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Trabajo Original

Pediatría

Lower levels of vitamin D are associated with an increase in carotid intima-media thickness in children and adolescents with obesity

Los niveles bajos de vitamina D se asocian a un aumento del grosor íntima-media carotídeo en los niños y adolescentes con obesidad

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Abstract

Background: the relationship between vitamin D deficiency and carotid intima-media thickness (CIMT) in children and adolescents with obesity is unknown. The aim of this study was to investigate the correlation between vitamin D levels and CIMT in children and adolescents with obesity.

Methods: a total of 440 children and adolescents aged 6-16 with obesity were included in the study. Anthropometric measurements, blood pressure measurements, blood lipids, blood glucose, and vitamin D levels were measured. Bilateral carotid ultrasound was performed to assess CIMT. The relationships between vitamin D levels and CIMT were assessed using multivariate linear regression with Generalized Linear Models and restricted cubic splines. Binary logistic regression analyses were conducted to explore the association between vitamin D status and the risk of abnormal CIMT.

Results: vitamin D levels were inversely correlated with CIMT in subjects with serum 25-hydroxyvitamin D [25(OH)D] levels less than or equal to 50 nmol/L (β = -0.147, 95 % CI [-0.263, -0.030], $p = 0.013$), but this correlation was not significant in subjects with serum 25(OH)D levels above 50 nmol/L. After correcting for various confounders, the risk of abnormal CIMT was significantly higher in the vitamin D deficiency group (OR = 2.080, 95 % CI [1.112, 3.891], $p = 0.022$).

Conclusions: vitamin D deficiency is an independent risk factor for abnormal CIMT, and vitamin D deficiency may play a promoting role in the atherosclerotic process in children and adolescents with obesity.

Keywords:

Children and adolescents. Obesity. Vitamin D. Carotid intima-media thickness.

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Resumen

Antecedentes: se desconoce la relación entre la deficiencia de vitamina D y el grosor íntima-media carotídeo (GIMC) en los niños y adolescentes con obesidad. El objetivo de este estudio fue investigar la correlación entre los niveles de vitamina D y el grosor íntima-media carotídeo en niños y adolescentes con obesidad.

Métodos: se incluyeron en el estudio un total de 440 niños y adolescentes de entre 6 y 16 años con obesidad. Se midieron los parámetros antropométricos, la presión arterial, los lípidos sanguíneos, la glucosa en sangre y los niveles de vitamina D. Se realizó una ecografía carotídea bilateral para evaluar el grosor íntima-media carotídeo (GIMC). Las relaciones entre los niveles de vitamina D y el GIMC se evaluaron mediante una regresión lineal multivariante con modelos lineales generalizados y "splines" cúbicos restringidos. Se realizaron análisis de regresión logística binaria para explorar la asociación entre el estado de la vitamina D y el riesgo de un GIMC anormal.

Resultados: los niveles de vitamina D se correlacionaron inversamente con el GIMC en los sujetos con niveles séricos de 25(OH)D inferiores o iguales a 50 nmol/L (ß = -0,147; IC del 95 %, [-0,263; -0,030], $p = 0,013$), pero esta correlación no fue significativa en los sujetos con niveles séricos de 25(OH)D superiores a 50 nmol/L. Una vez corregidos varios factores de confusión, el riesgo de un GIMC anormal fue significativamente mayor en el grupo con deficiencia de vitamina D (OR = 2,080; IC del 95 %, [1,112; 3,891], $p = 0,022$).

Conclusiones: la deficiencia de vitamina D es un factor de riesgo independiente para la anomalía del GIMC, y la deficiencia de vitamina D puede desempeñar un papel promotor en el proceso aterosclerótico en niños y adolescentes con obesidad.

Palabras clave:

Niños y adolescentes. Obesidad. Vitamina D. Grosor íntima-media carotídeo.

BACKGROUND

Childhood obesity is one of the most prevalent global public health issues (1,2). According to current estimates, there are 381 million children globally who are affected by overweight or obesity (3). Obesity has become a serious health issue in China. The latest national prevalence estimates for 2015-2019 showed that 7.9 % of children and adolescents aged 6-17 and 16.4 % of adults (≥ 18 years) suffer from obesity (4). Children with risk factors such as obesity, dyslipidemia, hypertension, and diabetes *mellitus* have a higher risk of cardiovascular disease (CVD) in adulthood. Children with obesity have a higher risk of vitamin D deficiency, systemic inflammation, dyslipidemia, and cardiometabolic risk factors (5,6).

Carotid intima-media thickness (CIMT) is recognized by the American Society of Echocardiography and the European Society of Pediatric Cardiology as a surrogate biomarker of atherosclerosis, providing important information about vascular health in the pediatric population (7,8). The process of atherosclerosis starts early in children and adolescents with obesity (9). Studies have shown that children and adolescents with obesity and cardiovascular risk factors tend to have higher CIMT (10).

Vitamin D, a fat-soluble vitamin with both endocrine and autocrine functions (11), may play an important role in endothelial and smooth muscle vascular cells. Its deficiency may lead to vascular homeostasis imbalance and decreased arterial compliance, which are associated with the development of atherosclerosis and abnormal arterial wall thickness in adults (12). A general deficiency in vitamin D has been found in a large number of studies among individuals with obesity (13). It is inconclusive whether vitamin D deficiency exacerbates dyslipidemia and atherosclerosis in children and adolescents with obesity. Vitamin D deficiency may be a cardiovascular risk factor from childhood; however, only a few studies have investigated the association of serum vitamin D with cardiovascular disease risk factors during childhood. The purpose of this research was to explore the potential association between serum 25(OH)D levels and CIMT.

METHODS

PARTICIPANTS

This study was a single-center, retrospective, cross-sectional analysis. A total of 440 children and adolescents with obesity aged 6-16 years who underwent physical examination in the Endocrinology Department and Clinical Nutrition Department of the Children's Hospital of Nanjing Medical University from January 1, 2018, to December 31, 2022, were selected as research subjects. According to the WHO 2007 criteria, obesity was diagnosed in participants with a BMI z score ≥ 2 SD.

Inclusion criteria were as follows: 6-16 years of age; obesity; no major comorbidities or underlying diseases; and complete data. The exclusion criteria were as follows: younger than 6 years old; incomplete basic information and biochemical indicators; severe liver and kidney diseases; children and adolescents with type 2 diabetes; secondary obesity caused by other factors.

RESEARCH METHOD

Height and weight were measured by professionals using the OMRON (SK-L08) measuring instrument. BMI (kg/m²) = weight (kg) / height² (m²). The BMI z-score was calculated for each participant using the WHO Anthroplus software and the WHO 2007 growth reference.

Waist and hip circumference were measured in centimeters at the narrowest level at the waist between the costal margin and iliac crest and hip circumference at the largest level across the buttocks. Blood pressure was measured by the OMRON electronic blood pressure monitor (HEM-705CP). Fasting venous blood was taken and centrifuged at 3000 rpm for 10 minutes (centrifugation radius: 15 cm). The serum and plasma were separated, and fasting blood glucose (FBG), 2 h postprandial glucose (2hPG), uric acid (UA), triacylglycerol (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were detected using the Cobas® 8000 automatic biochemical analyzer. Glycated hemoglobin (HbA1c) was tested by high-performance liquid chromatography (Bio-Rad D10 Automatic Analyzer,

Hercules, CA, USA). An automatic electrochemiluminescence immunoanalyzer (Roche, Basel, Switzerland) was used to determine 25(OH)D. According to the standard (14), 25(OH)D level > 50 nmol/L was considered sufficient, 30-50 nmol/L was insufficient, and < 30 nmol/L was deficient.

Netherlandish Philips IU22 color Doppler ultrasound diagnostic instrument (Amsterdam, The Netherlands) was adopted, and the probe frequency was set at 5~37 MHz. Ultrasound scans were performed to assess CIMT of the right and left carotid arteries. The common carotid IMT was measured at its thickest part 1 cm proximal to the bifurcation. CIMT was expressed as the average of left and right CIMT ([Left CIMT + Right CIMT] / 2). Abnormal CIMT was determined if the value was ≥ 95th percentile for age, sex, and height (15). Season was defined as: winter: December-February; spring: March-May; summer: June-August; autumn: September-November.

STATISTICAL ANALYSIS

Statistical analysis was performed using with SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) and the R version 4.3.1. The total number of cases (*n*) and percentage (%) are used to represent count data. Normally distributed variables are described by the mean standard deviation, while skewed variables are described by the median, 25th, and 75th percentiles. The chi-square test was used for the statistical analysis of the counting data. Pairwise comparisons of measurement data subject to normal distribution were tested by independent sample t-test while those among multiple groups were analyzed by one-way analysis of variance (ANOVA), and the LSD (least significant difference) test was used for pair comparison after one-way ANOVA. If the samples did not meet the requirements of ANOVA, such as a normal distribution or homogeneity of variance, then a non-parametric test (Kruskal-Wallis) was used, and the Bonferroni method was used for comparison. We performed a multivariate linear regression using Generalized Linear Models to explore the association between CIMT and vitamin D levels after adjustment for other variables. In the multiple linear regression analysis, all data were transformed to z scores to obtain standardized regression coefficients. Restricted cubic splines were used to evaluate linear and nonlinear associations. Binary logistic regression analyses were used to explore the association between vitamin D status and the risk of abnormal CIMT. The difference of $p < 0.05$ was statistically significant.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

In this study we included 440 children and adolescents aged 6-16 years. Table I summarizes the demographic characteristics, anthropometric and biochemical measurements, and carotid intima-media thickness according to vitamin D status. There were 119 patients with vitamin D deficiency (79 males and 40 females; median age, 11.68 years, 27.1 % of total subjects); 228 patients with vitamin D insufficiency (155 males and 73 females; median age, 11.34 years, 51.8 % of total subjects); and 93 patients with vitamin D sufficiency (70 males and 23 females; median age, 11.35 years, 21.1 % of total subjects). There were no significant differences in sex, HAZ (height-for-age z-score), BMI z-score, WC (waist circumference), SBP (systolic blood pressure), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose), 2hPG (2 h postprandial plasma glucose), UA (uric acid), TC (total cholesterol), or LDL-C (low-density lipoprotein cholesterol) among the three groups (all $p > 0.05$). However, we found significant differences in CIMT and the risk of abnormal CIMT among the three groups. A post-hoc Bonferroni analysis revealed that CIMT was significantly higher in the vitamin D deficient group than in the vitamin D insufficient and vitamin D sufficient groups. Additionally, the risk of abnormal CIMT was significantly higher in the vitamin D-deficient group compared to the vitamin D-sufficient group.

On the basis of CIMT values, the subjects were divided into normal CIMT group and abnormal CIMT group. The basic characteristics of subjects according to CIMT were shown in table II. No significant differences were observed in age, sex, HAZ, BMI z-score, WC, HC, SBP, DBP, FPG, 2hPG, UA, TG, TC, HDL-C, LDL-C, or season of blood collection (all $p > 0.05$). However, we observed that vitamin D levels were significantly lower in the CIMT abnormal group than in the CIMT normal group.

CORRELATIONS BETWEEN CIMT AND VITAMIN D LEVELS

To adjust for the effects of confounding factors, we used Generalized Linear Models for multiple linear regression analysis to assess the relationship between vitamin D levels and CIMT. Table III reports the standardized regression coefficients (ß) and 95 % CIs for the Generalized Linear Models. Vitamin D levels are categorized as: low vitamin D levels (vitamin D levels (≤ 50 mmol/L) and normal vitamin D levels (> 50 mmol/L). Our results showed a significant negative correlation between vitamin D levels and CIMT in the low vitamin D level group, even after adjusting for various confounding factors ($p < 0.05$). However, in the vitamin D normal group, vitamin D levels were not associated with CIMT ($p > 0.05$). and the interaction in all models $p > 0.05$. The significance of the multiplication interaction between vitamin D and BMI z-score was estimated by adding cross-product terms in models, in all the models the interaction term was non-significant ($p > 0.05$). Restricted cubic splines were also generated to visualize this relationship, adjusting for age, sex and BMI z-score (Fig. 1). Modeling of vitamin D levels using restricted triplicate spline revealed that vitamin D levels did not correlate with CIMT in the vicinity of a reference vitamin D concentration of 50 nmol/L, low vitamin D levels were linearly and negatively correlated with CIMT (p for nonlinear = 0.2708).

Figure 1 shows fitted restricted cubic spline and 95 % CI, indicating no evidence of non-linear association between vitamin D levels and CIMT (p for nonlinearity = 0.2708). The restricted cubic splines model adjusted for age, sex, and BMI z-score.

Table I. Characteristics of the study population according to vitamin D status

Variables	Sufficient group (*n* = 93)	Insufficient group (*n* = 228)	Deficient group (*n* = 119)	*p*
Age (years)	11.35 (9.38, 12.32)	11.34 (9.61, 12.34)	11.68 (10.07, 13.17)	*0.017*†
Sex, boys (%)	70 (75.3 %)	155 (68.0 %)	79 (66.4 %)	0.333
HAZ	1.37 (0.69, 2.15)	1.49 (0.76, 2.04)	1.59 (0.56, 2.43)	0.736
BMI z-score	3.08 (2.75, 3.57)	2.88 (2.59, 3.57)	2.96 (2.61, 3.58)	0.510
WC (cm)	93.00 (86.00, 100.00)	92.25 (86.25, 100)	95 (86.50, 104.50)	0.139
HC (cm)	97.00 (92.25, 105.00)	98.60 (91.95, 104.00)	101.00 (92.50, 110.20)	*0.044*
SBP (mmHg)	129.00 (120.00, 139.50)	126.00 (118.00, 135.00)	130.00 (119.00, 141.00)	0.113
DBP (mmHg)	73.73 ± 1.14	72.86 ± 0.64	75.76 ± 1.01	*0.047*‡
HbA1c (%)	5.40 (5.15, 5.70)	5.30 (5.18, 5.60)	5.30 (5.20, 5.60)	0.627
FPG (mmol/L)	4.65 ± 0.04	4.55 ± 0.03	4.63 ± 0.04	0.07
2hPG (mmol/L)	6.22 (5.64, 6.98)	6.50 (5.80, 7.27)	6.57 (5.87, 7.25)	0.379
UA (µmol/L)	410.00 (345.00, 463.50)	389.00 (329.50, 453.00)	408.00 (345.00, 476.00)	0.578
TG (mmol/L)	1.12 (0.82, 1.61)	1.11 (0.88, 1.51)	1.33 (0.92, 1.79)	*0.040*
TC (mmol/L)	3.96 (3.50, 4.57)	3.99 (3.36, 4.49)	3.99 (3.53, 4.53)	0.560
HDL-C (mmol/L)	1.15 (1.01, 1.32)	1.07 (0.96, 1.22)	1.08 (0.98, 1.27)	*0.045**
LDL-C (mmol/L)	2.29 (1.92, 2.69)	2.23 (1.82, 2.74)	2.19 (1.83, 2.64)	0.850
25(OH)D (nmol/L)	59.51 (54.49, 69.42)	40.16 (36.53, 44.14)	25.49 (22.44, 28.17)	*< 0.001*,†,‡*
CIMT (mm)	0.47 (0.41, 0.53)	0.48 (0.43, 0.54)	0.5 (0.47, 0.57)	*0.002†,‡*
Abnormal CIMT (%)	51 (54.8 %)	154 (67.5 %)	90 (75.6 %)	*0.006*†
Season of blood collection				
Spring	17 (18.3 %)	38 (16.7 %)	26 (21.8 %)	
Summer	50 (53.8 %)	120 (52.6 %)	41 (34.5 %)	
Autumn	17 (18.3 %)	46 (20.2 %)	22 (18.5 %)	
Winter	9 (9.7 %)	24 (10.5 %)	30 (25.2 %)	*0.002*

Italics type denotes significant ($p < 0.05$*) values; *insufficient group vs. sufficient group,* $p < 0.05$*; †deficient group* vs. *sufficient group,* $p < 0.05$*; ‡deficient group* vs. *insufficient group,* $p < 0.05$*. BMI: body mass index; HAZ: height-for-age z-score; WC: waist circumference; HC: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; 2hPG: 2 h postprandial plasma glucose; UA: uric acid; TG: triacylglycerol; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CIMT: carotid intima-media thickness.*

ODDS RATIOS (95 % CIS) OF ABNORMAL CIMT ACCORDING TO VITAMIN D STATUS

Multivariate logistic regression was applied to assess the association between vitamin D status and abnormal CIMT (Table IV). In the unadjusted model, the ORs for abnormal CIMT in the vitamin D insufficient and vitamin D deficient groups compared with the vitamin D sufficient group were 1.714 (1.046-2.808) and 2.556 (1.424-4.586), respectively. After further adjustment for various confounders, the vitamin D deficiency group remained significantly associated with an increased risk of abnormal CIMT (OR: 2.080, 95 % CI: 1.112-3.891). However, the vitamin D insufficiency group was no longer associated with a risk of abnormal CIMT. No significant interaction was found between serum 25(OH)D levels and BMI z-score (*p* for all interactions > 0.05).

Table II. Characteristics of the study population according to carotid intima-media thickness

Variables	Normal CIMT (*n* = 145)	Abnormal CIMT (*n* = 295)	*p*
Age (years)	11.27 (9.40, 12.67)	11.46 (9.80, 12.56)	0.318
Sex, boys (%)	99 (68.3 %)	205 (69.5%)	0.795
HAZ	1.51 (0.55, 2.21)	1.46 (0.75, 2.16)	0.914
BMI z-score	2.98 (2.62, 3.58)	2.96 (2.64, 3.57)	0.886
WC (cm)	92.50 (87.00, 98.50)	93.50 (86.00, 102.80)	0.161
HC (cm)	98.00 (92.00, 104.00)	99.50 (91.50, 107.00)	0.250
SBP (mmHg)	128.00 (118.00, 140.00)	127.00 (119.00, 138.00)	0.823
DBP (mmHg)	73.34 ± 9.92	74.07 ± 10.62	0.485
HbA1c (%)	5.40 (5.30, 5.60)	5.30 (5.10, 5.60)	*0.006*
FPG (mmol/L)	4.61 ± 0.42	4.58 ± 0.44	0.611
2hPG (mmol/L)	6.36 (5.64, 7.25)	6.46 (5.81, 7.17)	0.917
UA (μmol/L)	400.00 (348.00, 454.00)	392.00 (330.00, 457.00)	0.319
TG (mmol/L)	1.11 (0.83, 1.48)	1.19 (0.90, 1.70)	0.052
TC (mmol/L)	3.94 (3.44, 4.49)	3.99 (3.43, 4.53)	0.704
HDL-C (mmol/L)	1.10 (1.00, 1.26)	1.07 (0.96, 1.24)	0.116
LDL-C (mmol/L)	2.24 (1.82, 2.64)	2.24 (1.84, 2.71)	0.907
25(OH)D (nmol/L)	42.18 (32.20, 52.93)	37.9 (29.02, 46.28)	*0.002*
CIMT (mm)	0.40 (0.40, 0.43)	0.52 (0.49, 0.58)	*< 0.001*
Season of blood collection			
Spring	32 (22.1 %)	49 (16.6 %)	
Summer	60 (41.4 %)	151 (51.2 %)	
Autumn	28 (19.3 %)	57 (19.3 %)	
Winter	25 (17.2 %)	38 (12.9 %)	0.186

Italics type denotes significant ($p < 0.05$) values. BMI: body mass index; HAZ: height-for-age z-score; WC: waist circumference; HC: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; 2hPG: 2 h postprandial plasma glucose; UA: uric acid; TG: triacylglycerol; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CIMT: carotid intima-media thickness.

SUBGROUP ANALYSES OF THE ASSOCIATION BETWEEN VITAMIN D STATUS AND ABNORMAL CIMT

A subgroup analysis was subsequently performed to evaluate the effect on different age groups (6-11 and 12-16 years), sex groups and BMI z-score groups (< 3/≥ 3). The forest plot of the subgroup analysis is presented in figure 2. Subgroup analyses by age group showed that vitamin D deficiency was not significantly different from the risk of abnormal CIMT in different age groups ($p > 0.05$). Sex-stratified subgroup analysis showed that the risk of abnormal CIMT was significantly higher in girls with vitamin D deficiency than in the vitamin D-sufficient group, but no similar association was found in boys. Subgroup analysis by BMI z-score showed that the risk of CIMT abnormalities was significantly higher in the vitamin D-deficient and vitamin D-insufficient groups than in the vitamin D-sufficient group in the BMI z-score ≥ 3 group, but was not significantly different in the BMI z-score < 3 group. Subgroup analyses indicated no significant interaction in the subgroup analysis (all *p*-values for interaction were > 0.05).

DISCUSSION

There has been controversy regarding the relationship between vitamin D and CIMT. Our findings support that there is a negative correlation between vitamin D and CIMT in the range of low vitamin D levels (≤ 50 nmol/L) and that vitamin D deficiency

Table III. Association between serum 25(OH)D levels and CIMT according to serum 25(OH)D levels

Subjects	Model	ß	95 % CI	*p*
All subjects (n = 440)	Model 1	-0.142	-0.234 to -0.05	*0.003*
	Model 2	-0.100	-0.196 to -0.003	*0.043*
	Model 3	-0.108	-0.205 to -0.011	*0.029*
Normal 25(OH)D level (n = 93)	Model 1	-0.042	-0.245 to 0.161	0.686
	Model 2	-0.019	-0.202 to 0.165	0.843
	Model 3	-0.003	-0.189 to 0.001	0.972
Low 25(OH)D level (n = 347)	Model 1	-0.155	-0.259 to -0.051	*0.003*
	Model 2	-0.144	-0.260 to -0.028	*0.015*
	Model 3	-0.147	-0.263 to -0.030	*0.013*

*Italics type denotes significant (p < 0.05) values. Model 1 was unadjusted. Model 2 is adjusted for age, sex, HAZ, BMI z-score, WC, HC, SBP, DBP, HbA1c, FPG, 2hPG, UA, blood lipid profile, and season of blood collection. Model 3 is adjusted as for Model 2 + BMI z-score * 25(OH)D.*

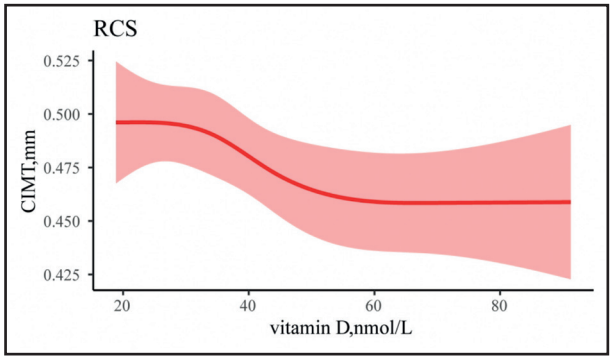

Figure 1.
Linear association between vitamin D levels and CIMT.

exacerbates the risk of CIMT abnormalities in children and adolescents with obesity.

Obesity during childhood and adolescence is significantly associated with an increased risk for cardiovascular and metabolic disease, colorectal cancer, and breast cancer in adulthood (16,17). Compared with their counterparts without obesity, children and adolescents with obesity have a higher risk of vitamin D deficiency (18,19). In our study, only 21.1 % of Chinese children and adolescents with obesity had normal vitamin D levels, and 27.1 % of children and adolescents were vitamin D deficient. Vitamin D levels are thought to be lower in people with obesity because it is sequestered in fat cells (20).

It is well known that CIMT is an accurate predictor of systemic atherosclerosis and an objective measure of early atherosclerosis, and obtaining CIMT using ultrasonography is currently a non-invasive tool for obtaining abnormal changes in blood vessels (21). Studies have linked vitamin D deficiency to atherosclerosis (22). Vitamin D deficiency may be an independent risk factor for atherosclerosis in children and adolescents with obesity. Vitamin D deficiency can lead to endothelial dysfunction, increased arterial stiffness and increased CIMT (23). A meta-analysis showed serum vitamin D levels as a preventive measure of carotid plaque (24). Many studies have reported an association between vitamin D

Table IV. Logistic regression of the association between different vitamin D status and abnormal CIMT

Vitamin D status	Model 1			Model 2		
	OR_1	95 % CI_1	p_1	OR_2	95 % CI_2	p_2
Vitamin D sufficient	1.000 (Ref.)	–	–	1.000 (Ref.)	–	–
Vitamin D insufficient	1.714	1.046-2.808	*0.032*	1.571	0.928-2.658	*0.093*
Vitamin D deficient	2.556	1.424-4.586	*0.002*	2.080	1.112-3.891	*0.022*
p for trend	0.002			0.022		

Italics type denotes significant (p < 0.05) values. Model 1 is unadjusted. Model 2 is adjusted for age, sex, HAZ, BMI z-score, WC, HC, SBP, DBP, HbA1c, FPG, 2hPG, UA, blood lipid profile, and season of blood collection.

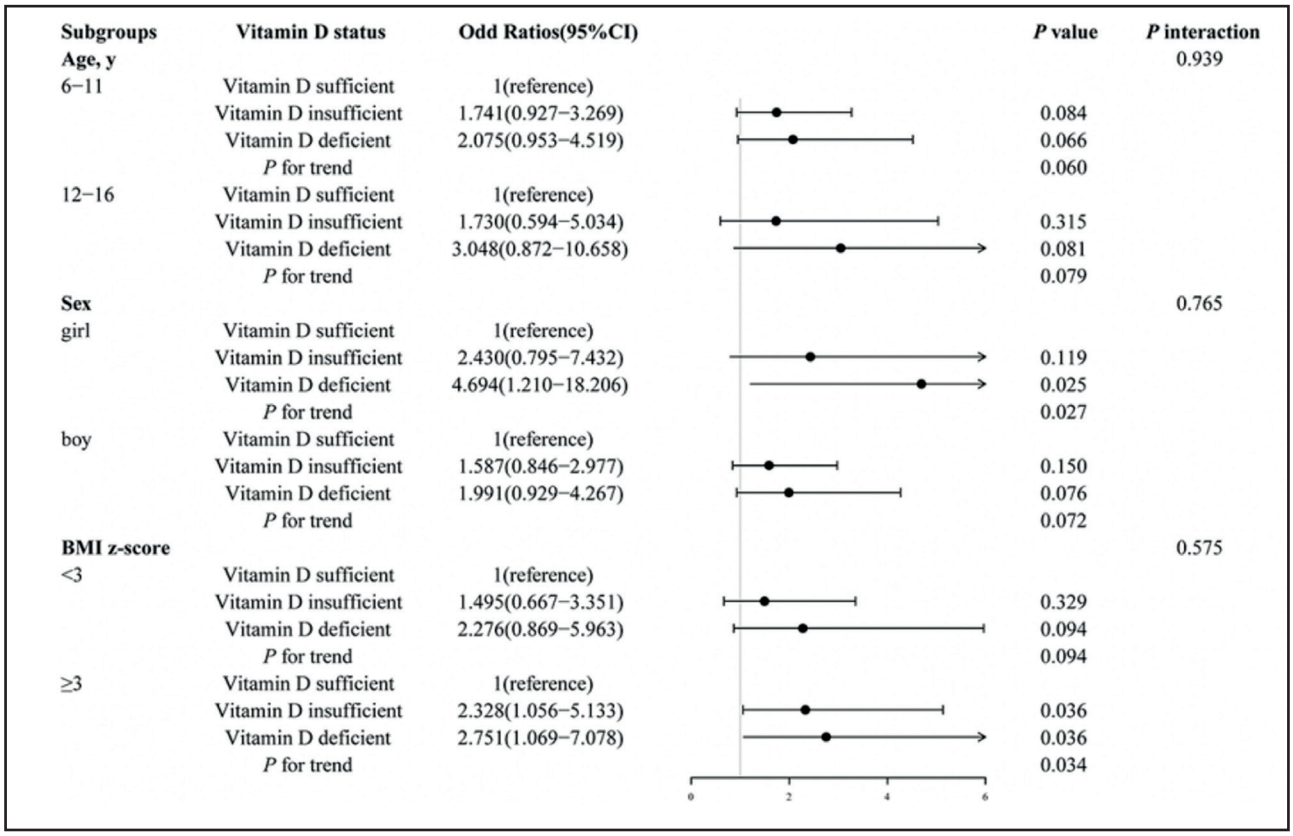

Figure 2.

Forest plot of subgroup analysis of the association between vitamin D status and abnormal CIMT. Each stratification adjusted for all the factors of model 2 in the multivariable logistic regression, except for the stratification factor itself.

status and carotid intima-media thickness; however, the available pediatric studies are very limited. According to a recent meta-analysis of 19 observational and 3 randomized studies, there is a negative correlation between serum vitamin D and CIMT. Additionally, the study found that vitamin D supplementation has a positive effect on reducing CIMT (25). In our study, we also found a negative association between vitamin D levels and CIMT, which is similar to other studies (26,27), but not consistent with previous studies (5,28). The discrepancy in findings may be due to differences in study populations, as most current studies on vitamin D and CIMT are based on the general population aged 18-75 years. A study in a cohort of children and adolescents with obesity found that CIMT was increased in vitamin D-deficient patients with obesity, and vitamin D levels were negatively correlated with CIMT, similar to our results (29). However, another study in children with obesity provided opposite results. In a cross-sectional study of children with obesity aged 15 to 17 years, no association was found between vitamin D and CIMT (12). To our knowledge, the present study is the first study to suggest a negative correlation between vitamin D and CIMT within low vitamin D levels.

The relationship between serum vitamin D and CIMT is not completely clear. However, most researchers currently believe that vitamin D plays a vital role in activating the renin-angiotensin system. Its deficiency leads to an increase in serum parathyroid hormone (PTH) and a decrease in insulin-like growth factor-1 (IGF-1). Accumulating evidence suggests that reduced IGF-1 concentrations contribute to cardiovascular disease (30). With regard to CIMT, thresholds in the pediatric population are still not standardized, but most studies suggest that obesity and the metabolic syndrome are contributing factors to an increase in CIMT, mainly due to inflammatory processes. The role of vitamin D deficiency in the development of atherosclerosis may be mediated by vascular inflammation, and these include elevated levels of inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin 6, as well as low levels of interleukin 10 (31). It has also been shown that 25 hydroxyvitamin D interacts with vascular endothelial vitamin D receptors and reduces smooth muscle cell proliferation, thereby providing cardiovascular protection (32). Some studies have found that vitamin D deficiency can lead to endothelial damage in the early stages of atherosclerosis without progression to clinical cardiovascular disease, which would have a key role in preventing cardiovascular mortality and morbidity (33).

There is no doubt that most researchers believe that children with obesity develop vascular destruction earlier than their normal-weight peers. The additive effect of obesity, independent of age, was evident in the CIMT values. Significant difference

in CIMT between normal weight and individuals with obesity (34,35). In normal-weight children and adolescents, CIMT is not affected by sex or age (36). Some researchers have found significantly higher values of vascular biomarkers in post-pubertal children with obesity compared to pre-pubertal children with obesity (37). In our study, there is no significant difference between vitamin D deficiency and the risk of abnormal CIMT in different age groups, which may be due to the sample size of subgroups. Our study found a significantly higher risk of abnormal CIMT in vitamin D-deficient girls than in the vitamin D-sufficient group, but no similar association was found in boys. Excess androgens in girls with obesity may lead to an acceleration of the atherosclerotic process, resulting in an increase in CIMT (38). The results could inform policymakers about developing effective strategies for preventing the development of cardiovascular disease in children and adolescents with obesity.

A healthy lifestyle intervention may be able to partially reverse cardiovascular impairment in children with obesity. Adopting prompt behavioral programs in childhood with obesity is crucial for preventing and treating precocious complications (39). A study indicated that adherence to a healthy dietary pattern could prevent increased CIMT in children and adolescents with overweight and obesity (40). A healthy diet and regular exercise combined with vitamin D treatment could reduce cardiovascular disease in children and adolescents with obesity and vitamin D deficiency.

However, our study was limited. First, it was a cross-sectional observational study. We could not determine whether CIMT had a predictive value for cardiovascular outcomes in children and adolescents with obesity, which required prospective longitudinal studies. Second, this study was a small sample study that enrolled patients only from the Children's Hospital of Nanjing Medical University and did not participate in the larger multicenter study. Third, this study did not collect information on physical activity levels or vitamin D supplements, all of which can affect vitamin D concentrations.

Although the study has many limitations, our findings highlight the need for more evidence to establish these links. Particularly, more research is needed to identify potential biological pathways supporting the independent association between vitamin D deficiency and CIMT, explore whether medical interventions improve arterial remodeling, and ultimately determine the effectiveness of targeted preventive interventions.

CONCLUSIONS

In this study, it was found that vitamin D deficiency is an independent risk factor for abnormal CIMT, and vitamin D deficiency may play a promoting role in the atherosclerotic process in children and adolescents with obesity. Therefore, supplementing adequate amounts of vitamin D in children and adolescents with obesity may help prevent atherosclerosis, but this needs to be further confirmed in a large-scale international multicenter clinical trial.

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