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Mariana Rodrigues Barreiros da Silva[1]
Cecília Lacroix de Oliveira[2]
Flávia dos Santos Barbosa Brito[3]
Paulo Ferrez Collett-Solberg[4]
Isabel Rey Madeira[5]
Beatriz Louise Costa Themístocles[6]
Fernanda Mussi Gazolla[7]

[1] Universidade do Estado do Rio de Janeiro, Instituto de Nutrição, Curso de Especialização em Terapia Nutricional. Rio de Janeiro, RJ, Brasil.

[2] Universidade do Estado do Rio de Janeiro, Instituto de Nutrição, Departamento de Nutrição Aplicada. Rio de Janeiro, RJ, Brasil.

[3] Universidade do Estado do Rio de Janeiro, Instituto de Nutrição, Departamento de Nutrição Social. Rio de Janeiro, RJ, Brasil.

[4] Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas, Departamento de Medicina Interna. Rio de Janeiro, RJ, Brasil.

[5] Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas, Departamento de Pediatria. Rio de Janeiro, RJ, Brasil.

[6] Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas, Programa de Pós-Graduação em Fisiopatologia Clínica e Experimental. Rio de Janeiro, RJ, Brasil.

[7] Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas, Hospital Universitário Pedro Ernesto. Rio de Janeiro, RJ, Brasil.

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Hyperinsulinemia as an associated factor with hypovitaminosis D in overweight children and adolescents

A hiperinsulinemia como um fator associado à hipovitaminose D em crianças e adolescentes com excesso de peso

Abstract

Introduction: Amongst children and adolescents, hypovitaminosis D has been associated with conditions such as obesity, insulin resistance, hypertension and metabolic syndrome. In Brazil, more data on the prevalence of hypovitaminosis D and its associated factors needs to be collected for the overweight population of children and adolescents. *Objective*: To describe the prevalence of hypovitaminosis D in overweight children and adolescents and to investigate its associated factors. *Methods*: This is a cross-sectional, descriptive and retrospective study that collected and analyzed data, between 2022 and 2023, from the medical records of 92 overweight individuals (5 to 12 years old) participating in a childhood obesity research clinic, regarding their biochemical, anthropometric, food consumption, physical activity and blood pressure profiles, among others, associated with serum 25(OH)D concentrations. The cut-off point for hypovitaminosis D was 25(OH)D values lower than 30 ng/ml. The Qui-square test, the Kruskal-Wallis test and the Spearman correlation were used to study the relationship between associated factors and hypovitaminosis D. *Results*: A prevalence of hypovitaminosis D was observed in 64.13% of the sample. There was also an association between the vitamin D profile and serum insulin levels (p-value = 0.009) and HOMA-IR (p-value = 0.025), as well as a negative correlation between serum 25(OH)D and serum insulin (ρ = - 0.300**) and HOMA-IR (ρ = - 0.275*). *Conclusion*: The data suggest that, in overweight children and adolescents, vitamin D deficiency is related to higher serum insulin and HOMA-IR values.

Keywords: Vitamin D deficiency. Insulin. Childhood obesity.

Resumo

Introdução: Em crianças e adolescentes, a hipovitaminose D tem sido associada a condições como obesidade, resistência insulínica, hipertensão e síndrome metabólica. No Brasil, mais dados sobre a prevalência da hipovitaminose D e seus fatores associados necessitam ser levantados para a população infanto-juvenil com excesso de peso. *Objetivo*: Descrever a prevalência de hipovitaminose D em crianças e adolescentes com excesso de

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Correspondence
Mariana Rodrigues Barreiros da Silva
mariana.mrbs@gmail.com

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Renata Brum Martucci

peso, investigando seus fatores associados. *Métodos*: Trata-se de um estudo transversal, descritivo e retrospectivo que coletou e analisou, entre os anos de 2022 e 2023, dados de prontuários de 92 indivíduos (5 a 12 anos) com excesso de peso, participantes de um ambulatório de pesquisa em obesidade infantil, quanto ao perfil bioquímico, antropométrico, de consumo alimentar, atividade física e pressão arterial, entre outros, associados às concentrações séricas de 25(OH)D. Adotaram-se como ponto de corte para hipovitaminose D valores de 25(OH)D menores que 30 ng/ml. Utilizaram-se o teste Qui-quadrado, o teste Kruskal-Wallis e a correlação de Spearman para se estudar a relação entre fatores associados e hipovitaminose D. *Resultados*: Foi observada prevalência de hipovitaminose D em 64,13% da amostra. Verificou-se, ainda, associação entre o perfil de vitamina D e os níveis séricos de insulina (p-valor = 0,009) e do HOMA-IR (p-valor = 0,025), além de correlação negativa entre 25(OH)D sérica e insulina sérica (ρ = - 0,300**) e HOMA-IR (ρ = - 0,275*). *Conclusão*: Os dados sugerem que, em crianças e adolescentes com excesso de peso, a deficiência de vitamina D relaciona-se com maiores valores de insulina sérica e HOMA-IR.

Palavras-chave: Deficiência de vitamina D. Insulina. Obesidade infantil.

INTRODUCTION

Vitamin D (calciferol) is a steroidal prohormone synthesized endogenously by the skin through the photolytic action of ultraviolet rays (UV-B).[1] Although its role in bone metabolism is well known, this vitamin has various extra-skeletal effects, such as immunomodulatory and anti-inflammatory effects.[2]

In the pediatric population, vitamin D deficiency has been associated with conditions such as increased risk of high blood glucose levels and insulin resistance, hypertension, metabolic syndrome, respiratory tract infections, asthma and others.[3,4]

In this sense, obesity has emerged as a factor associated with hypovitaminosis D in childhood, which can extend into adolescence. As shown in a systematic review with meta-analysis that chose cross-sectional studies evaluating patients aged between 0 and 18 years with obesity and vitamin D deficiency, when compared with the control group composed of eutrophic patients, it was found that the relative risk for the association between vitamin D deficiency and obesity was 1.41 (95% CI 1.26 - 1.59), ($p < 0.01$).[5]

The prevalence of vitamin D insufficiency (25(OH)D < 30 ng / mL) is over 90% in overweight children in countries such as Germany and Russia.[6] In Brazil, more data needs to be collected on the prevalence of hypovitaminosis D in overweight and obese children and adolescents. However, considering a healthy population, a retrospective study conducted by Leão et al.[7] found that average 25(OH)D values decreased from the first years of life to adolescence. According to the authors, a prevalence of 25(OH)D < 20 ng / mL was found in 6% of girls and 13.6% of female adolescents, a higher percentage compared to male children and adolescents (3.6% and 12.6%, respectively).[7]

A similar result was found by De Oliveira et al.[8] for adolescents living in the city of Rio de Janeiro (prevalence of 16% of 25(OH)D ≤ 20 ng / mL). In this multicenter study, it was observed that obese boys had a higher proportional odds ratio of presenting hypovitaminosis D than boys with normal weight, an association that may be involved with unhealthy lifestyle choices, with the theory of the sequestration of fat-soluble vitamins by adipose tissue and by the possible reduction in the activity of 25-hydroxylase in the liver of people with obesity.[8]

According to Cediel, Pacheco-Acosta, Castillo-Durán,[4] considering the effects of the active form 1,25(OH)2D associated with obesity, this hormone regulates gene transcription in adipogenesis, inflammation and insulin resistance in the adipose tissue of obese patients, and calcitriol can promote better insulin sensitivity in muscle and pancreatic tissues.

On the other hand, although there is still no consensus among the various scientific societies on the cut-off point for vitamin D deficiency, it is essential to take 25(OH)D levels for individuals who are part of the risk group for vitamin D deficiency, such as children and adolescents with obesity.[9]

Given the need in Brazil to gather more data on the prevalence of hypovitaminosis D in overweight children and adolescents and its associated factors, this study aimed to describe the prevalence of hypovitaminosis D in the overweight child and adolescent population treated at a Children's Obesity Research Outpatient Clinic at a University Hospital, investigating its associated factors

METHODS

Study design and population

This is a cross-sectional, descriptive and retrospective study that used data from the medical records of patients treated at the Projeto Ambulatório de Pesquisa em Obesidade Infantil (APOIO) (Childhood Obesity Research Outpatient Project) of the Unidade Docente Assistencial (UDA) (Endocrinology Teaching and Care

Unit) of the Hospital Universitário Pedro Ernesto (HUPE/UERJ) (Pedro Ernesto University Hospital), located in the city of Rio de Janeiro-RJ. This is a teaching outpatient clinic that is part of the Sistema Único de Saúde (SUS) (Unified Health System), providing primary care for children mainly from the city of Rio de Janeiro and the metropolitan region of the state of Rio de Janeiro.

In this study, a convenience sample was taken of 92 individuals of both sexes, classified between pre-pubertal and pubertal according to the pubertal staging proposed by Tanner,[10] with a diagnosis of excess weight and aged between 5 and 12 years, classified between children (0 to 9 years, 11 months and 29 days) and adolescents (10 to 19 years, 11 months and 29 days), according to the definition established by the World Health Organization.[11]

Inclusion criteria were patients who completed the outpatient clinic's initial protocol between 2013 and 2022 and who presented laboratory tests for vitamin D dosage. On the other hand, patients whose biochemical vitamin D data was missing from their medical records, who were taking vitamin D supplements or who had a chronic disease that compromised vitamin D metabolism were excluded.

The "Data Collection Protocol" document was filled in manually by the team doctors at the time of the initial consultation, with data on personal identification, socio-economic information, history of current and previous illnesses, gestational, birth and development history, as well as information obtained from the physical examination, anthropometry and previous dietary history. Other documents were also included in the patients' medical records, such as the 24-hour Dietary Recall (applied by the nutrition team) and the results of biochemical, imaging and bioimpedance tests.

From the above mentioned documents, Excel software version 2007 (Microsoft Corporation, Redmond, WA, USA) was used to tabulate the respective information: gender, age, pubertal stage, skin color, biochemical variables (plasma levels of vitamin D, calcium, phosphorus, PTH, glucose and insulin, as well as the HOMA-IR calculation), anthropometric profile (weight, height, BMI, z-score, waist circumference and waist-to-height ratio), average food intake from three 24-hour recalls (calories, carbohydrates, proteins, lipids, calcium and vitamin D), physical activity, systemic blood pressure and date of blood collection.

All the legal guardians of the participants signed an informed consent form. The research was previously approved by the HUPE/UERJ's Research Ethics Committee, registered under number 2218-CEP/HUPE and CAAE 0292.0.228.000-12.

How the outpatient clinic works

After the legal guardian had been previously informed about the research, if they agreed to take part, the patient entered the service through the initial protocol, which consisted of three appointments.

At the first appointment, weight and height were measured during screening. The team doctor would then fill out a protocol with information about the individual's health, as well as carrying out a clinical assessment with anamnesis and detailed physical examination, including measuring blood pressure (BP), and the nutritionist would collect the first 24-hour recall (24hR). At the second appointment, routine biochemical tests were taken at the HUPE/UERJ Clinical Analysis Laboratory after a 12-hour fast, a bioimpedance test (BIA) during screening, BP measurement and the collection of the second 24hR. Finally, on the third visit, an abdominal and neck ultrasound was carried out, as well as screening, BP measurement and collection of the third 24hR.

Depending on the flow of appointments at the outpatient clinic, the interval between each consultation in the initial protocol was at least one week and a maximum of three weeks. Once this data was available, the nutritionist would draw up an individualized diet plan for each patient at the third appointment, which was followed up monthly in consultations with the multi-professional team.

Laboratory analysis and cut-off points

Serum concentrations of calcium, phosphorus, PTH, 25(OH)D, glucose and insulin were analyzed using routine automated laboratory methods at the HUPE/UERJ Clinical Analysis Laboratory, with calcium and phosphorus being analyzed using the colorimetric method; PTH, 25(OH)D and insulin using the electrochemiluminescence method; and glucose using the enzymatic hexokinase method.

According to the recommendations of the Endocrine Society, plasma vitamin D levels were defined as follows: deficiency if 25(OH)D < 20 ng/ml; insufficiency if 25(OH)D is between 21 and 29 ng/ml; and sufficiency if 25(OH)D > 30 ng/ml.[9]

In order to classify whether the patients were hyperinsulinemic or not, the cut-off points were 15 mcUI/ml and 20 mcUI/ml for prepubertal and pubertal patients, respectively.[12]

Using the information on fasting serum glucose available in the medical records, it was possible to calculate HOMA-IR using the equation: fasting insulin (µUI/mL) x fasting glucose (mmol/L) / 22.5. The cut-off point of 3.43 was adopted to define increased HOMA-IR.[13]

Anthropometric measurement

The children and adolescents were weighed without shoes and in light clothing on a calibrated electronic scale with a precision of 0.050Kg, by Welmy®, and their height was measured without shoes on a wall-mounted Halpender-Holtain stadiometer with a precision of 1mm, by Tonelli®. Weight and height were measured by the same trained professional.

The patients' nutritional status was classified according to the z-score, based on the anthropometric index Body Mass Index (BMI)/age, in accordance with the guidelines recommended by the Sistema de VigilânciaAlimentar e Nutricional(SISVAN) (Food and Nutrition Surveillance System).[14]

In addition, using an inelastic, millimetric anthropometric tape, the patients were classified in terms of waist circumference (WC) (through the midpoint between the last rib and the upper edge of the iliac crest, at the end of a normal exhalation) according to the percentile values proposed by Fernández et al.,[15] adopting the 90th percentile as the cut-off point, since this is the criterion used by the International Diabetes Federation (IDF) to define metabolic syndrome in children and adolescents.[16] The waist-to-height ratio (WHtR) was calculated and a value of 0.50 was adopted as the cut-off point for both genders.[17]

Food consumption

The Dietbox software (Dietbox Informática LTDA, Porto Alegre, RS, Brazil) was used to analyze the food consumption recorded in three 24-hour food recalls, carried out on non-consecutive days and collected by a team of trained nutritionists. Once these results had been obtained, the average of the three food records

was calculated and, for those individuals whose food records were missing, the average of the remaining food records was calculated.

At this stage, energy, carbohydrate, protein, lipid, calcium and vitamin D intake were analyzed, as well as the percentage of adequacy for calcium and vitamin D, which were calculated according to the Dietary Reference Intakes (DRIs) for each micronutrient.[18] A daily intake of vitamin D of 10 µg/d (400 IU/d) was considered adequate.[19]

Physical activity, blood pressure, seasonal variation and skin color

Physical activity was classified at the time of the first consultation as sedentary, moderately active and active, according to the questionnaire recommended by Murphy et al.[20]

BP was measured from the right arm, with the individual seated and at rest, using a Tycos® sphygmomanometer and cuffs of the appropriate sizes. The method used was auscultatory, following Hoekelman's recommendations.[21] In this study, BP was classified as that measured at the first consultation using the classification established for children and adolescents by the Brazilian Society of Pediatrics.[22]

The season of the year in which the blood was collected was ascertained in order to determine seasonal variation, and based on the patients' or their legal guardians' self-reporting of their skin color, the individuals were classified as white or non-white.

Statistical analysis

Statistical analysis was carried out using SPSS Statistics software version 25 (IBM, Armonk, NY, USA), with a significance level of 5%. Categorical variables were presented as absolute (n) and relative (%) frequencies. After verifying the non-parametric distribution of the continuous variables using the Shapiro-Wilk test, the results were presented as medians and interquartile ranges (Percentiles 25-75).

The Chi-square test or the Kruskal-Wallis test were used to compare groups, depending on the characteristics of the variables. Finally, to verify the relationship between continuous variables, Spearman's correlation coefficient was calculated.

The following parameter was used to classify the degree of correlation, that is, the strength between the variables: weak when 0 and 0.3 (or -0.3 and 0); moderate when 0.4 and 0.7 (or -0.4 and -0.7); and strong when 0.7 and 1.0 (or -0.7 and -1.0).[23] Statistically significant correlations were those with $p \leq 0.05$.

RESULTS

The sample was composed of a higher proportion of prepubescent individuals (64.13%), classified as children (54.35%), obese (46.74%), sedentary (48.32%), normotensive (66.30%), with WC above the 90th percentile (62.20%) and WHtR greater than 0.50 (91.46%). A prevalence of hypovitaminosis D was observed in 64.13% of the individuals studied (32.61% had insufficient serum vitamin D and 31.52% had deficient serum vitamin D) (Table 1). It was also possible to observe that the highest medians for the variables weight (57.70 Kg) and WC (85.35 cm) were found in individuals who had 25(OH)D ≤ 20 ng/mL. It should be noted that 100% of the sample did not meet the recommended intake of 10 µg/day of vitamin D, with a median intake of 2.18 µg/d. The characterization of the study's categorical and continuous variables can be found in Tables 1 and 2, respectively.

Table 1. Distribution of vitamin D according to sociodemographic and health characteristics (bivariate association measures). Rio de Janeiro, RJ, 2023.

Variables	Total		25(OH)D						p-value
			≤ 20 ng/mL		≥ 21 and ≤ 29 ng/mL		≥ 30 ng/dL		
	n	(%)	n	(%)	n	(%)	n	(%)	
Total	92	100.00	29	31.52	30	32.61	33	35.87	-
Sex									
Female	45	48.91	17	58.62	17	56.67	11	33.33	0.081
Male	47	51.09	12	41.38	13	43.33	22	66.67	
Color									
White	42	45.65	13	44.83	18	60.00	11	33.33	0.105
Not white	50	54.35	16	55.17	12	40.00	22	66.67	
Age group									
Child	50	54.35	14	48.28	15	50.00	21	63.64	0.405
Teenager	42	45.65	15	51.72	15	50.00	12	36.36	
Pubertal stage									
Pre-pubertal	59	64.13	19	65.52	17	56.67	23	69.70	0.550
Pubertal	33	35.87	10	34.48	13	43.33	10	30.30	
BMI/Age									
Overweight	12	13.04	6	20.69	4	13.33	2	6.06	0.188
Obesity	43	46.74	9	31.03	17	56.67	17	51.52	
Severe obesity	37	40.22	14	48.28	9	30.00	14	42.42	
*WC**									
< P90	31	37.80	8	30.77	13	50.00	10	33.33	0.294
> P90	51	62.20	18	69.23	13	50.00	20	66.67	
*WHtR**									
< 0.50	7	8.54	2	7.69	2	7.69	3	10.00	0.937
≥ 0.50	75	91.46	24	92.31	24	92.31	27	90.00	
*Physical Activity**									
Active	23	25.84	7	25.00	11	39.29	5	15.15	0.088
Moderately active	23	25.84	4	14.29	7	25.00	12	36.36	
Sedentary	43	48.32	17	60.71	10	35.71	16	48.48	
Blood pressure									
Normotensive	61	66.30	20	68.97	18	60.00	23	69.70	
Altered BP	4	4.35	1	3.45	1	3.33	2	6.06	0.585
Grade I SAH	24	26.09	6	20.69	11	36.67	7	21.21	
Grade II SAH	3	3.26	2	6.90	0	0.00	1	3.03	
*Insulin**									
No hyperinsulinemia	41	47.13	10	37.04	10	34.48	21	67.74	0.016
With hyperinsulinemia	46	52.87	17	62.96	19	65.52	10	32.26	
*HOMA-IR**									
< 3.43	36	43.90	11	42.31	10	34.48	15	55.56	0.278
≥ 3.43	46	56.10	15	57.69	19	65.52	12	44.44	
Season									
Summer	8	8.70	1	3.45	4	13.33	3	9.09	
Autumn	29	31.52	7	24.14	9	30.00	13	39.39	0.639
Winter	22	23.91	9	31.03	6	20.00	7	21.21	
Spring	33	35.87	12	41.38	11	36.67	10	30.30	

Caption: WC - Waist circumference; SAH - Systemic arterial hypertension; BP - Blood pressure; WHtR - Waist-to-height ratio. *There were missing values for the following variables: waist circumference (n=82), WHtR (n= 82), physical activity (n=89), insulin (n=87) and HOMA-IR (n=82).).

Table 2. Distribution of serum vitamin D according to anthropometric, food consumption and health characteristics (bivariate association measures).Rio de Janeiro, RJ, 2023.

Variables	Total		25(OH)D						p-value
			≤ 20 ng/mL		≥ 21 and ≤ 29 ng/mL		≥ 30 ng/dL		
	Median	Interquartile Range (p 25 - p 75)	Median	Interquartile Range (p 25 - p 75)	Median	Interquartile Range (p 25 - p 75)	Median	Interquartile Range (p 25 - p 75)	
Anthropometry									
Weight (Kg)	53.00	(41.30 - 58.64)	57.70	(44.47 - 64.94)	53.30	(39.72 - 56.97)	49.17	(41.00 - 55.10)	0.390
BMI (Kg/m²)	25.17	(22.61 - 28.43)	24.48	(22.75 - 28.97)	24.91	(22.04 - 27.82)	26.49	(23.69 - 28.82)	0.826
Z-score	2.90	(2.06 - 3.77)	2.65	(1.69 - 3.63)	2.84	(2.02 - 3.39)	3.76	(2.75 - 4.65)	0.605
WC (cm)	82.10	(75.23 - 89.45)	85.35	(75.70 - 94.15)	81.25	(74.37 - 85.60)	79.25	(76.37 - 88.05)	0.515
WHtR	0.58	(0.54 - 0.63)	0.59	(0.52 - 0.63)	0.57	(0.53 - 0.62)	0.61	(0.56 - 0.64)	0.596
Food consumption									
Calories (Kcal)	1708.50	(1447.00 - 1927.00)	1772.42	(1271.25 - 2096.67)	1492.00	(1189.00 - 1713.25)	1868.33	(1578.25 - 1933.50)	0.382
Protein (g)	68.69	(57.01 - 88.69)	80.92	(57.01 - 107.75)	65.74	(44.97 - 71.55)	75.20	(59.70 - 88.69)	0.603
Carbohydrates (g)	218.79	(166.87 - 270.58)	248.18	(134.49 - 287.35)	197.84	(158.02 - 253.91)	242.35	(214.03 - 296.74)	0.205
Lipids (g)	50.84	(42.22 - 68.65)	57.12	(40.76 - 71.05)	47.75	(34.76 - 60.56)	59.34	(45.37 - 71.72)	0.973
Calcium (mg)	472.86	(354.03 - 596.77)	529.13	(364.01 - 653.19)	437.30	(301.40 - 490.69)	551.43	(386.97 - 673.46)	0.246
Vitamin D (mcg)	2.18	(1.00 - 4.02)	2.25	(0.79 - 5.01)	1.73	(0.48 - 3.85)	2.36	(1.39 - 4.31)	0.846
% calcium adequacy	39.94	(32.37 - 49.70)	40.70	(31.41 - 64.37)	36.29	(24.98 - 46.18)	48.78	(34.92 - 56.47)	0.237
% adequacy of vit D	14.51	(6.65 - 26.79)	15.01	(5.26 - 33.43)	11.53	(3.22 - 25.68)	15.73	(9.27 - 28.71)	0.846
Blood pressure									
Systolic BP	103	(93.0 - 110.0)	110	(90.5 - 110.0)	100	(100.0 - 111.5)	105	(90.0 - 110.0)	0.385
Diastolic BP	70	(60.0 - 76.0)	66	(60.0 - 70.0)	70	(60.0 - 79.5)	70	(60.0 - 70.0)	0.182
Biochemistry									
25(OH)D (ng/mL)	25.93	(18.62 - 30.74)	16.74	(15.22 - 18.27)	25.92	(23.43 -27.14)	33.21	(31.00 - 40.31)	0.000
Calcium (mg/dL)	10.10	(9.83 - 10.50)	10.15	(9.92 - 10.80)	10.10	(9.80 - 10.50)	10.15	(9.87 - 10.45)	0.235
Phosphorus (mg/dL)	5.30	(4.83 - 5.78)	5.50	(4.85 - 5.97)	5.20	(4.67 - 5.50)	5.35	(4.85 - 6.07)	0.352
PTH (pg/mL)	33.69	(27.45 - 42.63)	31.13	(24.44 - 37.19)	38.01	(28.42 - 46.86)	32.76	(27.47 - 45.39)	0.385
Glucose (mg/dL)	88.85	(85.00 - 92.75)	87.85	(85.00 - 97.85)	88.35	(83.25 - 92.75)	89.55	(85.52 - 93.87)	0.895
Insulin (µUI/mL)	15.95	(12.79 - 22.50)	16.70	(13.25 - 29.22)	21.60	(13.82 - 29.05)	13.84	(10.20 - 18.02)	0.009
HOMA-IR	3.63	(2.92 - 4.81)	3.82	(3.07 - 6.33)	4.23	(3.08 - 6.17)	3.24	(2.15 - 3.77)	0.025

Caption: WC - waist circumference; BMI - body mass index; BP - blood pressure; WHtR - waist-to-height ratio; PTH - parathyroid hormone.

Among the analyzed variables, no associations were found between anthropometric profile, food consumption, physical activity, seasonal variation, skin color and plasma concentrations of calcium, phosphorus and serum PTH. However, the Chi-square test showed an association between vitamin D profile and insulin profile (p-value = 0.016) (Table 1). The Kruskal-Wallis test also showed an association between the vitamin D profile and serum insulin levels (p-value = 0.009) and the HOMA-IR result (p-value = 0.025) (Table 2).

The correlation test showed a negative and significant correlation (ρ = - 0.300**) between serum vitamin D and serum insulin, as well as a negative and significant correlation (ρ = - 0.275*) between serum vitamin D and HOMA-IR. In addition, there was a negative and significant correlation (ρ = - 0.206*) between serum vitamin D and diastolic blood pressure (Table 3).

Table 3. Correlations between serum vitamin D and other study variables. Rio de Janeiro, RJ, 2023.

Variables	25(OH)D	
	Spearman's ρ	p-value*
Anthropometry		
Weight (Kg)	-0.200	0.056
BMI (Kg/m²)	-0.133	0.206
Z-score	0.027	0.796
WC (cm)	-0.190	0.087
WHtR	-0.042	0.707
Food consumption		
Calories (Kcal)	0.103	0.329
Protein (g)	-0.023	0.826
Carbohydrates (g)	0.164	0.121
Lipids (g)	0.043	0.686
Calcium (mg)	0.054	0.614
Vitamin D (mcg)	-0.039	0.713
% calcium adequacy	0.060	0.572
% adequacy of vit D	-0.039	0.713
Bloodpressure		
Systolic BP	-0.137	0.192
Diastolic BP	-0.206*	0.049
Biochemistry		
Calcium (mg/dL)	0.112	0.386
Phosphorus (mg/dL)	0.050	0.704
PTH (pg/mL)	0.055	0.678
Glucose (mg/dL)	-0.024	0.827
Insulin (μUI/mL)	-0.300**	0.005
HOMA-IR	-0.275*	0.012

Caption: WC - Waist circumference; BMI - Body mass index; BP - Blood pressure; WHtR - Waist-to-height ratio; PTH - Parathormone. *Statistically significant values of p<0.05.

DISCUSSION

This study found a prevalence of hypovitaminosis D in 64.13% of the participants, of whom 31.52% were vitamin D deficient. This result is similar to the prevalence of hypovitaminosis D found by De Oliveira et

al.[8] in their multicenter study which investigated 1152 Brazilian adolescents. However, in terms of deficiency, that is, 25(OH)D levels < 20 ng/ml, the present study showed a slightly higher prevalence than that found by the aforementioned authors.

On the other hand, prevalence rates of vitamin D deficiency of over 60.00% were found in Brazilian children and adolescents in studies that aimed to associate vitamin D levels with anthropometric profile and other associated factors, including insulin resistance.[24,25] However, it should be noted that in the study by Coelho et al.[24] the prevalence found included both eutrophic and overweight individuals, whereas Mori et al.[25] assessed only 26 obese individuals, comparing them with a control group of 19 healthy eutrophic individuals.

Unlike the studies by Coelho et al.[24] and Mori et al.,[25] which failed to find a relationship between vitamin D deficiency and insulin resistance, in this study (which only assessed overweight children and adolescents) we found a negative and significant correlation between serum vitamin D and fasting insulin and HOMA-IR.

This result is similar to that presented in a study conducted in Sri Lanka with 202 children between 5 and 15 years of age, all of whom were obese, which also showed a negative and significant correlation between serum vitamin D and fasting insulin and HOMA-IR values.[26] Another study showed that the vitamin D levels of obese children and adolescents with insulin resistance were significantly lower than those children without insulin resistance ($p < 0.001$).[27]

According to Contreras-Bolívar et al.,[28] one of the possible mechanisms associating hypovitaminosis D with insulin resistance and its clinical outcomes, such as obesity, type 2 diabetes (T2D) and metabolic syndrome is that, at the molecular level, vitamin D seems to be involved in the transcriptional control of insulin, since a region of the vitamin D response element has been identified in the promoter of the insulin receptor gene.

In addition, the authors explain that vitamin D may play an important role in regulating beta cell function in patients with T2D, since calcitriol acts as a chemical messenger, interacting with receptors that regulate calcium flow in beta cells. On the other hand, vitamin D could influence insulin secretion by regulating the opening and closing of calcium channels, and calcitriol could improve insulin sensitivity by stimulating the expression of insulin receptors, among other things.[28]

In this study, it was not possible to establish an association between vitamin D levels and sociodemographic variables, anthropometric variables, food consumption, blood pressure, physical activity levels, seasonal variation and biochemical data (with the exception of fasting insulin and HOMA-IR), which can be explained by the homogeneity and sample size and the limitation of this study in not having a control group composed of eutrophic patients.

However, it is known that obese children and adolescents are at greater risk of vitamin D deficiency.[5] An Iranian nationwide study showed that the average BMI and WC were higher for the group of children with vitamin D deficiency than the group with sufficiency, as well as an inverse association between vitamin D status and anthropometric parameters such as WC and WHtR.[29] One of the theories that tries to explain this relationship is the sequestration of vitamin D in obese people, since it is a fat-soluble vitamin and could possibly accumulate in adipose tissue.[8,30]

However, Durá-Travé et al.[30] argue that the inverse relationship between vitamin D levels and obesity may have a simpler explanation: inadequate sun exposure. The authors came to this conclusion when they observed a seasonal variation in the serum vitamin D levels of Spanish children and adolescents with severe

obesity, that is, higher concentrations of 25(OH)D in the summer months, which may be related to a more sedentary lifestyle on the part of children with severe obesity.[30]

Even in a sunny country like Brazil, it was possible to observe seasonal variation in vitamin D levels, which could be explained by the transition to a more sedentary lifestyle on the part of Brazilian children and adolescents.[8,31] In this sense, Da Silva et al.[32] state that regular physical activity seems to be more closely related to higher levels of 25(OH)D in Brazilian adolescents, especially males.

This study found that 100% of the sample did not meet the daily recommendation of 10 µg of vitamin D, and this median intake (2.18 µg/d) is similar to the average daily intake of vitamin D by adolescents who took part in the 2017-2018 Family Budget Survey (2.0 µg/d for men and 1.8 µg/d for women).[33] This is a worrying finding given that, among lifestyle-related aspects, vitamin D intake from dietary sources may represent a protective factor against hypovitaminosis D for those individuals whose sun exposure is inadequate.[8]

Altered BP levels also seem to be related to vitamin D deficiency, especially diastolic BP.[34-36] Although no association was found between the classification of vitamin D levels and BP classification in overweight children and adolescents, this study found a negative and significant correlation between serum vitamin D and diastolic BP for this population. According to Krivošíková et al.,[36] while seasonal variation in vitamin D and BMI appear to be the most significant predictors of changes in systolic BP in obese children, diastolic BP appears to be more closely related to insulin and serotonin levels.

Finally, it is well known that, along with PTH and calcitonin, the main biological function of vitamin D in humans is to maintain the homeostasis of serum calcium and phosphorus concentrations.[3] Although this study showed no significant correlation between 25(OH)D levels and calcium, phosphorus and PTH levels in overweight children and adolescents, Durá-Travé et al.[37] found a negative correlation between calcidiol and PTH levels in Hispanic children with severe obesity ($p < 0.01$).

The authors explain that in this group there is a clear tendency to have low levels of calcidiol and high levels of PTH, and clarify that in obesity low levels of calcidiol stimulate an increase in PTH, which, in turn, stimulates renal hydroxylation of calcitriol, increasing the influx of calcium into adipocytes, causing lipogenesis and potentially reducing catecholamine-induced lipolysis.[37]

However, the researchers point out that this hypothesis is quite controversial, and that weight loss in obese individuals is associated with normalization of serum vitamin D and PTH levels, which seems to demonstrate that this mechanism is a consequence (and not the cause) of excess body weight.[37]

Although there are many studies published in the literature on obesity-related hypovitaminosis D and its associated factors, few Brazilian studies have dealt with hypovitaminosis D in overweight children and adolescents. For that matter, despite the limitations of this study in not having a control group composed of eutrophic individuals, as well as presenting bivariate statistical analyses that suggest caution in interpreting the results found, this study stands out for pointing out an association between hypovitaminosis D and insulin resistance in overweight children and adolescents, which should be better understood.

CONCLUSION

In this study, it was not possible to find an association between vitamin D levels and some of the variables assessed, such as sociodemographic variables, anthropometric profile, food consumption, blood pressure, physical activity, seasonal variation and plasma concentrations of calcium, phosphorus, PTH and

fasting glucose, which can be explained, as discussed above, by the homogeneity and sample size and the limitation of this study in not having a control group composed of eutrophic individuals.

However, it was found that, in overweight children and adolescents, hypovitaminosis D was significantly associated with insulin resistance, as well as showing a negative and significant correlation between vitamin D levels and fasting serum insulin and HOMA-IR values. It was also possible to find a negative and significant correlation between serum vitamin D levels and diastolic BP.

Considering the findings of this study, more research on the subject needs to be performed so that more robust results help to elucidate the mechanisms involved in the relationship between hypovitaminosis D and insulin resistance in overweight children and adolescents.

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Contributors

Silva MRB, Oliveira CL and Brito FSB participation in the idealization of the study design, in the data collection, analysis and interpretation; in the writing of the study and in the final review and approval for the manuscript's submission; Collett-Solberg PF and Madeira IR participation in the final review and approval for the manuscript's submission; Gazolla FM and Themístocles BLC participation in the data collection, analysis and interpretation, final review and approval for the manuscript's submission.

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