Original Article

Serum vitamin D status among healthy children in Hainan, South China: a multi-center analysis of 10,262 children

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Background: There are limited data regarding the prevalence and risk factors relating to vitamin D deficiency (VDD) in children of Hainan, a tropical city with abundant sunlight in China. To gather and analyze the serum VD levels of healthy children in Hainan, so as to understand their VD nutritional status and improve the representative data of VD nutritional status in South China.

Methods: Children who presented to the outpatient clinic for physical examination at 4 hospitals in the Hainan Province from 2012 to 2020 were enrolled in this study. The serum 25-hydroxyvitamin D (25-OHD) levels was analyzed. 25-OHD levels <50 nmol/L is considered VDD, 50–75 nmol/L is vitamin D insufficiency (VDI), and ≥75 nmol/L is VD sufficient (VDS).

Results: The average serum 25-OHD level was 94.63±49.99 nmol/L [95% confidence interval (CI): 93.67–95.60]. VDD was detected in 13.98% of participants (1,435 cases), VDI was detected in 30.60% of participants (3,140 cases), and 55.42% presented with VDS (5,687 cases). The average 25-OHD level of boys was significantly higher than that of girls (t=3.67, P<0.001). The average serum 25-OHD levels in the following age groups 0–1, 1–3, 3–7, 7–14, and 14–18 years were 105.92±57.39, 100.55±53.22, 86.35±39.19, 73.61±34.21, and 54.97±19.19 nmol/L, respectively. These results suggested that with an increase in age, the 25-OHD levels decreased. The average 25-OHD levels of children with a body mass index (BMI) <85th percentile were significantly higher than that of children in the overweight and obese group (F=7.393, P=0.001).

Conclusions: A certain proportion of all age groups showed vitamin D deficiency and insufficiency in Hainan. A formal recommendation for vitamin D supplementation should be considered, especially in autumn and winter seasons for children over 7 years old, and in those with BMI ≥85th percentile or BMI ≥95th percentile.

Keywords: 25-hydroxyvitamin D (25-OHD); healthy children; South China

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Introduction

Vitamin D (VD) plays an important role in calcium/phosphorus metabolism, bone health, and a variety of other biological functions (1). Besides the traditional vitamin D deficiency (VDD) associated rickets and tetany, VDD or vitamin D insufficiency (VDI) is also closely related to many non-skeletal diseases, including neuropsychological diseases (such as autism, schizophrenia, and depression), cardiovascular and metabolic diseases (including obesity, diabetes, and hypertension), rheumatoid immune diseases (such as rheumatoid arthritis and systemic lupus erythematosus), infectious diseases (including pneumonia and tuberculosis), and even certain types of cancers (2-10). Studying vitamin D status in children aged ≤18 can help guide children's reasonable vitamin D supplementation, which is very important for children's health.

Global epidemiological surveys showed that the prevalence of VDD in European countries is up to 40.4% (11). The VD levels in Asian countries are highly variable. For example, the prevalence of VDD among children in southern India is about 30%, while that in northern India is as high as 50%. In Japan, 7.2% of the infants younger than 48 months have VDD and 13.8% present with VDI (12). Among American countries, the prevalence of VDD and VDI among children in the United States is 9.7% and 56%, respectively. In Canada, the prevalence of VDD is 6%, and that of VDI is 24% (13). In Southern Tasmania, 8% of 8-year-old children and 68% of 16-year-old children have VDD (14). The prevalence of VDD among African children in Ethiopian is up to 42% (15). In China, Wu *et al.* measured the serum 25-hydroxyvitamin D (25-OHD) levels of 222 healthy adolescents (12–15 years old) in Beijing, China and reported that the prevalence of VDD was up to 97% (16), which is much higher than that in other cities. Xu *et al.* (17) found that, in Hong Kong between 2009 and 2010, children aged 6–17 years had significantly lower serum 25-OHD levels compared to adults. Ke *et al.* reported that Chinese people, aged 18–93 years old, living in Macau had a VDD prevalence of 55% (18) and the prevalence of VDD in pregnant women in Wuxi City, China (latitude: 31.50 N) was 38.0% (19).

Hainan is the southernmost province in China and is also the only province that completely lies in a tropical region (latitude: 3.30–20.17 N). Hainan has a maritime tropical monsoon climate, with plenty of sunshine throughout the year. Moreover, the daily diet of the Hainanese includes many marine products (such as fish), which are rich in VD. However, there is still a paucity of data related to VD levels in large populations of Chinese children, especially for such a uniquely located province in China. This current multicenter study evaluated the VD status of children in Hainan using a large sample size, so as to provide scientific data for the prevention and treatment of children with VDD or VDI in this region. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-235/rc).

Methods

Study subject

A total of 10,262 healthy children who underwent health examinations at four hospitals in Hainan (including Hainan Women and Children's Medical Center, Hainan General Hospital, Haikou Maternity and Child Health Hospital, and Sanya Maternity and Child Health Hospital) from 2012 to 2020 were included in this study. Children with abnormal renal function or other metabolic diseases that may interfere with VD metabolism were excluded. The age range of the included children was 0.09–17.00 years old, with an average age of 3.32±2.96 years. Children were divided into five age groups: 0–1, 1–3, 3–7, 7–14, and 14–18 years. There were 2,093 cases in the 0–1 year group, 4,242 cases in the 1–3 years old group, 2,707 cases in the 3–7 years group, 1,184 cases in the 7–14 years old group, and 36 cases in the 14–18 years group. There were 5,861 boys and 4,401 girls. Based on the time of examination, the children were divided into 4 groups: spring (from February to April, 2086 cases), summer (from May to July, 2,877 cases), autumn (from August to October, 2917 cases), and winter (from November to January, 2,382 cases). According to the growth curve of the body mass index (BMI) of children aged 0 to 18 years old in China (20), children with BMI

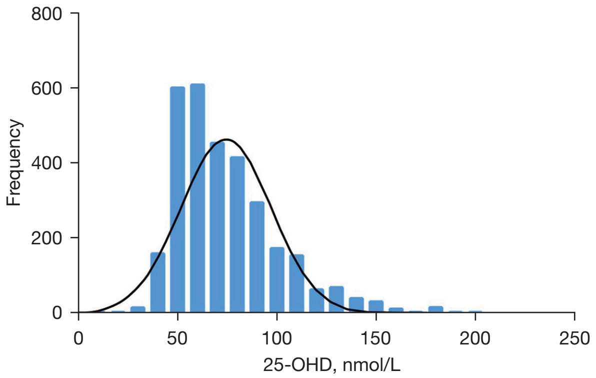

Figure 1 The frequency distribution of the 25-OHD measurements. The 25-OHD concentration is shown as a normal distribution, and most of the values are in the range of 50 to 90 nmol/L. 25-OHD, 25-hydroxyvitamin D.

≥95th percentile of normal children with the same age range and sex were defined as obese, and those with BMI between the 85th and 95th percentile were defined as overweight. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical Ethics Committee of Hainan Women and Children's Medical Center (HNWCMC Ethical Approval 2011[01]). Hainan General Hospital, Haikou Maternity and Child Health Hospital, and Sanya Maternity and Child Health Hospital were informed and agreed with this study. The legal guardians of enrolled children signed informed consent forms.

Detection methods and diagnostic criteria

Venous blood samples were collected from children in the early morning before meals. The samples were sent to the laboratory for testing within 2 h of collection. The serum 25-OHD levels were measured using a Roche automatic chemiluminescence detector. According to the International Classification of Children's VD Nutritional Status, the results were classified using the seven-category method or the three-category method. According to the seven-category method, 25-OHD levels <12.5 nmol/L is considered severe deficiency, 12.5–25 nmol/L is moderate deficiency, 25–50 nmol/L is mild deficiency, 50–75 nmol/L is VDI, 75–250 nmol/L is normal, 250–375 nmol/L is excessive, and ≥375 nmol/L is VD poisoning. According to the three-category method, 25-OHD levels <50 nmol/L is considered VDD, 50–75 nmol/L is VDI, and ≥75 nmol/L is VD sufficient (VDS).

Statistical methods

Statistical analysis was performed using SPSS 20.0 software. Analyses of the data for the serum 25-OHD concentrations revealed a normal distribution. The data were therefore described using mean ± standard deviation. The *t*-test was used to compare differences of VD levels between groups. The nonparametric chi-square test was used to compare different rates between groups. Logistic regression analysis was used to obtain odds ratio in the presence of possible factors and estimate partial correlation coefficients. A two-sided P value of 0.05 was considered to be statistically significant.

Results

The overall levels of serum 25-OHD in the test population

The serum 25-OHD levels of 10,262 children showed a normal distribution, with an average of 94.63±49.99 nmol/L [95% confidence interval (CI): 93.67–95.60] and a range of 50–90 nmol/L (*Figure 1*). The average serum 25-OHD levels of the 5,861 boys was significantly higher than that of the 4,401 girls (96.21±51.27 and 92.55±48.16 nmol/L, respectively; t=3.67, P<0.001).

Among the participating children, 14% had VDD (1,435/10,262), including 2 cases of severe deficiency, 49 cases of moderate deficiency, and 1,384 cases of mild deficiency. VDI was detected in 30.6% of participants (3,140/10,262) and VDS was noted in 55% of the study population (5,687/10,262), including 5,583 cases with acceptable VD levels and 104 cases with VD overdose. There was no cases of VD poisoning. Therefore, according to the seven-category method, 54.4% children (5,583/10,262) had an acceptable VD level (50–75 nmol/L), 30.6% children (3,140/10,262) were VDI (50–75 nmol/L), 13.5% children (1,384/10,262) were mild deficiency (25–50 nmol/L), last 1.5% (155/10,262) contained 104 cases VD overdose (250–375 nmol/L), 49 cases moderate deficiency (12.5–25 nmol/L) and 2 cases sever deficiency (<12.5 nmol/L) (*Figure 2*). There were 1,590 children with complete height and weight data, including 1,442 cases in the normal group, 64 cases in the overweight group, and 84 cases in the obese group.

A comparison of the serum 25-OHD levels and the VD nutritional status in different age groups

The 25-OHD levels and VD nutritional status varied in different age groups of children (*Table 1*). The highest

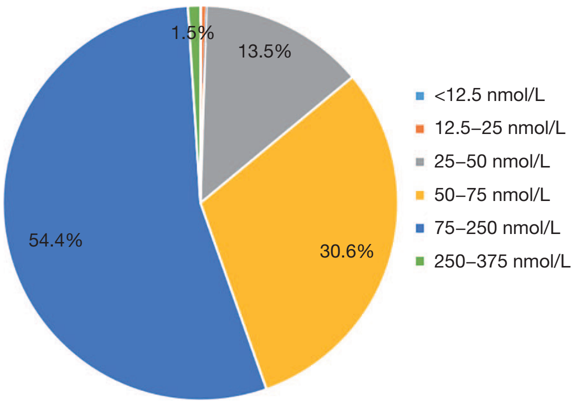

Figure 2 The proportion of children with different vitamin D levels.

average 25-OHD levels were found in the 0–1 year old group (105.92±57.39 nmol/L), while children aged 14–18 years old had the lowest 25-OHD levels (54.97±19.19 nmol/L). As the age increased, the 25-OHD levels showed a downward trend, and the difference among different age groups was statistically significant (F=123.78, P<0.001). Among the 5 age groups, children aged 14–18 years had the highest VDD and VDI ratios (VDD accounted for 38.9% and VDI accounted for 44.4%), and VDS only accounted for 16.7%. Children aged 0–1 and 1–3 years had a higher prevalence of VDS, at 60% and 59.2%, respectively. The distribution of VD nutritional status was significantly different among all age groups (χ^2=237.134, P<0.001).

A comparison of serum 25-OHD levels in different seasons

The serum 25-OHD levels of children varied according to different seasons (*Table 2*). The average 25-OHD levels in spring and summer were relatively high (96.56±45.76 and 96.85±52.23 nmol/L, respectively), declining in autumn (94.53±50.40 nmol/L), and reaching the lowest average levels in winter (90.41±50.03 nmol/L). The difference in the 25-OHD levels among different seasons was statistically significant (F=8.606, P<0.01). Moreover, the seasonal changes of serum 25-OHD levels were similar in different age groups (*Figure 3*).

A comparison of the serum 25-OHD levels and VD nutritional status in children with different body weights

In this study cohort, 1,590 children had valid height and weight data (*Table 3*). Children with normal weight (BMI <85th percentile) had higher 25-OHD levels (115.72±31.62 nmol/L) compared to the obese group (BMI ≥95th percentile) and the overweight group (BMI ≥85th percentile). The average 25-OHD levels of the overweight group was the lowest (103.13±36.20 nmol/L). There was a significant difference in 25-OHD levels among these three groups (F=7.393, P=0.001). For VD nutritional status, children with BMI <85th percentile had the lowest VDD ratio (0.83%) and the highest VDS ratio (91.82%); while overweight children had the highest VDD ratio (6.25%), and obese children had the highest VDI ratio (19.05%). The difference in VD nutritional status among the three groups was statistically significant (χ^2=37.177, P<0.001).

Logistic regression analysis of the factors affecting 25-OHD levels in children

A backward (conditional) logistic regression analysis was performed where VD sufficiency was used as the independent variable Y (0 is insufficient, where 25-OHD <75 nmol/L and 1 is sufficient, where 25-OHD ≥75 nmol/L). The dependent variables were gender (X1, where 1 is male and 2 is female), age (X2, where 1–5 represent the different age groups), and season (X3, where 1–12 represent the 12 months of the year). The results indicated that gender, age, and season all had a certain impact on VD sufficiency (*Table 4*).

Discussion

This study analyzed the distribution of serum 25-OHD levels in 10,262 children in the Hainan province. Children with VD insufficiency (serum 25-OHD <75 nmol/L) accounted for 44.58%, which is nearly half of the study population. Interestingly, the serum 25-OHD levels of children in Hainan was higher than that reported in Beijing (16). The overall levels of VD varied greatly between the northern and southern cities, and this may be related to diet and living habits, regional latitude and altitude, sunshine exposure time, awareness of VD insufficiency and associated preventive measures, as well as the general knowledge of the population (21).

There were 104 cases (1.01%) with VD overdose. A review of the outpatient data and follow-up record revealed that most of the VD overdose cases had a history of single or multiple high-dose VD intake, and their 25-OHD levels had not been regularly monitored. This is consistent with the

Table 1 The 25-OHD levels and VD nutritional status in children of different ages

Parameters	No. of cases	25-OHD (nmol/L)		VD nutritional status, n (%)		
		$\bar{x}$±s	95% CI	VDD	VDI	VDS
Age group (years)						
0–1	2,093	105.92±57.39	103.46–108.39	289 (13.8)	549 (26.2)	1,255 (60.0)
1–3	4,242	100.55±53.22	98.95–102.15	542 (12.8)	1,190 (28.1)	2,510 (59.2)
3–7	2,707	86.35±39.19	84.88–87.84	346 (12.8)	888 (32.8)	1,473 (54.4)
7–14	1,184	73.61±34.21	71.66–75.56	244 (20.6)	497 (42.0)	443 (37.4)
14–18	36	54.97±19.19	48.48–61.47	14 (38.9)	16 (44.4)	6 (16.7)
Total	10,262	94.63±49.99		1,435 (14.0)	3,140 (30.6)	5,687 (55.4)
F/χ^2		123.78			237.134	
P		<0.001			<0.001	

25-OHD, 25-hydroxyvitamin D; VD, vitamin D; CI, confidence interval; VDD, vitamin D deficiency; VDI, vitamin D insufficiency; VDS, vitamin D sufficiency.

Table 2 The levels of 25-OHD in children during different seasons

Parameters	Number of cases	25-OHD (nmol/L)	
		$\bar{x}$±s	95% CI
Season			
Spring	2,086	96.56±45.76	94.60–98.53
Summer	2,877	96.85±52.23	94.94–98.76
Autumn	2,917	94.53±50.40	92.70–96.36
Winter	2,382	90.41±50.03	88.40–92.42
Total	10,262	94.64±49.99	
F		8.606	
P		<0.01	

25-OHD, 25-hydroxyvitamin D.

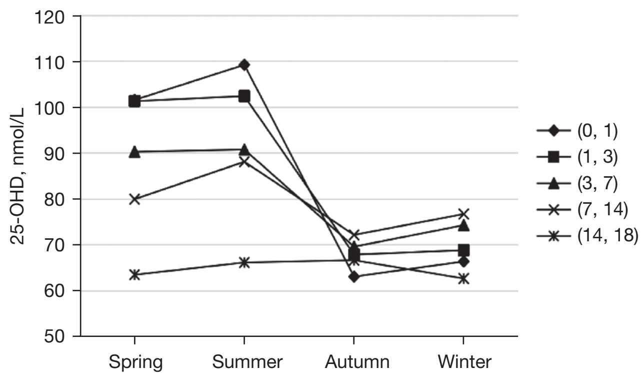

Figure 3 The seasonal change of serum 25-OHD levels in different age groups. 25-OHD, 25-hydroxyvitamin D.

common causes of VD overdose reported in other regions (22,23). Further stratifying the VD overdose group by age demonstrated that, among the children with VD overdose, 39 cases (37.5%) were in 0–1 year group, 55 cases (52.9%) were in 1–3 years group, 8 cases (7.7%) were in 3–7 years group, and 2 cases (1.9%) were in 7–14 years group. The children under 3 years accounted for 90.4% of the VD overdose cases, which may be related to parents focusing on VD supplementation for infants but overlooking VD monitoring. Therefore, it is important to pay attention to the monitoring of VD levels in children under 3 years of age.

This study found that gender, age, and season all had a certain impact on VD sufficiency, which is consistent with other reports (24,25). The overall serum VD levels of boys was significantly higher than that of girls, which may be related to more outdoor activities, less physical sun protection measures, longer exposure to sunlight, different hormone levels, and different dietary structures of boys. In addition, VD levels were negatively correlated with age, which may be related to dietary factors such as the discontinuation of VD supplementation after 3 years of age and reduction in dairy product intake, environmental factors such as reduced outdoor activities and reduced exposure to sunshine, and social factors such as reduced concern from parents about the VD nutrition status after school age. The serum VD levels of children under 3 years old was

Table 3 The 25-OHD levels and VD nutritional status in groups with different body mass index

Parameters	No. of cases	25-OHD (nmol/L)		VD nutritional status, n (%)		
		$\bar{x}$±s	95% CI	VDD	VDI	VDS
BMI group						
<85th percentile	1,442	115.72±31.62	114.08–117.35	12 (0.83)	106 (7.35)	1,324 (91.82)
≥85th percentile	64	103.13±36.20	94.08–112.17	4 (6.25)	10 (15.63)	50 (78.12)
≥95th percentile	84	106.94±34.29	99.50–114.38	2 (2.38)	16 (19.05)	66 (78.57)
Total	1,590	114.74±32.09	113.16–116.32	18 (1.13)	132 (8.30)	1440 (90.57)
F/χ^2		7.393			37.177	
P		0.001			<0.001	

25-OHD, 25-hydroxyvitamin D; BMI, body mass index; VD, vitamin D; CI, confidence interval; VDD, vitamin D deficiency; VDI, vitamin D insufficiency; VDS, vitamin D sufficiency.

Table 4 Multivariate logistic regression analysis of the factors influencing vitamin D levels

Factors	B	SE	Wald (χ^2)	P	OR	95% CI
Gender	–0.096	0.041	5.565	0.018	0.909	0.839–0.984
Age	–0.266	0.022	150.715	<0.001	0.767	0.735–0.800
Season	–0.038	0.006	35.488	<0.001	0.963	0.951–0.975

SE, standard error; OR, odds ratio; CI, confidence interval.

significantly higher than that of other age groups, which may be related to the VD from the mother's milk, and the continuous supplementation of VD 400–800 IU/d as recommended in the "Recommendations for the Prevention and Treatment of Rickets" in China (mainly for infants and young children) (26). Therefore, it should be recommended to systematically manage the VD nutritional status of children after 3 years of age. The seasonal analysis revealed that the 25-OHD levels in winter were significantly lower than those in the other three seasons, which is consistent with the annual radiation change in Hainan, in which March, July, and October experience peak sunshine levels, while December is the winter-spring transition, when the cold air frequently goes southward, leading to thicker clouds and shorter sunshine hours (27).

There were some limitations to this study. This investigation was unable to retrospectively collect height and weight data for all the children. Only 1,590 children had complete height and weight data, which were used to analyze the relationship between BMI and VD nutritional status. This study did not collate other parameters such as VD supplementation status, dairy product consumption, outdoor activity time, and the guardian's educational level and economic situation. Thus, it is unclear whether other factors may affect VD levels. In addition, the sample size in this study was large and the time span was also long. Therefore, the economic level, living habits, and nutritional status of residents may change during the course of the study. These factors may have affected the study results.

In summary, this report found that healthy children of all ages in Hainan showed a certain percentage of VDD and VDI, especially in those over 7 years old. In 2011, the American Endocrine Society recommended that the amount of VD supplementation should be 400–1,000 U/d for infants and 600–1,000 U/d for children aged 1–18 years old. The "Recommendations for the Prevention and Treatment of Rickets" of China recommends that the prevention of VDD should be continued from the perinatal period to adolescence, and should be "adjusted according to time, place, and person" (26). Therefore, in addition to sunbathing and dietary intake, VD supplementation should be considered, especially for children over 3 years old. Moreover, regular monitoring of VD levels is required during VD supplementation to avoid VD overdose.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-235/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-235/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-235/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical Ethics Committee of Hainan Women and Children's Medical Center (HNWCMC Ethical Approval 2011[01]). Hainan General Hospital, Haikou Maternity and Child Health Hospital, and Sanya Maternity and Child Health Hospital were informed and agreed with this study. The legal guardians of enrolled children signed informed consent forms.

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