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Trabajo Original

Pediatría

Association between vitamin D levels and cardiovascular risk factors in obese children and adolescents

Asociación entre los niveles de vitamina D y factores de riesgo cardiovascular en niños y adolescentes obesos

Ali Gul[1], Samet Ozer[1], Resul Yilmaz[1], Ergun Sonmezgoz[1], Tuba Kasap[1], Şahin Takçi and Osman Demir[2]

Departments of [1]Pediatrics and [2]Biostatistics. School of Medicine. Gaziosmanpasa University. Tokat, Turkey

Abstract

Background and aim: Childhood obesity is associated with an increased risk of chronic disease. We aimed to determine the association between vitamin D deficiency and cardiovascular risks in obese children.

Method: The studied children were selected from obese children who were followed up at obesity clinic, aged 6-17 years. Basic demographic information and laboratory data were collected retrospectively from hospital records.

Results: A total of 310 students (178 [57.4%] girls) were evaluated for 25-hydroxyvitamin D (25[OH] D) levels in late winter/spring. The prevalence rates of vitamin D deficiency, insufficiency, and sufficiency were 62.3%, 34.5%, and 3.2%, respectively. Insulin resistance was observed in 146 (47.1%) children; the frequencies of dyslipidemia and hypertension were 31% and 19.4%, respectively. The mean atherogenic dyslipidemia ratio was higher in the deficient group ($p = 0.049$). Inverse correlations of 25(OH) D levels were observed with homeostasis model assessment of insulin resistance values ($r = -0.146$, $p = 0.010$). The mean values of 25(OH) D (ng/mL) were lower in girls (12.15 ± 6.60) than in boys (16.48 ± 8.69) ($p < 0.05$) and in children with hypertension (11.92 ± 5.48) than in those without (14.50 ± 8.24) ($p < 0.05$).

Conclusions: Vitamin D deficiency is observed more frequently than expected in obese children and adolescents. Our findings indicate that low 25(OH) D levels are associated with insulin resistance. Vitamin D deficiency could contribute to the morbidities associated with childhood obesity, such as insulin resistance or diabetes mellitus, increased cardiovascular/cardiometabolic risks, atherogenic dyslipidemia, and hypertension.

Key words:

Vitamin D.
Obesity. Child.
Cardiovascular risk.
Insulin resistance.
Hypertension.

Resumen

Introducción y objetivo: la obesidad infantil se asocia a un riesgo aumentado de enfermedades crónicas. El objetivo de este estudio es determinar la relación entre la deficiencia en vitamina D y el riesgo cardiovascular en niños obesos.

Método: se seleccionaron niños tratados en la clínica de obesidad, con edades entre 6 y 17 años. Los datos de laboratorio y la información demográfica básica se recogieron de forma retrospectiva a partir de las historias clínicas.

Resultados: se evaluaron 310 estudiantes (178, 57,4% mujeres) midiendo los niveles de vitamina D a finales de invierno y en primavera. La prevalencia de deficiencia en vitamina D, insuficiencia y suficiencia fueron 62,3%, 34,5% y 3,2% respectivamente. Se encontró resistencia insulínica en 146 niños (47,1%); mientras que la frecuencia de dislipemia e hipertensión fue de 31% y 19,4%, respectivamente. La razón de aterogenicidad debida a dislipemia fue mayor en el grupo deficiente ($p = 0,049$). Se encontró una correlación inversa entre los niveles de 25-OH-D y los valores de HOMA ($r = -0,146$; $p = 0,01$). Los valores medios de vitamina D (ng/Ml) fueron inferiores en niñas ($12,15 \pm 6,60$) que en niños ($16,48 \pm 8,69$) ($p < 0,05$) y en niños con hipertensión ($11,92 \pm 5,48$ *vs.* $14,50 \pm 8,24$ en normotensos) ($p < 0,05$).

Conclusiones: se encontró una prevalencia de deficiencia en vitamina D en niños y adolescentes obesos superior a lo esperado. Nuestros hallazgos indican que los niveles bajos de vitamina D se asocian con resistencia insulínica. La deficiencia en vitamina D podría contribuir a las morbilidades que se asocian a la obesidad infantil, como la resistencia insulínica o la diabetes mellitus, el aumento del riesgo cardiovascular, la dislipemia y la hipertensión.

Palabras clave:

Vitamina D. Obesidad.
Niño. Riesgo cardiovascular.
Resistencia insulínica.
Hipertensión.

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Correspondence:

Ali Gul. Department of Pediatrics. School of Medicine.
Gaziosmanpasa University TIP Fakultesi Pediatri AD
60030 Tokat, Turkey
e-mail: draligul@yahoo.com

INTRODUCTION

The global prevalence of childhood obesity has increased considerably over the past 3 decades (1). Ten percent of school-aged children worldwide are estimated to have excess body fat, which is associated with an increased risk of chronic disease. Of these overweight children, a quarter are obese and thus have a significant likelihood of possessing multiple risk factors for the development of type 2 diabetes, heart disease, and various other co-morbidities before or during early adulthood. The increasing incidence of disorders in children, such as type 2 diabetes, is a consequence of the obesity epidemic (1,2).

Although the main physiologic role of vitamin D is the regulation of calcium and phosphorus homeostasis, it plays a variety of nonskeletal roles, such as the pathogenesis of several endocrine diseases, modification of immune competence, regulation of blood pressure, and modulation of cancer and infectious disease risks, and propensity for autoimmune diseases (3-5). However, cynicism surrounds the lack of randomized controlled trials to support association studies concerning the nonskeletal health benefits of vitamin D (5).

To date, many studies have observed low 25-hydroxyvitamin D (25[OH] D) levels in overweight and obese populations (6-8). In US children, the prevalence of vitamin D deficiency is nearly 21% among normal-weight population, 29-34% in overweight and obese populations, and 49% in a severely obese population (9).

Evidence from many studies indicates the existence of a strong association between vitamin D and cardiovascular risks, particularly blood pressure. Vitamin D deficiency might be linked to the pathophysiology of hypertension through its influence on the renin-angiotensin system (10). Vitamin D receptor (VDR) null mice exhibit significantly elevated renin activity and circulating plasma angiotensin II concentrations, as well as increased activity of the local cardiac tissue renin-angiotensin system (11).

Vitamin D has also been shown to modulate insulin synthesis and secretion (12). An analog of the active metabolite of vitamin D, $1,25(OH)_2$ D, has been found to directly enhance glucose-stimulated insulin release by increasing intracellular calcium levels in pancreatic β-cells (13).

In this study, we aimed to determine the associations between vitamin D deficiency and cardiovascular risks, such as hypertension, dyslipidemia, and insulin resistance (IR), in obese children and adolescents.

MATERIALS AND METHODS

PARTICIPANTS AND STUDY AREA

A total of 872 obese children who were followed up at the hospital of the Gaziosmanpasa University School of Medicine between January 2012 and February 2016 were retrospectively investigated, and we enrolled only children who were tested between February and May (i.e., in late winter and spring). Subjects were diagnosed with obesity according to a body mass index (BMI) value > 95th percentile in accordance with the sex-specific growth curves and cut-off levels proposed by Neyzi et al. (14). We excluded 562 obese children because of missing data, syndromic obesity, renal or hepatic disorders, metformin or vitamin D derivative usage, testing season, and age. Finally, 310 obese children aged 6-17 years were included in this study.

Subjects' demographic and clinical data, basic demographic information (age and sex), and physical data (body height, body weight, BMI, and systolic and diastolic blood pressure [BP]) were collected retrospectively from hospital records.

LABORATORY TESTS

Laboratory tests, including 25(OH) D, glucose, and insulin levels and lipid profiles, were conducted using fasting blood samples drawn from each participant. Laboratory and BP details were collected retrospectively from the electronic medical records used at the hospital.

Serum fasting glucose, triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) levels were detected using reagent kits adapted to the COBAS 6000 Autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA). Vitamin D levels were analyzed using chemiluminescence immunoassay methods and a COBAS C-501&E-601 analyzer (Roche Diagnostics).

DEFINITIONS OF OBESITY, IR, AND ATHEROGENIC RISK

Children were weighed on a digital scale (Seca Corp., Chino, CA, USA) and subjected to height measurement with a portable stadiometer (Seca Corp.) while they were barefoot and wearing light clothing. If BMI was > 95th percentile, the children was recorded as obese. BP was measured using a digital sphygmomanometer (OMRON 705IT; Omron Healthcare Co., Kyoto, Japan); if the measured BP was high with respect to age and sex, the mean of two measurements was recorded. Hypertension was defined as a BP ≥ 95th percentile according to age, sex, and height.

The homeostasis model assessment of IR (HOMA-IR) index was calculated using the following equation: HOMA-IR = (fasting insulin [mIU/mL] × fasting glucose [mmol/L])/22.5. Positive IR was defined as a HOMA-IR > 2.67 in boys and > 2.22 in girls during the prepubertal period or > 5.22 in boys and > 3.82 in girls during the pubertal period (15).

Dyslipidemia was defined as the presence of any of the following criteria: TGs > 105 mg/dL in children < 10 years of age and > 136 mg/dL in children ≥ 10 years of age, HDL-C < 35 mg/dL, and TC > 95th percentile (16). We calculated the atherogenic dyslipidemia (AD) ratio (log [TGs/HDL-C]) (17,18) to determine the effect of 25(OH) D on the cardiovascular atherogenic risk.

Vitamin D groups were determined according to measured levels. Vitamin D deficiency, insufficiency, and sufficiency were defined as a 25(OH) D level < 15 ng/mL (19), 15-29 ng/mL, and ≥ 30 ng/mL, respectively (20).

Study children were divided into healthy obese and non-healthy obese groups. Non-healthy obesity was defined as the presence of metabolic disturbances, such as IR according to HOMA-IR, dyslipidemia, and hypertension. Children without any such disturbances were considered healthy obese.

STATISTICAL ANALYSIS

Descriptive analyses were performed to obtain information about the general characteristics of the study population. A one-way analysis of variance was used to compare continuous data among the groups. For multiple comparisons, Tukey's honest significant difference (HSD) test was used. Continuous data are presented as means ± standard deviations. Categorical variables are presented as numbers and percentages. The chi-square test was used to compare categorical variables between groups. A p-value < 0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY, USA).

RESULTS

There were 310 obese children aged 6-17 years (178 [57.4%] females and 132 [42.6 %] males) who met the aforementioned inclusion criteria. In this cohort, the prevalence rates of vitamin D deficiency, insufficiency, and sufficiency were 62.3%, 34.5%, and 3.2%, respectively.

IR was observed in 146 (47.1%) obese children. Dyslipidemia and hypertension were found in 96 (31%) and 60 (19.4%), respectively. Only 109 (35.2%) children were classified as healthy obese. Table I summarizes the distributions of qualitative variables in the entire cohort according to vitamin D status.

The means of subject age (p = 0.008), BMI (p = 0.010), and AD ratio (p = 0.049) were higher in the vitamin D deficient group.

Non-healthy obese children were more frequently recorded as vitamin D deficient than healthy obese children (p = 0.023). Otherwise, no statistically significant differences were observed between 25(OH) D groups with respect to hypertension frequency (p = 0.074).

The mean age of the cohort was 12.10 ± 2.82 years, and the mean BMI was 29.21 ± 4.71. The mean HOMA-IR value was 3.78 ± 2.23. Table II summarizes the mean values of laboratory and clinic quantitative variables in the cohort according to vitamin D status.

No correlations of 25(OH) D levels were observed with lipid levels (TC, r = -0.032 and p = 0.571; TGs, r = -0.041 and p = 0.472; HDL, r = -0.01 and p = 0.858) or systemic BP (systolic, r = -0.099 and p = 0.082; diastolic, r = -0.065 and p = 0.256) (p > 0.01). Otherwise, weak but significant inverse correlations of 25(OH) D levels were observed with BMI (r = -0.167, p = 0.003) and HOMA-IR values (r = -0.146, p = 0.010). Figures 1 and 2 present scatter plots of 25(OH) D with BMI and HOMA-IR values, respectively.

The mean 25(OH) D values (ng/mL) were lower in girls (12.15 ± 6.60) *vs.* boys (16.48 ± 8.69) (p < 0.05), in children with hypertension (11.92 ± 5.48) *vs.* non-hypertensive children (14.50 ± 8.24) (p < 0.05), and in the nonhealthy obese group (13.29 ± 6.90) *vs.* the healthy obese group (15.30 ± 9.24) (p < 0.05). Table III summarizes the mean 25(OH) D levels according to sex and cardiovascular risk status.

DISCUSSION

Hypovitaminosis D (both insufficiency and deficiency) was observed more frequently than expected in obese children and

Table I. Distribution of qualitative variables in entire participant cohort according to vitamin D status (n = 310)

Variables		Total n = 310	Group of 25(OH) D status n (%)			p
			Deficient 193 (62.3)	Insufficient 107 (34.5)	Sufficient 10 (3.2)	
Sex	Female	178 (57.4)	126 (70.8)	49 (27.5)	3 (1.7)	0.001
	Male	132 (42.6)	67 (50.8)	58 (43.9)	7 (5.3)	
Insulin resistance (IR)	No	164 (52.9)	98 (50.8)	58 (54.2)	8 (80)	0.185
	Yes	146 (47.1)	95 (49.2)	49 (45.8)	2 (20)	
Dyslipidemia	No	214 (69)	130 (67.4)	76 (71)	8 (80)	0.602
	Yes	96 (31)	63 (32.6)	31 (29)	2 (20)	
Hypertension	No	250 (80.6)	149 (77.2)	91 (85)	10 (100)	0.074
	Yes	60 (19.4)	44 (22.8)	16 (15)	0 (0)	
Obesity group	Non-healthy	201 (64.8)	133 (68.9)	65 (60.7)	3 (30)	0.023
	Healthy obese	109 (35.2)	60 (31.1)	42 (39.3)	7 (70)	

Data are shown as n(%). Chi-square test was used. Deficient: 25(OH) D level < 15 ng/Ml; insufficient: 25(OH) D level = 15-29 ng/mL; sufficient: 25(OH) D level ≥ 30 ng/mL.

Table II. The mean values of quantitative variables in the cohort according to vitamin D status

Variables	Total n = 310	Group of vitamin D status (Mean)			p
		Deficient (n = 193)	Insufficient (n = 107)	Sufficient (n = 10)	
Age	12.10 ± 2.82	12.48 ± 2.68[a]	11.43 ± 2.9[b]	12.1 ± 3.51[a]	0.008
BMI	29.22 ± 4.71	29.82 ± 4.87[a]	28.1 ± 4.34[b]	29.62 ± 3.48[a]	0.010
Systolic BP (mmHg)	115.93 ± 13.74	116.73 ± 14.32	114.83 ± 12.61	112.2 ± 13.69	0.357
Diastolic BP (mmHg)	73.74 ± 10.67	73.88 ± 11.28	73.64 ± 9.65	72 ± 9.36	0.859
Glucose (mg/dL)	86.80 ± 10.84	86.87 ± 11.49	87.16 ± 9.32	81.7 ± 12.82	0.312
Insulin (ulU/mL)	17.45 ± 10.00	18.45 ± 10.58	16.01 ± 8.84	13.56 ± 7.82	0.059
HOMA-IR	3.78 ± 2.23	3.99 ± 2.37	3.5 ± 1.95	2.8 ± 1.78	0.067
HDL-C (mg/dL)	47.99 ± 12.09	47.63 ± 10.95	48.03 ± 13.46	55.12 ± 16.88	0.192
LDL-C (mg/dL)	102.21 ± 27.47	104.52 ± 28.07	98.41 ± 26.46	97.77 ± 23.19	0.166
Total cholesterol (mg/dL)	160.82 ± 30.70	161.97 ± 31.05	158.66 ± 30.77	161.81 ± 23.81	0.669
Triglycerides (mg/dL)	109.46 ± 53.74	111.1 ± 50.94	108.73 ± 59.24	85.53 ± 41.95	0.337
25 (OH) D (ng/mL)	14.00 ± 7.84	9.34 ± 3.25[a]	20.01 ± 3.5[b]	39.56 ± 11.02[c]	< 0.001
AD ratio	0.33 ± 0.25	0.34 ± 0.23[a]	0.32 ± 0.29[ab]	0.14 ± 0.28[b]	0.049

Data are shown as mean ± standard deviation. Different superscripts in the same row (one way ANOVA) indicate statistical significant difference. BMI: body mass index; BP: blood pressure; HOMA-IR: the homeostasis model assessment of insulin resistance index; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; 25 (OH) D: 25-hydroxyvitamin D. AD ratio: atherogenic dyslipidemia ratio, p = 0.045 for AD ratio between deficient and sufficient groups.

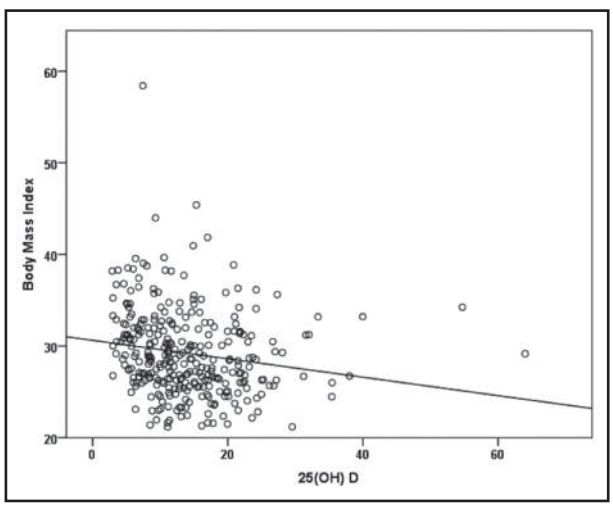

Figure 1.

Scatter plot of 25(OH) D (ng/mL) and body mass index (r = -0.167; p = 0.003).

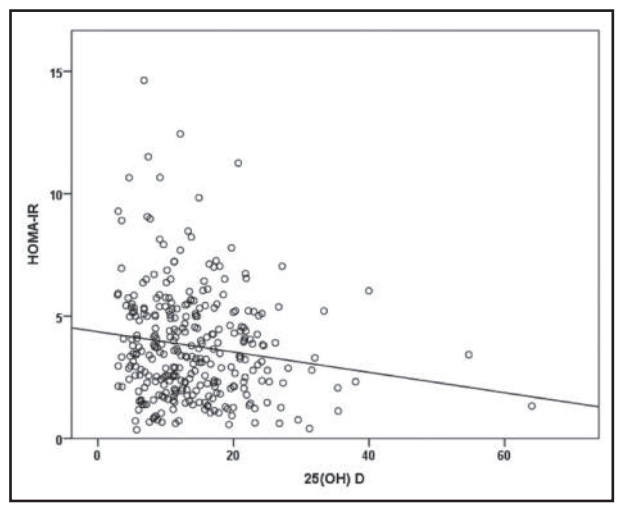

Figure 2.

Scatter plot of 25(OH) D (ng/mL) and HOMA-IR (r = -0.146; p = 0.010).

adolescents. In a previous meta-analysis, the prevalence of vitamin D deficiency was 24% in obese adults and 14% in obese children and adolescents (21). In another study, hypovitaminosis D was identified in 74% of obese subjects, whereas vitamin D deficiency was observed in 32.3% of the cohort (22). The higher prevalence of vitamin D deficiency observed in our study might be attributable to decreased exposure of these obese children to sunlight, as testing was conducted in late winter and spring, and might also be a consequence of a low intake of vitamin D-rich foods. However, we did not have access to dietary data for these children. This should be considered a limitation of this study. Nevertheless, our findings with consistent with those of Buyukinan et al. who reported vitamin D deficiency and insufficiency values of 62.2% and 34.0%, respectively, in obese children (23).

Previously, obese children were reported to have a greater risk of developing vitamin D deficiencies. The association between

Table III. The mean values of the 25(OH) D levels according to qualitative variables

Variables		25(OH) D		p
		Mean	Standard deviation	
Sex	Female	12.15	6.60	< 0.001
	Male	16.48	8.69	
IR	No	14.69	8.82	0.093
	Yes	13.22	6.52	
Dyslipidemia	No	14.11	7.83	0.710
	Yes	13.75	7.91	
Hypertension	No	14.50	8.24	0.004
	Yes	11.92	5.48	
Obesity group	Non-healthy obese	13.29	6.90	0.047
	Healthy obese	15.30	9.24	

obesity and 25(OH) D deficiency is complex because in addition to the sequestration of vitamin D in adipose tissue (24), obese children might also have more sedentary, indoor lifestyles. In addition, obese children might obtain lower levels of vitamin D than non-obese children from food sources (22); however, a combination of the above factors, as well as other potential factors, is most likely.

In our study, vitamin D levels were lower in girls, consistent with the findings of previous studies (20,25); girls also more frequently exhibited vitamin D deficiency. These findings were consistent with an earlier study that reported a higher prevalence of vitamin D insufficiency among girls relative to boys (26).

As in previous studies (3,27), we observed a weak but significant inverse relationship between BMI and 25(OH) D levels. This finding has been attributed to the sequestration of vitamin D within adipose tissue (24) and the reduced hepatic synthesis of 25(OH) D in obese individuals with nonalcoholic fatty liver disease (28). In contrast, another study found no significant association between BMI and 25(OH) D (25).

In an analysis of multiple cohorts, Vimaleswaran et al. calculated that each 10% increase in BMI would lead to a 4.2% decrease in the 25(OH) D concentrations. The authors concluded that the efforts of vitamin D deficiency monitoring and treatment in obese individuals would alleviate the adverse influences of excess adiposity on health; in addition, attempts to reduce BMI are expected to reduce the prevalence of vitamin D deficiency (29).

Inconsistent with a recent report (25), our study did not observe any correlation of 25(OH) D levels with TG, LDL-C, or HDL-C levels. However, Dolinsky et al. suggested that there was insufficient evidence to support an association between vitamin D and lipid levels, which is consistent with our findings (30).

In recent years, the AD ratio, derived from a log transformation of the ratio of fasting TG to HDL-C levels, has gained importance as an indicator of atherosclerosis, an established cardiovascular risk factor (17,18). In the present study, the AD ratio was higher in the vitamin D-deficient group, consistent with many other reported findings (20). Vitamin D deficiency causes an increase in AD, a component of cardiovascular risk factors, and thus leads to worse long-term consequences (20).

In our study, hypertensive children exhibited lower 25(OH) D levels. Accordingly, and consistent with many recent studies, hypertension in obese patients was associated with reduced vitamin D levels; in an earlier study, a lower HDL-C level and higher systolic BP were associated with lower levels of 25(OH) D (31). In addition, 25(OH) D deficiency in children and adolescents has been associated with hypertension as a cardiovascular risk factor (20).

As we specified earlier, vitamin D deficiency has been linked to the pathophysiology of hypertension through its augmenting influence on renin–angiotensin system activity (10) both in obese individuals (32) or independently of obesity (33). On the other hand, VDRs are present in vascular smooth muscle, which suggests that vascular smooth muscle is a target organ of vitamin D (34). Furthermore, studies have linked vitamin D deficiency with low levels of adiponectin (35), a protein associated with hypertension.

An inverse correlation was observed between 25(OH) D levels and HOMA-IR values. In other words, 25(OH) D levels affect insulin sensitivity, consistent with previous research (22). Hypovitaminosis D has been implicated in the pathogenesis of IR, β-cell dysfunction, and both type 1 and type 2 diabetes mellitus (36,37). Furthermore, obese children and adolescents with low levels of vitamin D might have an increased risk of glucose metabolism impairment, independent of body adiposity (22).

A previous study found a significant positive association between vitamin D and β-cell function, as well as significant relationships of vitamin D with IR and β-cell function in a multi-ethnic sample at risk for type 2 diabetes (12). In addition, vitamin D has been implicated in the development of type 1 diabetes mellitus through its modulatory effects on the immune system (38).

Multiple factors, such as the levels of vitamin D and reactive oxidative species, might have a synergistic effect on the pathogenesis of obesity-related morbidities. In recent decades, some studies have demonstrated that similar to vitamin D, oxidative stress, which increases in the context of obesity, is directly and indirectly associated with IR pathogenesis via the respective inhibition of insulin signals and dysregulation of adipocytokines/adipokines (39). We believe that other factors, in addition to vitamin D, affect and contribute to IR in obese children.

Over time, oxidative stress in several other cells or tissues (e.g., pancreatic β-cells, myocytes, vascular endothelial cells, and some types of tumors) has been implicated in the pathogenesis of diabetes, hypertension, atherosclerosis, and cancer (40).

Metabolic disturbances and/or hypertension would be expected to occur more frequently in the context of vitamin D hypovitaminosis. We observed lower 25(OH) D levels in non-healthy obese children than in healthy obese children. Accordingly, we can suggest that some of the long-term morbidities associated with obesity might be prevented by improving vitamin D levels.

The main limitations of our study involved the lack of data regarding dietary habits and physical activity. Therefore, we could not exclude lifestyle factors, such as dietary habits and social

status, that might have affected vitamin D metabolism and the other laboratory variables measured in our study participants. In addition, because the children were evaluated retrospectively, we could not incorporate methods to measure adiposity. Furthermore, we did not observe statistical significance in the comparisons of some variables with respect to vitamin D status, possibly because of the very small number of vitamin D sufficient children.

CONCLUSION

Vitamin D deficiency is observed more frequently than expected in obese children and adolescents. Lower 25(OH) D levels are associated with a high BMI, and this relationship might be attributable to the increased adiposity of obese individuals. In addition, low 25(OH) D levels might be associated with IR. Vitamin D deficiency might therefore be prevented by reducing the BMI and incorporating some simple lifestyle precautions. Vitamin D deficiency might contribute to obesity-related morbidities, such as IR or diabetes mellitus, increased cardiovascular/cardiometabolic risk, atherogenic dyslipidemia, and hypertension. The long-term morbidities associated with obesity could be reduced by improving vitamin D levels.

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