Vitamin D Deficiency in Children and Adolescents: Role of Puberty and Obesity on Vitamin D Status

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ABSTRACT

BACKGROUND: Vitamin D deficiency is common among children and adolescents and can be affected by several factors such as puberty and obesity.

OBJECTIVE: The aim of this study was to evaluate vitamin D status in children and adolescents and to analyse the influence of puberty and obesity on its level.

METHOD: A cross-sectional study was carried-out, in which clinical and biochemical data were gathered from 384 healthy children and adolescents between May 2019 to May 2020.

RESULTS: 220 females and 164 males were enrolled (aged 7-16 years; mean ± SD: 11 ± 2.5). Vitamin D deficiency was found in 49% of the total cases and was significantly more prevalent in females than males (33.1% in female; 15.9% in male, $P < .001$). Mean vitamin D level was lower in obese children compared with non-obese ($P < .001$). Non-obese group had significantly higher levels of vitamin D in Tanner stage IV of puberty than obese individuals (20.1 ± 17.0 vs 5.4 ± 2.0) ($P = .03$). Vitamin D levels were significantly lower in females than males only in Tanner stage II (12.3 ± 9.0 vs 19.6 ± 16.6) ($P = .005$). The lowest level of Vitamin D was in Tanner stage Ⅳ-Ⅴ in boys and in Tanner stage Ⅱ-Ⅲ in girls ($P < .001$).

CONCLUSION: Puberty is an additional risk factor for vitamin D deficiency especially in girls and obese children. This increased risk, together with the fact that most important time for building a proper skeleton is during childhood and adolescent, makes it essential to monitor vitamin D in these age groups.

KEYWORDS: $25(OH)_2D_3$, puberty, obesity, season

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Introduction

Vitamin D, a fat-soluble vitamin and a pro-hormone, is essential for calcium and phosphorus hemostasis and bone metabolism. The most important sources of vitamin D are sunlight, supplements and diet.[1] The liver and kidneys are 2 essential organs that activate vitamin D as 1,25dihydroxy vitamin D.[2] In addition to bone health and growth, vitamin D plays a crucial role in protecting the body from many conditions such as cancers, cardiovascular events, autoimmune and infectious diseases.[3-5] Hence, in recent years there is an increasing trend in investigating the prevalence and long-term effects of vitamin D deficiency.[6] Vitamin D deficiency is common among children and adolescents and negatively affects bone density, muscle function, glucose metabolism and insulin sensitivity.[7] About 1 billion people in the world have low vitamin D levels; however, the prevalence of its deficiency is still uncertain worldwide.[1] Theoretically, vitamin D deficiency is not expected among people living in regions with intense sunlight. However, some studies indicate a high prevalence of vitamin D deficiency in people who lives in these regions, such as Iran, probably due to clothing, culture and diet.[8-13] Vitamin D level is measured by serum 25-hydroxyvitamin D [$25(OH)_2D_3$] and is related to various factors, including race, season, sunlight exposure, diet and adiposity.[14] Furthermore, the prevalence of its deficiency is higher in adolescents compared with prepubertal children; suggesting the effect of puberty on vitamin D levels.[15] The physiologic increase of adipose tissue during puberty decreases the bioavailability of $25(OH)_2D_3$.[16] Besides, puberty is a critical phase in bone development,[17] and there is an increase demand for vitamin D during puberty due to an increase in bone accretion.[18] This study aimed to evaluate the correlation of $25(OH)_2D_3$ status with pubertal stages, winter and summer, BMI, weight and height in children and adolescents.

Subjects and Methods

Subject selection

This is a cross-sectional study conducted in Iran, Tehran, from May 2019 to May 2020. Data were obtained from 384 children and adolescents that referred to paediatric endocrinology clinic. Exclusion criteria were as follows: (1) History of the specific underlying disease (kidney, liver, or seizure, . . .). (2) Specific drug consumption (vitamin D supplements, multivitamins, anticonvulsive drugs). All demographic information and physical examinations, including height, weight and stage of puberty, were taken by a paediatric resident. The stage of puberty was determined according to Tanner scaling.[19] The height and weight of subjects were measured by stadiometer and secca scale. Body mass index (BMI) [weight (Kg)/height $(m)^2$] was calculated. Standard deviation score (SDS) (subject's value – mean value for age and sex of CDC 2000 data/SD) was detected for height, weight and BMI. Obesity is defined as BMI more than 95th percentile according to CDC growth chart-2000.

To determine the prevalence of different vitamin D levels, we used the definition of vitamin D deficiency, insufficiency and sufficiency according to the serum level of $25(OH)_2D_3$. Participants were categorized according to the serum level of $25(OH)_2D_3$ into 3 groups according to the classification given by the US Endocrine Society[20]: deficient <20 ng/mL, insufficient 20-30 ng/mL and sufficient >30 ng/mL. After discussing with parents and getting written consent, blood samples were taken in the morning following an overnight fast to measure serum $25(OH)_2D_3$. All subjects gave written informed consent to the use of their health records for analysis. This study was approved by The Research Deputy and Ethics Committee of Shahid Beheshti University of Medical Sciences and Health Services (IR.SBMU.MSP.REC.1391.5), and was conducted in accordance with the Declaration of Helsinki.

Biochemical analysis

Two cc clotted blood sample were taken from the patient and immediately centrifuged for evaluation of serum level of $25(OH)_2D_3$. ELISA method used to evaluate $25(OH)_2D_3$ level. Devices which used was from Biotech, America, furthermore; Euro immune kit, Germany was the main kit in this study.

Anthropometric indices measurement

Weight was assessed with a digital scale (Beurer, GS49, Germany), and only light clothing was allowed. Height was measured using an inflexible measurement tape with a precision of 0.1 cm, with subjects asked to stand erect without shoes and socks. Weight was measured using a portable digital scale with a precision of 0.1 kg. Subjects were asked to wear light clothing. Body mass index (BMI) was calculated on admission by measuring height and weight (kg/height $[m^2]$).

Statistical analysis

Data were analysed by using SPSS 25 (SPSS Inc, Chicago). Means and standard deviations were used to summarize continuous variables that were normally distributed. The normality of 25-hydroxy vitamin D levels was checked by Kolmogorov–Smirnov test, which used non-parametric tests because *P*-value was less than .05. Statistically significant differences were tested for quantitative items by Mann–Whitney and Kruskal–Wallis tests and for qualitative items by Fisher's exact and χ^2 tests. Multinominal regression analysis was made to evaluate the relative risk for each variable.

Results

The clinical characteristics of the study group are shown in Table 1. Three hundred and eighty-four healthy children and adolescents (220 females; 164 males) were enrolled in this study. Their age was 7 to 16 years old (mean ± SD: 11 ± 2.5). Vitamin D deficiency was found in 49% of the total cases and was significantly more prevalent in females than males (33.1% in females; 15.9% in males, $P < .001$). Table 2 illustrates the characteristic of subjects according to vitamin D status. The total level of vitamin D was significantly lower in females than in males (16.8 ± 15.3 vs 20.5 ± 14.9) ($P < .001$). The mean level of vitamin D in vitamin D deficient subjects was also significantly lower in females than males (7.9 ± 2.8 vs 8.8 ± 3.5) ($P = .026$), but the difference was not significant in sufficient and insufficient groups. There was no significant difference between mean serum levels of vitamin D in different age groups. There was no statistical correlation between total vitamin D level with height (P-value: 0.144) and weight percentiles (P-value: 0.106). In the vitamin D deficient group, vitamin D was significantly higher in weight percentile <3% ($P = .045$). Total $25(OH)_2D_3$ level was significantly higher in Tanner stage I (mean ± SD: 22.7 ± 15.7) ($P < .001$) and lower in Tanner stage V (mean ± SD: 14.6 ± 13.8) ($P < .001$), and it had inverse relationship with BMI percentile ($P = .023$). Table 3 illustrates the mean vitamin D status according to the obese and non-obese groups' pubertal stage. Mean vitamin D level was lower in obese children compared with non-obese ($P < .001$). The non-obese group had significantly higher vitamin D levels in Tanner stage IV than obese individuals (20.1 ± 17.0 vs 5.4 ± 2.0) ($P = .03$). We found differences in vitamin D levels in Tanner stage II−V with regards to Tanner stage I in both obese and non-obese groups ($P < .001$). Vitamin D levels were significantly lower in females than males only in Tanner stage II (12.3 ± 9.0 vs 19.6 ± 16.6) ($P = .005$). The lowest level of Vitamin D was in Tanner stage IV−V in boys and Tanner II-III in girls ($P < .001$) (Table 4). Relative risk for Vitamin D deficiency reported in Table 5. Female gender, age, puberty and winter season estimated as risk factor for vitamin D deficiency, which could be also found in Figure 1.

Discussion

In this study, we evaluated the vitamin D status in 384 healthy children and adolescents. The prevalence of vitamin D deficiency

Table 1. Characteristic of the study subjects.

	CHARACTERISTIC	FEMALE	MALE	P-VALUE	TOTAL
		N: 220	N: 164		N: 384
Vitamin D status	Deficient	127 (33.1%)	61 (15.9%)	<.001	188 (49%)
	Insufficient	63 (16.4%)	69 (18%)		132 (34.4%)
	Sufficient	30 (7.8%)	34 (8.9%)		64 (16.7%)
Age	7.0-10.99	150 (68.2%)	61 (37.2%)	<.001	211 (54.9%)
	11.0-13.99	43 (19.5%)	64 (39%)		107 (27.9%)
	14.0-16.99	27 (12.3%)	39 (23.8%)		66 (17.2%)
Height percentile	<3%	29 (13.2%)	25 (15.2%)	.432	54 (14.1%)
	3%-97%	187 (85%)	133 (81.1%)		320 (83.3%)
	⩾97%	4 (1.8%)	6 (3.7%)		10 (2.6%)
Weight percentile	<3%	24 (10.9%)	17 (10.4%)	.244	41 (10.7%)
	3%-97%	167 (75.9%)	115 (70.1%)		282 (73.4%)
	⩾97%	29 (13.2%)	32 (19.5%)		61 (15.9%)
BMI percentile	<5%	21 (9.5%)	12 (7.3%)	.438	33 (8.6%)
	5%-95%	138 (62.7%)	113 (68.9%)		251 (65.4%)
	⩾95%	61 (27.7%)	39 (23.8%)		100 (26%)
Puberty stage	1	77 (35%)	70 (42.7%)	.51	147 (38.3%)
	2	48 (21.8%)	44 (26.8%)		92 (24%)
	3	34 (15.5%)	25 (15.2%)		59 (15.4%)
	4	17 (7.7%)	9 (5.5%)		26 (6.8%)
	5	44 (20%)	16 (9.8%)		60 (15.6%)
Season	Spring and summer	106 (48.2%)	79 (48.2%)	1.0	185 (48.2%)
	Autumn and winter	114 (51.8%)	85 (51.8%)		199 (51.8%)

was 49% and was more prevalent in girls than boys. Our study demonstrated an inverse relationship between total $25(OH)_2D_3$ level and BMI percentiles. We also evaluated the association between vitamin D level and pubertal stages. Serum level of $25(OH)_2D_3$ decreased after the onset of puberty. Vitamin D was lowest in Tanner stage IV−V in boys and Tanner stage II−III in girls. Girls had lower levels of vitamin D than boys in Tanner stage II. Obese children had lower vitamin D levels in Tanner stage IV and V compared with the non-obese group.

Vitamin D deficiency has been reported with high frequency among Iranian children and adolescents and may be related to insufficient sun exposure, type of clothing, lack of receiving sufficient amount of vitamin D and low physical activity. Like our results, Saki et al[21] conducted a study in southern Iran and showed that vitamin D deficiency was highly prevalent (81.3%) among children and adolescents. In agreement with our study, Moussavi et al[8] and Razzaghy-Azar et al[22] showed that vitamin D deficiency was more frequent in girls than boys.

Puberty is a period of transition from childhood to adulthood, during which thelarche, adrenarche, pubarche, peak height velocity (PHV), and ultimately menarche occurs in girls and gonadarche, pubarche and PHV occur in boys. The mean age of PHV is 11.9 years in girls and 14.2 years in boys.[23] Tanner-stage determined according to Marshall-Tanner criteria, which is based on secondary sexual characteristics, breast stages in girls and genital development by inspection in boys.[19] The categories are divided into 5 main groups including, Tanner Stage I (prepubertal), Tanner Stage II (early puberty), Tanner Stage III (mid-puberty), Tanner Stage IV (mid-puberty) and Tanner Stage V (late puberty/adult).

Peak height velocity occurs in Tanner stage II and IV in most girls and boys respectively.[24,25] Hence, puberty is a crucial time in bone mineral mass development, and vitamin D demand increases in this period.[26] Our study found that

Table 2. Characteristic of subjects according to vitamin D status.

CHARACTERISTIC	TOTAL	VITAMIN D DEFICIENT	VITAMIN D INSUFFICIENT	VITAMIN D SUFFICIENT	P-VALUE
No. of participants	384	188	132	64	
Serum $25(OH)_2D_3$	18.4 ± 15.2	8.2 ± 3.1	19.8 ± 4.3	45.5 ± 16.5	<.001
Sex					
Female	16.8 ± 15.3	7.9 ± 2.8	20.2 ± 4.2	47.6 ± 18.2	<.001
Male	20.5 ± 14.9	8.8 ± 3.5	19.4 ± 4.4	43.7 ± 14.9	<.001
P-value	<.001	.026	.272	.303	
Age					
7-10	20.1 ± 16.8	8.0 ± 2.9	20.0 ± 4.4	47.5 ± 16.9	<.001
11-14	16.1 ± 11.5	8.1 ± 3.3	19.6 ± 4.3	40.3 ± 9.3	<.001
14-16	16.6 ± 14.4	8.7 ± 3.2	19.3 ± 4.0	43.5 ± 22.0	<.001
P-value	.180	.490	.789	.298	
Height percentile					
<3%	18.8 ± 17.8	7.5 ± 3.5	21.5 ± 4.9	64.6 ± 22.1	<.001
3%-97%	18.6 ± 15.1	8.2 ± 3.0	19.4 ± 4.1	43.9 ± 15.2	<.001
⩾97%	10.2 ± 3.9	9.3 ± 2.8	18.5		.200
P-value	.144	.303	.193	.023	
Weight percentile					
<3%	20.8 ± 16.1	9.7 ± 2.8	20.9 ± 4.7	52.2 ± 9.3	<.001
3%-97%	18.4 ± 14.6	7.9 ± 3.3	19.6 ± 4.3	44.3 ± 15.2	<.001
⩾97%	16.8 ± 17.2	8.3 ± 2.4	19.5 ± 3.6	46.5 ± 25.1	<.001
P-value	.106	.045	.585	.095	
BMI percentile					
<5%	22.5 ± 15.3	9.1 ± 3.0	22.2 ± 4.7	50.1 ± 8.1	<.001
5%-95%	18.2 ± 14.1	8.2 ± 3.5	19.5 ± 4.3	44.5 ± 14.4	<.001
⩾95%	17.6 ± 17.5	7.9 ± 2.0	19.2 ± 3.8	46.0 ± 22.2	<.001
P-value	.023	.252	.090	.219	
Puberty stage					
1	22.7 ± 15.7	8.9 ± 2.9	19.8 ± 4.3	45.9 ± 15.2	<.001
2	15.8 ± 13.6	8.5 ± 3.3	20.1 ± 4.3	41.2 ± 18.5	<.001
3	16.6 ± 15.2	7.4 ± 3.1	18.5 ± 5.0	46.8 ± 14.3	<.001
4	16.0 ± 15.2	7.1 ± 3.7	23.3 ± 3.3	51.5 ± 6.7	<.001
5	14.6 ± 13.8	8.2 ± 2.6	19.2 ± 3.7	47.8 ± 29.2	<.001
P-value	<.001	.133	.092	.294	
Season					
Spring and summer	19.7 ± 17.7	8.1 ± 3.2	19.1 ± 4.1	46.6 ± 19.2	<.001
Autumn and winter	17.1 ± 12.4	8.3 ± 3.0	20.3 ± 4.4	43.6 ± 10.8	<.001
P-value	.385	.601	.084	.912	

Table 3. Mean vitamin D status according to the pubertal stage in obese and non-obese groups.

PUBERTAL STAGE	OBESE GROUP		NON-OBESE GROUP		P-VALUE
	NO.	$25(OH)_2D_3$ MEAN ± SD	NO.	$25(OH)_2D_3$ MEAN ± SD	
1	39	22.7 ± 19.3	96	22.9 ± 14.4	.373
2	35	16.7 ± 18.1	55	15.3 ± 10.3	.358
3	7	18.3 ± 18.4	51	16.4 ± 15.1	.583
4	6	5.4 ± 2.0	17	20.1 ± 17.0	.030
5	13	9.9 ± 5.6	47	15.9 ± 15.2	.054
Total	100	17.6 ± 17.5	266	18.6 ± 14.4	<.001
P-value	<.001		<.001		

Table 4. Mean vitamin D status according to the pubertal stages in males and females.

PUBERTAL STAGE	MALE		FEMALE		P-VALUE
	NO.	$25(OH)_2D_3$ MEAN ± SD	NO.	$25(OH)_2D_3$ MEAN ± SD	
1	70	23.2 ± 14.5	77	22.2 ± 16.9	.410
2	44	19.6 ± 16.6	48	12.3 ± 9.0	.005
3	25	20.6 ± 15.9	34	13.6 ± 14.2	.068
4	9	12.3 ± 9.8	17	17.9 ± 17.4	.458
5	16	15.4 ± 9.0	44	14.3 ± 15.3	.176
Total	164	20.5 ± 14.9	220	16.8 ± 15.3	<.001
P-value	.030		<.001		

Table 5. Relative risks for vitamin D deficiency and insufficiency.

VARIABLE	DEFICIENCY		INSUFFICIENCY	
	RELATIVE RISK [95% CI]	P VALUE	RELATIVE RISK [95% CI]	P VALUE
Female	2.360 [1.325, 4.206]	.004	1.035 [0.569, 1.882]	.911
Age	1.186 [1.055, 1.334]	.004	1.066 [0.943, 1.206]	.306
Obesity	1.203 [0.969, 1.493]	.095	0.881 [0.700, 1.170]	.277
Puberty stage	1.518 [1.210, 1.903]	<.001	1.087 [0.854, 1.386]	.497
Winter and autumn season	1.854 [1.037, 3.316]	.037	2.262 [1.226, 4.174]	.009

vitamin D level was lower in girls in Tanner stage II and III, and boys in Tanner stage IV and V. This may be due to pubertal growth spurt in these stages. Cediel et al[18] conducted a cohort study in Santiago, Chile. In agreement with our results, they found that there is a significant decline in serum $25(OH)_2D_3$ level between prepuberty (Tanner stage 1) and puberty onset (Tanner stage 2) in both boys and girls.

Obesity is associated with early puberty due to elevated leptin level, which have a permissive effect on puberty and pubertal growth.[27] There is an association between increasing BMI

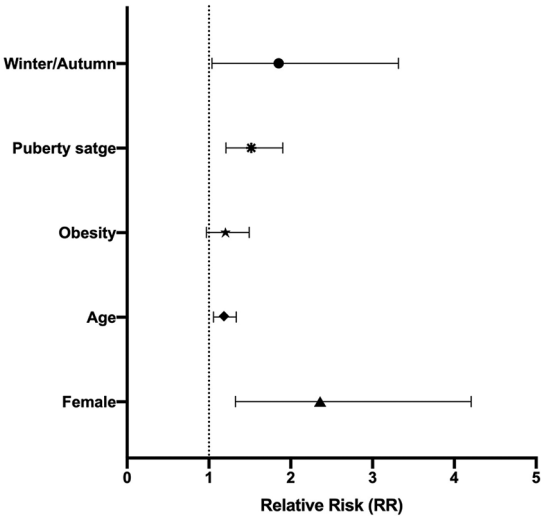

Figure 1. Relative risk for vitamin D deficiency.

and lower serum 25-hydroxyvitamin D3 concentrations[28]; this may be due to reduced cutaneous synthesis and intestinal absorption, altered metabolism and sequestration of $25(OH)_2D_3$ in adipose tissue in obese individuals.[29] Vitamin D receptors (VDR) are present on human adipocytes, and $25(OH)_2D_3$ appears to influence lipogenesis, lipolysis, adipogenesis and reducing adipose tissue inflammation.[30-33] Besides, low vitamin D status can lead to obesity due to secondary hyperparathyroidism and an increase in intracellular calcium.[34,35] Moreover, there are evidences that vitamin D supplementation may prevent obesity.[32,35]

Similar to our findings, Reis et al,[36] in a study of 3377 adolescents, found significantly low levels of vitamin D in subjects with BMI percentile >95. Another study done by Gutiérrez Medina et al[37] showed that vitamin D deficiency was more prevalent in obese children. Razzaghy-Azar et al[22] conducted a cross-sectional study in Iran, Tehran. They showed that vitamin D deficiency was more prevalent in females than males, and the serum level of $25(OH)_2D_3$ decreased after the onset of puberty. Moreover, they found a negative correlation between serum level of $25(OH)_2D_3$ and BMI-SDS, similar to our observations. Another cross-sectional, conducted by Gutiérrez Medina et al,[37] reported a higher vitamin D deficiency in the pubertal group than the prepubertal group. In constant with our results, they found lower levels of vitamin D in pubertal obese subjects compared with their prepubertal counterparts.

In this study, we indicated that there is no significant difference in vitamin D levels according to seasonal changes. In agreement with our results, several studies showed that the prevalence of vitamin D deficiency did not differ by seasonal changes and remained stable even in sunny climates.[38-40] Accordingly, it could be emphasized that seasonal variations do not reduce vitamin D levels significantly, and other factors are also contributed between changes in vitamin D levels over different seasons.

Our study has several limitations, such as its cross-sectional nature, the absence of a nutritional survey, and the absence of data about exercise and sun exposure.

Conclusion

Vitamin D deficiency is common among Iranian children and adolescents despite the sunny climate. This study demonstrated that puberty is an additional risk factor for vitamin D deficiency, especially in girls and obese children. This increased risk, together with the fact that the most crucial time for building a proper skeleton is during childhood and adolescence, makes it essential to monitor vitamin D in these age groups.

However, further longitudinal studies are required to evaluate the influence of puberty and obesity on vitamin D levels.

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Author Contributions

HS and MS: Study design and Draft revision. AS and AF: Drafting. LB: Data gathering. FAG: Data Analysis.

Ethical Aproval

This study was approved by The Research Deputy and Ethics Committee of Shahid Beheshti University of Medical Sciences and Health Services (IR.SBMU.MSP.REC.1391.5), and was conducted in accordance with the Declaration of Helsinki.

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