that a 1% increase in fat mass is associated with a 1.15 ± 0.55 nmol/l reduction in serum 25(OH)D[37].

Although there is still no consensus regarding the cause of decreased 25(OH)D levels in these individuals, the most frequently raised hypothesis is the sequestration of VD in adipose tissue. Low exposure to sunlight caused by the sedentary lifestyle of obese individuals and thus lower endogenous synthesis of VD

Table 2. Metabolic profile alterations in adolescents according to obesity degree

Metabolic profile[a]	Non severe obesity n = 144 (58%)	Severe obesity n = 106 (42%)	Total n = 250	Valor - p
Altered fasting blood glucose %	5	8	6	0.53
Glycemia mg/dl	87.5 ± 7.0	88.8 ± 7.0	88.1 ± 0.4	0.15
RI %	31	68	47	0.0000*
HOMA	4.2 ± 2.8	6.3 ± 4.2	5.1 ± 3.6	0.0000*
Insulin U/ml	19.4 ± 12.4	28.6 ± 18.9	23.3 ± 16.1	0.0000*
Altered total cholesterol %	43	35	40	0.24
Cholesterol mg/dl	168.6 ± 39.8	163.4 ± 32.8	166.4 ± 36.8	0.27
Altered c-LDL %	31	22	27	0.24
c-LDL mg/dl	101.8 ± 31.1	97.0 ± 25.7	99.7 ± 29.0	0.19
Altered c-HDL%	62	78	69	0.0082*
c-HDL mg/dl	43.2 ± 9.5	41.6 ± 10.6	42.5 ± 10.0	0.20
Altered Triglycerides %	71	80	75	0.12
Triglycerides mg/dl	143.6 ± 78.2	153.4 ± 67.7	147.7 ± 68.8	0.30

Data expressed as media plus standard deviation and percentages. Abbreviations: HOMA-IR: Homeostatic model assessment for insulin resistance, c-HDL: High density lipoproteins cholesterol, c-LDL: Low density lipoproteins cholesterol. [a]T-test.

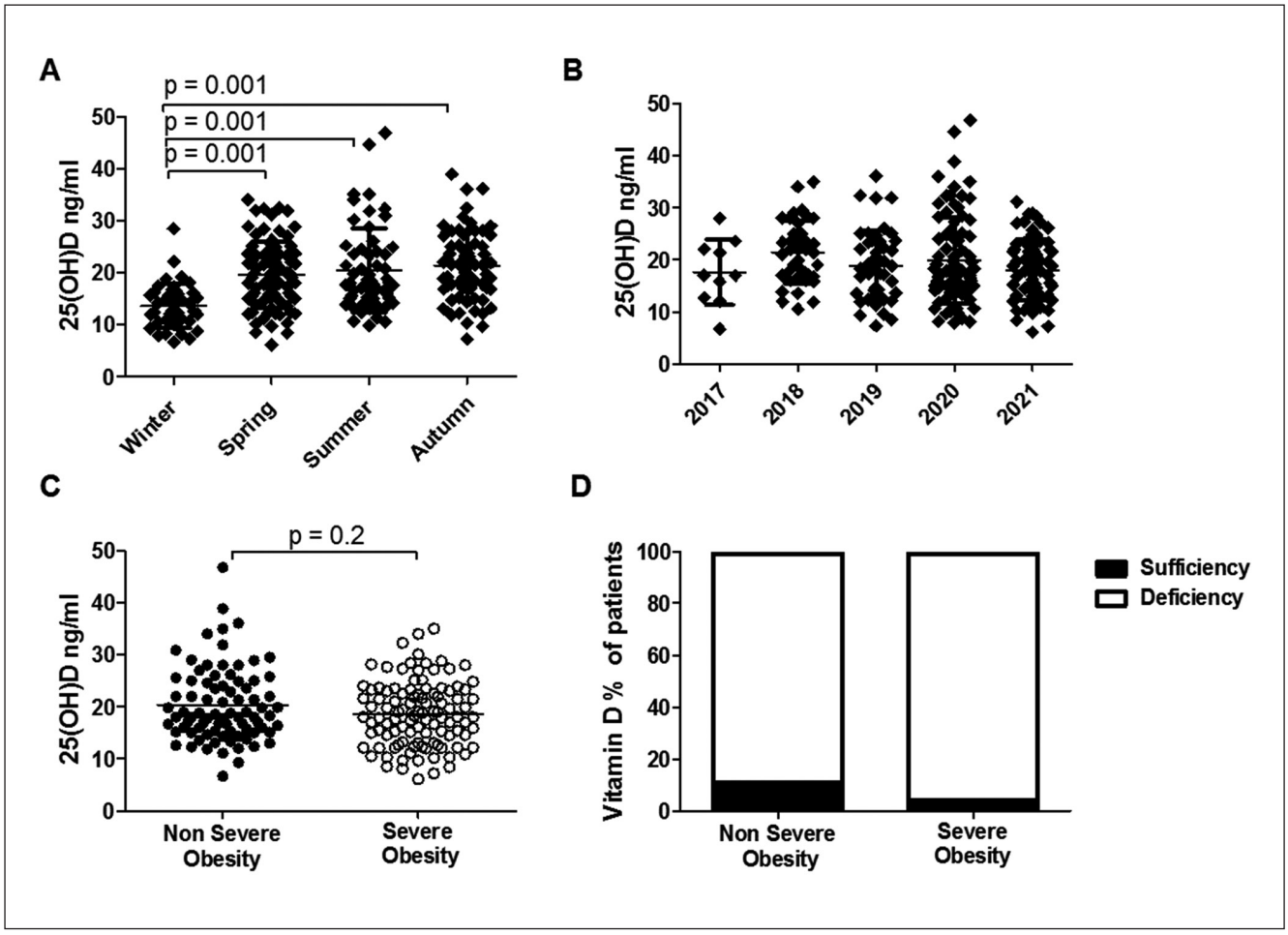

Figure 1. A) Serum VD levels according to season of recruitment in the study. **B**) Serum VD levels differences according to year of recruitment in the study. Data are presented as individual point per patients plus mean and standard deviation. Analysis was performed using one way ANOVA plus Tukey post-test. **C**) Serum VD in adolescents with different degree of obesity. Data are presented as individual point per patients plus mean and standard deviation. Analysis was performed using Mann Whitney test. **D**) Percentage of patients according to VD sufficiency status and obesity degree. Analysis was performed using chi-square test with Fisher correction.

Table 3. Vitamin D status and metabolic profile alterations associations

Altered metabolic parameter	Vitamin D status		Total n = 250	P value
	Deficient n = 229 (91%)	Sufficient n = 21 (9%)		
Total cholesterol	(41)	(23)	(40)	0.18
c-LDL	(28)	(23)	(28)	0.84
c-HDL	(70)	(57)	(69)	0.33
Triglycerides	(77)	(48)	(75)	0.0062*
HOMA	(57)	(34)	(55)	0.14
Glycemia	(6)	(5)	(6)	1.00

Chi square analysis (χ^2) for VD status Vs % Patients with altered metabolic parameters. Abbreviations: HOMA-IR: Homeostatic model assessment for insulin resistance, c-HDL: High density lipoproteins cholesterol, c-LDL: Low density lipoproteins cholesterol.

Tabla 4. Correlación entre la deficiencia de vitamina D y variables metabólicas alteradas

Altered metabolic parameter	Vitamin D (r_{xy})	Vitami-naD ($r_{12.3}$)	P value	Degree of correlation
Total cholesterol	-0.13	-0.15	0.0354*	Low
c-LDL	-0.09	-0.09	0.13	Very Low
c-HDL	0.02	0.02	0.77	Very Low
Triglycerides	-0.17	-0.20	0.0065*	Low
HOMA	-0.07	-0.05	0.26	Very Low
Glycemia	-0.07	-0.06	0.30	Very Low

Pearson multiple correlation coefficient (r_{xy}). Pearson multiple correlation coefficient controlled by BMI effect ($r_{12,3}$). HOMA-IR: Homeostatic model assessment for insulin resistance, c-HDL: High density lipoproteins cholesterol, c-LDL: Low density lipoproteins cholesterol.

also seems to play a role. Other hypotheses propose the alteration of VD synthesis and metabolism because of hepatic steatosis secondary to obesity and elevated levels of leptin and interleukin-6 (IL-6) that affect hepatic VD receptors[38].

In relation to 25(OH)D levels, we observed a seasonal behavior similar to that described in the literature, with significantly lower levels in the winter months. When analyzing 25(OH)D levels in the period studied (January 2017 to June 2021), surprisingly, we did not find an effect secondary to recruitment during the pandemic years. Serum VD levels showed no significant differences by year of recruitment and, despite the confinement of adolescents between 2020 and 2021, no lower serum VD values were recorded compared with the values obtained in previous years.

The excessive screen time exposure reported in both groups along with the scarce hours of physical activity, especially in severely obese adolescents, show a tendency of a markedly sedentary lifestyle in our adolescents. Considering that more than 80% of endogenous VD synthesis depends on sun exposure, the high level of a sedentary lifestyle in the sample could partly justify the high frequency of VD deficit observed.

The highest frequency of VD deficiency was observed in the severely obese group (95%) and did not reach statistical significance to establish an association between the degree of obesity and VD deficiency. However, we suggest interpreting this result with caution because, although the difference between the z-BMI of the groups was significant, in the group with non-severe obesity, the z-BMI values are very close to the cut-off point that defines severity, which could explain the absence of significance found. Another reason could be attributed to the low frequency of VD sufficiency (9%) in our group.

The results of this work show a significant inverse correlation between 25(OH)D, triglycerides, and total cholesterol levels after adjusting for confounding factors such as BMI. Gutierrez et al.[39] reported a significant inverse correlation between VD levels and TG values in a population of children and adolescents aged 6 to 17 years with obesity, with no difference from other lipid profile variables. On the other hand, Pecoraro et al.[40] found that VD supplementation was associated with significant changes in serum levels of total cholesterol, LDL-c, and HDL-c, with no changes in triglycerides. A meta-analysis of randomized clinical trials (RCTs) in patients aged 4 to 18 years found that VD supplementation did not affect cardiometabolic risk markers, including HDL-c, LDL-c, triglycerides, and TC; however, VD supplementation showed a beneficial effect on TC levels and fasting glycemia in the subgroup analysis of total vitamin D supplementation with vitamin D ≥ 200 000 IU[41].

Previous studies have confirmed the association between VD levels and lipid profile in obese children and adolescents[42,43]. Among the pathophysiological hypotheses that are used to explain the relationship between VD level and lipid profile is the intestinal absorption of calcium, which leads to an increase in serum calcium concentration that promotes the conversion of cholesterol into bile acids in the liver and, therefore, reduces the serum TC level[43]. It has also been proposed that VD deficiency stimulates parathyroid hormone production and secretion, which increases the stimulation of lipogenesis and decreases lipolysis, resulting in elevated triglyceride levels[44]. In addition, it is thought that VD increases the expression of the VLDL receptor and reduces the synthesis and secretion of triglycerides from the liver, therefore, its deficit could produce the opposite effect, with the consequent elevation of VLDL-c, decrease in HDL-c, and increase in triglycerides[43].

The study by Texeira et al., which included a cohort of 60 severely obese adolescents, showed a significant negative correlation between insulin resistance as assessed by the HOMA-IR index and VD levels, where 25(OH)D deficiency was associated with elevated HOMA-IR values[45]. In our study, 68% of severely obese adolescents presented insulin resistance (adjusted for Tanner stage and sex) and, although no significant correlation with VD deficiency was evidenced, this group also presented the highest frequency of deficiency.

Previous studies have provided strong evidence that VD deficiency may be associated with B-cell dysfunction and insulin resistance[46]. However, the evidence on the effect of VD supplementation on insulin sensitivity is still conflicting. A meta-analysis including 18 RCTs found no evidence that VD supplementation had a beneficial effect on peripheral insulin sensitivity in people with or at risk for insulin resistance[47].

Several limitations of this work should be considered when interpreting its results. First, the most important limitation was not having a group of eutrophic patients for comparison, given that multiple studies have shown that overweight and obese individuals are at higher risk of VD deficiency compared with eutrophic patients[39,48,49]. Second, all participants live in the same commune, which limits the generalizability of the results. Third, the data obtained in the cross-sectional studies do not reflect causality and we do not have data from the food survey or daily sun exposure, so we do not know the real impact of these variables on the results. As strengths we highlight the number of patients recruited, that all participants had complete anthropometric data for analysis, the blood samples for biochemical studies were collected without intervention on the lifestyle of the patients or VD supple-

mentation, and all samples were processed with the same techniques and in the same laboratory.

In conclusion, the frequency of VD deficiency among obese adolescents is of concern due to the increasing numbers of obesity in the pediatric population, there is a growing interest in the prevention and early management of cardiovascular disease risk factors to decrease the occurrence of such diseases in adulthood. Although the clinical consequences of non-severe VD deficiency are less well established, it has been shown that these chronically low concentrations may also affect bone mineral density. Our results highlight the importance of early prevention, detection, and treatment of VD deficiency in obese children and adolescents to avoid deterioration of bone health and prevent cardiometabolic risk in adulthood. It is important to promote population strategies aimed at stimulating a healthy lifestyle, including a balanced diet, and increased outdoor physical activity, as well as to establish public health policies to improve vitamin D intake in the population[50].

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.

Annex 1. Summary of scientific evidence of the association between vitamin D and metabolic alterations

Vitamin D functions	Evaluated parameter	Results	Degree of evidence	Reference
Glucose metabolic regulations and insulin resistance	Insulin resistance (IR)	VD deficiency is associated with higher levels of IR	Systematic review and meta-analysis of observational studies	Rafiq S. 2021[19]
		Improvements in VD status increases insulin sensitivity	Systematic review and meta-analysis of controlled clinical trials	Mirhosseini N. 2018[20]
	Diabetes mellitus type 2 (DM2)	VD supplementation is effective for glycemia control in DM2 patients with VD deficiency	Systematic review and meta-analysis of controlled clinical trials	Wu C. 2017[21]
		VD supplementation reduces fasting glycemia, HbA1c and HOMA-IR index in DM2 patients	Systematic review and meta-analysis of controlled clinical trials	Mirhosseini N. 2017[22]
Cardiovascular risk factors modification	Cardiovascular disease (CVD)	VD supplementation protects against CVD improving blood pressure, high levels of PTH, dyslipidemia and inflammation	Systematic review and meta-analysis of controlled clinical trials	Mirhosseini N. 2018[23]
		VD supplementation is beneficial in patients ≥50 years in >800 IU/day during <6 months	Systematic review and meta-analysis of controlled clinical trials	Golzarand M. 2016[24]
Possible protection against pathogenesis and progression of NAFLD	Non-alcoholic fatty liver disease (NAFLD)	In NAFLD patients, increasing levels of 25(OH)D associated with lower cardiovascular and general mortality risk	Retrospective cohort analysis	Chen Y. 2022[25]
		VD supplementation increases glycemia control and insulin sensitivity in NAFLD patients.	Systematic review and meta-analysis of controlled clinical trials	Guo XF. 2020[26]

Possible improvement on lipid profile	Lipid profile	Higher serum levels of 25(OH)D correlate with a favorable lipid profile in pediatric patients	Systematic review and meta-analysis of observational studies	Kelishadi R. 2014[27]
		VD supplementation improved seric total cholesterol, c-LDL and triglycerides but not c-HDL levels	Systematic review and meta-analysis of controlled clinical trials	Dibaba DT. 2019[28]
Positive effect on obesity indexes	Body mass index (BMI), Waist circumference (WC)	VD supplementation improved obesity index such as BMI and WC	Systematic review and meta-analysis	Musazadeh V, 2022[29]
		Adequate VD levels associated with better anthropometric measurements	Retrospective analysis	Abboud M. 2019[30]

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