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Original Article

Suboptimal Vitamin D Status Despite Supplementation in Children with Cystic Fibrosis and Its Association with Growth Indices

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ABSTRACT

Background and Objectives: Vitamin D deficiency is prevalent in patients with cystic fibrosis. However, possible effects of vitamin D deficiency on growth of children with cystic fibrosis is still unclear. The aim of this study was to assess vitamin D status and its associations with growth indices in cystic fibrosis children.

Materials and Methods: This cross-sectional descriptive study was carried out on registered cystic fibrosis patients residing in West Azerbaijan Province, Iran. Demographic, anthropometric and dietary assessments were carried out as well. The growth indicators, including weight-for-age, length-for-age, weight-for-length and body mass index-for-age Z-scores and percentiles, were assessed based on recommendations by World Health Organization and Centers for Disease Control and Prevention. Vitamin D status was assessed using serum 25-hydroxycalciferol [25(OH)D3] assay and concentrations of less than 20 and 20–30 ng/ml were considered deficiency and insufficiency, respectively.

Results: A total of 38 cystic fibrosis patients aged 91.7 m ±62.6 were enrolled in the study. Numbers of participants with no supplementation, insufficient (< 400 IU [< 1 y] and < 800 IU [> 1 y]) and sufficient supplementation were 12 (31.6%), 12 (31.6%) and 14 (36.8%), respectively. However, frequency of vitamin D insufficiency and deficiency was 30 (78.9%). Positive correlations between serum concentration of (25(OH)D3) and weight-for-age and body mass index for age Z-scores were reported. Based on body mass index for age percentile, healthy weight participants had higher serum concentrations of (25(OH)D3), compared to underweight patients (28.8 ±11 against 20.9 ±3.4; $p < 0.05$).

Conclusions: This study revealed that supplementation could improve serum concentrations of (25(OH)D3); however, rate of vitamin D insufficiency was high (64%)even in sufficiently supplemented participants. Appropriate supplementation and maintaining desired levels of 25(OH)D3 may have beneficial effects on cystic fibrosis patients' growth.

Keywords: Cystic fibrosis, Vitamin D, Growth, Children

Introduction

Cystic Fibrosis (CF) is a lethal recessive autosomal inherited disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on the long arms of Chromosome 7 with widespread prevalence in Caucasian populations. Cystic fibrosis is responsible for premature deaths and shortened lifespans. The major organ systems affected in CF patients include pulmonary, digestive and reproductive systems [1]. Up to date, myriads of mutations have been reported, which lead to diminished or attenuated function of CFTR protein. Defects in CFTR protein preclude chloride and subsequently water from passing across mucus-producing cells, which leads to thick sticky mucosa [2]. Mucociliary clearance failure results in numerous infections and subsequent immune responses. In digestive system, gall bladder and pancreas obstructions by abnormal mucosa result in poor nutritional statuses in CF patients [3].

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Vitamin D deficiency is widely seen in patients with CF due to the malabsorption of nutrients as a result of pancreatic insufficiency [4, 5]. Vitamin D includes several important roles in bone and skin health as well as immune responses. Moreover, patients with pulmonary infectious diseases show low levels of vitamin D [6]. Preliminary data have suggested that vitamin D deficiency is associated with decreased lung function. Optimal vitamin D is essential for achieving effective anti-microbial responses and avoiding exaggerated immune responses in CF patients. This may be beneficial in improving CF adverse outcomes and delaying its progression [7]. Because of vitamin D sufficiency benefits, European and American guidelines (2016) have recommended that daily intakes of vitamin D for CF patients aged < 1, 1–10 and > 10 years old should be 400, 800 and 800 IU, respectively. Despite vitamin D supplementation based on the highlighted recommendations, one-third of the CF cases did not reach the sufficient levels [8].

Inappropriate growth in CF young patients has been a serious challenge and is strongly associated with inappropriate lung function and malnutrition [9]. Vitamin D is a critical contributor to appropriate growth not only due to its roles in the metabolism of calcium and phosphorous and skeletal growth, but also because of its possible interactions with growth hormones. However, relationships between vitamin D and undernutrition indices are still controversial [10]. From the studies, it can be hypnotized that patients with optimal levels of vitamin D may have appropriate growth indices. Nowadays, no investigations are available in West Azerbaijan Province, Iran, on assessing serum levels of vitamin D in young CF patients and their relationships with growth indices. Therefore, the aim of this cross-sectional study was to investigate nutritional status of vitamin D in young patients with CF and its associations with growth indices, West Azarbaijan Province, Iran, 2021.

Materials and Methods

Study population

This cross-sectional study was carried out on registered CF patients of West Azerbaijan Province, Iran, winter 2021. The CF patients were diagnosed using sweat test. Results of sweat chloride of 60 mM per litter or higher indicated a diagnosis of CF [11]. This study included CF patients aged 6 m to 20 y old (n = 40). Of all the participants, two cases were excluded due to simultaneous CF disease and celiac. The other participants (n = 38) did not have any serious underlying diseases (e.g., acute inflammation, cancer, diabetes, gastrointestinal diseases and pulmonary diseases). Patients did not receive corticosteroids.

Ethics

This study was approved by the Ethics in Medical Research Committee of Urmia University of Medical Sciences (Reference no. IR.UMSU.REC.1399.272). Written informed consents were received from all participants or their legally authorized representatives. This study was carried out in accordance with the Declaration of Helsinki.

Data collection and anthropometric measurements

Data on occupational status, number of family members and CF familial history were collected using questionnaires. Height and weight were measured by trained medical staff using calibrated weighting scale with the precision of 0.1 Kg. Adult participants were asked to stand on the center of the scale with their arms hanging loosely at their sides. Adult weight measurements were carried out based on NIHR Southampton Biomedical Research Centre procedures. Baby weighting scale was used for children under two years old. The weighting process was carried out three times for each participant until differences between the three records were less than 100 g. The average of three records was recorded. Participants wore light clothes with no shoes during weighting. For height measurements in adults, they were asked to stand on the stadiometer with faces forward. Adult height measurements were carried out based on NIHR Southampton Biomedical Research Centre procedures. Recumbent length (less than two years old) was measured using length board. Participants were asked to lie down and a distance from the top of the head to the soles (heels) of the feet was measured by two trained people. Body mass index (BMI) was calculated using weight (kg) divided by squared height (m) [12].

Blood sampling and vitamin D assessment

Blood samples were collected into clot activator tubes on the day of the primary interviews. Tubes were set for 30 min at room temperature (RT). Then, tubes were centrifuged at 4000 rpm for 10 min. Supernatants were transferred into 1 ml vials and stored at -20 C until use. The 25(OH)D3 was assessed using commercial ELISA kit according to the manufacturer's instructions (Diasource, Belgium). To ensure correct analytical assessments, all standards, controls (including low and high levels) and specimens were assessed in duplicates. Standard curve was generated using plotting of mean absorbance of each standard against concentration.

Dietary assessment

To assess nutritional intakes, 24-h recall method was used for all cases within 3 d. Nutritionist IV Software v.7.0 (N-Squared Computing, Salem, OR, USA) modified for Iranian food items was used to assess quantities of the vitamin D intakes [13]. Participants or their legal guardians were asked to interview for carrying out the first 24-h recall at the sampling day. The second and third recalls were carried out by the researchers using phone calls [14]. To eliminate possible bias, the second recall was carried out on non-holiday days, while the third recall was carried out on

holidays. Information on the use of vitamin and mineral supplements were achieved using questionnaires. The nutrient content and dose of each supplement were used to calculate intakes of the supplemental vitamin D.

Vitamin D supplementation and serum levels of vitamin D

Patients were categorized into three groups, including no supplementation, insufficient and sufficient supplementation groups [8]. In no supplementation group, participants did not receive any vitamin D supplements; in Insufficient supplementation group, participants received supplements of less than 400 IU for those < 1-year-old and less than 800 IU for those > 1-year-old; and in sufficient supplementation group, participants received supplements of greater than 400 IU for those < 1-year-old and greater than 800 IU for those > 1-year-old. The following classification was used to classify the patients: 1) vitamin D deficiency with serum level of vitamin D less than 20 ng/ml; 2) vitamin D insufficiency with serum level of vitamin D 20–30 ng/ml; and 3) vitamin D sufficiency with serum level of vitamin D >30 ng/ml.

Growth indices

For growth assessment, weight-for-age (WFA), length-for-age (LFA), weight-for- length (WFL) and BMI-for-age (BFA) percentiles and Z-scores were calculated based on World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommendations. Anthro Software v.3.2.2 was used to collect growth indices for participants whose ages were under 60 m based on WHO criteria [15]. AnthroPlus Software v.1.0.4 was used for participants of 5–19 years old [16]. Growth indices for participants of 2–20 years old were calculated using UpToDate Software based on CDC recommendations. For participants under two years old, weight-for-age and height-for-age percentiles were measured using MedSacpe Software.

Statistical analysis

Statistical analyses were carried out using SPSS Software v.22 (IBM, USA). Demographic information were summarized using descriptive statistics. Mann-Whitney U test and independent T-test were used for the evaluation of differences in quantitative variables. Chi-square and Fisher's exact tests were used for the evaluation of differences in categorical variables.

Results

In this study, 38 CF young patients participated. Frequencies of males and females were 21 (55.3%) and 17 (44.7%), respectively. The youngest and the oldest participants were eight and 227 months old, respectively. The mean ±SD (standard deviation) of age for the participants was 91.7 m ±62.6. Nine participants were reported with familial history of CF. Table 1 contains demographic and baseline characteristics of the participants. Based on WHO and CDC recommendations, mean ±SD of WAZ (weight for age Z-score), HAZ (height for age Z-score) and BAZ (BMI for age Z-score) are listed in Table 2. Based on WHO and CDC recommendations, the median [IQR; 25%, 75%] percentiles for weight were 28.3 [6.1,57.8] and 22.3 [4.1, 54.1], respectively.

Table 1. Demographic and baseline characteristics of the participants

Variable		Frequency
Age	<12 months	3 (7.9%)
	>12 months	35 (92.1%)
Gender	male	21 (55.3%)
	Female	17 (44.7%)
CF familial history	yes	9 (23.7%)
	no	29 (76.3%)
Number of family members	≤3	7 (18.4%)
	>3	31 (91.6%)
Mother's education	Illiterate	5 (13.2%)
	Under diploma	18 (47.4%)
	Diploma or associate degree	9 (23.7%)
	Bachelor's degree	3 (7.9%)
	Master's or doctoral degree	3 (7.9%)
Father's education	Illiterate	2 (5.3%)
	Under diploma	18 (47.4%)
	Diploma or associate degree	11 (28.9%)
	Bachelor's degree	4 (10.5%)
	Master's or doctoral degree	3 (7.9%)
Father's occupation	Employee	9 (23.7%)
	Self-employed	29 (76.3%)
Mother's education	Employee	2 (5.3%)
	Housewife	36 (94.7%)

Table 2. WAZ, HAZ and BAZ based on WHO and CDC recommendations

Recommendations		Z-score[a]	Percentile[b]
WHO (n=27)		-0.54±1.6	28.3 [6.1,57.8]
CDC (n=38)	Wight for age	-0.9±1.6	22.3 [4.1, 54.1]
WHO (n=38)		-0.25±1.6	44.7 [9.9,74]
CDC (n=38)	Height for age	-0.16±1.6	40.8 [11.3, 74.8]
WHO(n=38)		-0.97±2.2	12.4 [1.5, 52.8]
CDC(n=33)	BMI for age	-1.63±2.4	26.5 [6, 51.4]

[a] data were represented as the mean±SD; [b] Data were represented as Median [IQR;25%, 75%].

Table 3. Distribution of cystic fibrosis patients based on growth indices recommended by WHO and CDC

Based on WHO recommendations		
Variable		Frequency
Weight for age percentile	Underweight	**6 (22%)**
	Healthy weight	19 (70.3%)
	Overweight and obesity	**2 (7.4%)**
Height for age percentile	Short stature	9 (23.6%)
	Normal stature	**24 (63.1%)**
	Tall stature	5(13.1%)
BMI for age percentile	Underweight	**11 (28.9%)**
	Healthy weight	22 (57.8%)
	Overweight and obesity	**5 (13.1%)**
Based on CDC recommendations		
Variable		Frequency
Weight for age percentile	Underweight	10 (26.3%)
	Healthy weight	26 (68.4%)
	Overweight and obesity	2 (5.3%)
Height for age percentile	Short stature	7 (18.4%)
	Normal stature	23 (60.5%)
	Tall stature	8 (21.1%)
BMI for age percentile	Underweight	12 (36.4%)
	Healthy weight	17 (51.5%)
	Overweight and obesity	4 (12.1%)

Table 3 shows distribution of CF patients based on growth indices recommended by WHO and CDC. Regarding weight-for-age percentile based on CDC recommendations, proportions for underweight, healthy weight and obese participants were 10 (26.3%), 26 (68.4%) and 3 (5.3%). Numbers of short, normal and tall participants based on height-for-age percentile (CDC recommendations) were seven (18.4%), 23 (60.5%) and eight (21.1%), respectively. Frequencies of underweight, healthy weight, overweight and obesity participants based on BMI for age percentile (CDC recommendations) were 12 (36.4%), 17 (51.5%) and four (12.1%), respectively. Proportions of the growth indices based on WHO recommendations were similar to those based on CDC recommendations.

The mean (±SD) of serum 25(OH)D3 concentration for the participants was 25.9 (9.8) ng/ml. Number of CF patients with 25(OH)D3 insufficiency and deficiency [25(OH)D < 30 ng/ml] was 30 (78.9%). Numbers of participants with no supplementation and insufficient and sufficient supplementations were 12 (31.6%), 12 (31.6%) and 14 (36.8%), respectively. The median 25(OH)D3 intake from food sources (achieved from recalls) was 17.9 (8.5, 34.8) IU/d. As illustrated in Figure 1, participants with sufficient supplementation represented higher levels of serum 25(OH)D3, compared to those without supplementation ($p < 0.05$).

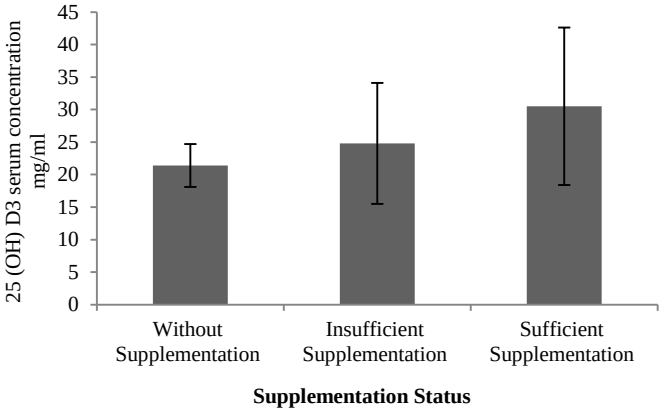


Figure 1. Serum levels of 25(OH)D3 in cystic fibrosis patients with no supplementation and insufficient and sufficient supplementations

Although serum 25(OH)D3 level in participants with sufficient supplementation was higher than that in participants with insufficient supplementation with no significant differences (p = 0.37). Significant correlations were seen between the quantities of vitamin supplements and serum 25(OH)D3 concentration in CF patients (r_p = 0.56, p < 0.010) (Figure 2). Rates of serum vitamin D deficiency (vitamin D < 20 ng/ml) in participants with no supplementation and insufficient and sufficient supplementations were 41.6, 25 and 0%.

Figure 3 demonstrates that WAZ was positively correlated with serum levels of vitamin D (r_p = 0.53; p = 0.005), based on WHO recommendations. Similarly, WAZ was correlated with vitamin D levels in CF patients with less than ten years old based on CDC recommendations (r_p = 0.49; p = 0.009) (Figure 4). Weight for age percentile were positively correlated with vitamin D levels in CF patients with age less than ten years old, based on WHO and CDC recommendations. Positive correlations between vitamin D and BAZ were shown in CF patients (age < 10 years old), based on WHO recommendations (Figure 5). Based on weight for age percentile, underweight participants had lower levels of serum 25(OH)D3, compared to participants with healthy weight (20 ±4.1 against 27.4 ±10.2; p < 0.05) (Figure 6). Overweight and obese participants showed higher levels of 25(OH)D3, compared to healthy and underweight participants. No significant differences were detected in levels of serum 25(OH)D3 in participants with short, normal and tall heights (p > 0.05). Based on BMI-for-age percentiles, healthy-weight participants had higher levels of serum 25(OH)D3 in contrast to underweight participants (28.8 ±11 against 20.9 ±3.4; p < 0.05).

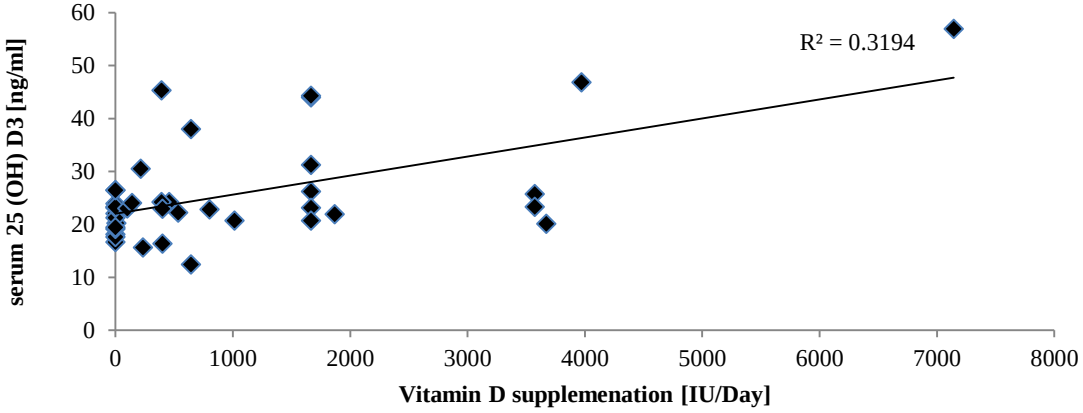


Figure 2. Correlations between serum 25(OH)D3 and vitamin supplementation

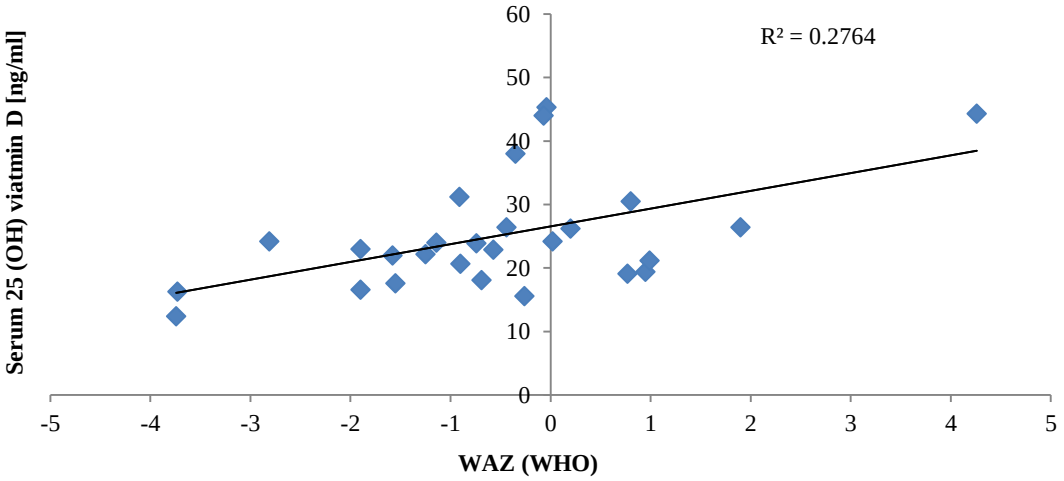


Figure 3. Correlations between serum 25(OH)D3 and weight-for-age Z-scores based on WHO recommendations

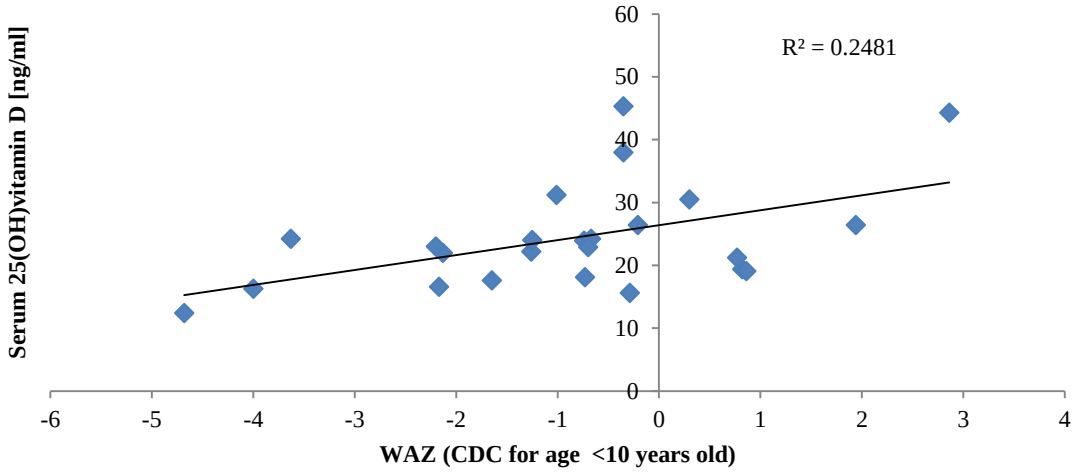


Figure 4. Correlations between serum 25(OH)D3 and weight-for-age Z-scores based on CDC recommendations in participants less than ten years old

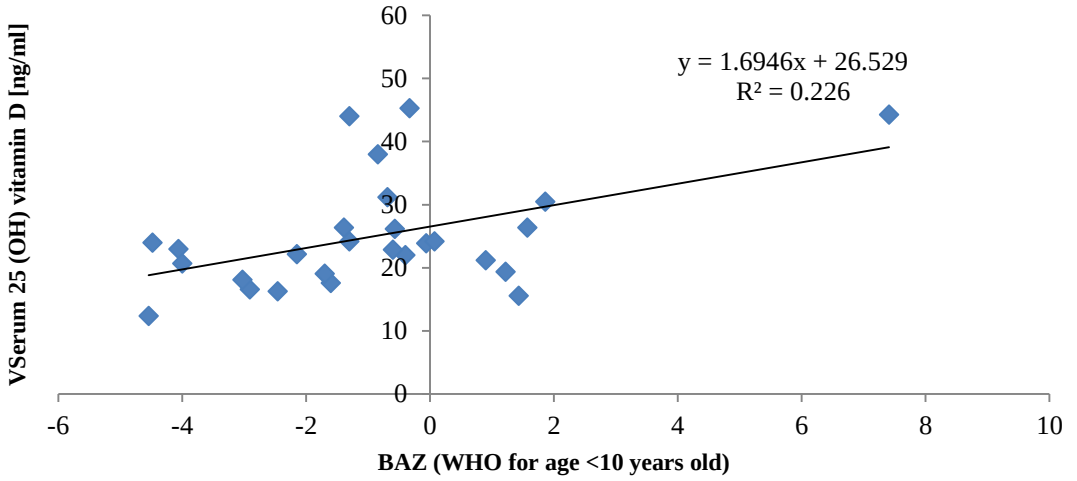


Figure 5. Correlations between serum 25(OH)D3 and BMI-for-age Z-scores based on WHO recommendations in participants less than ten years old

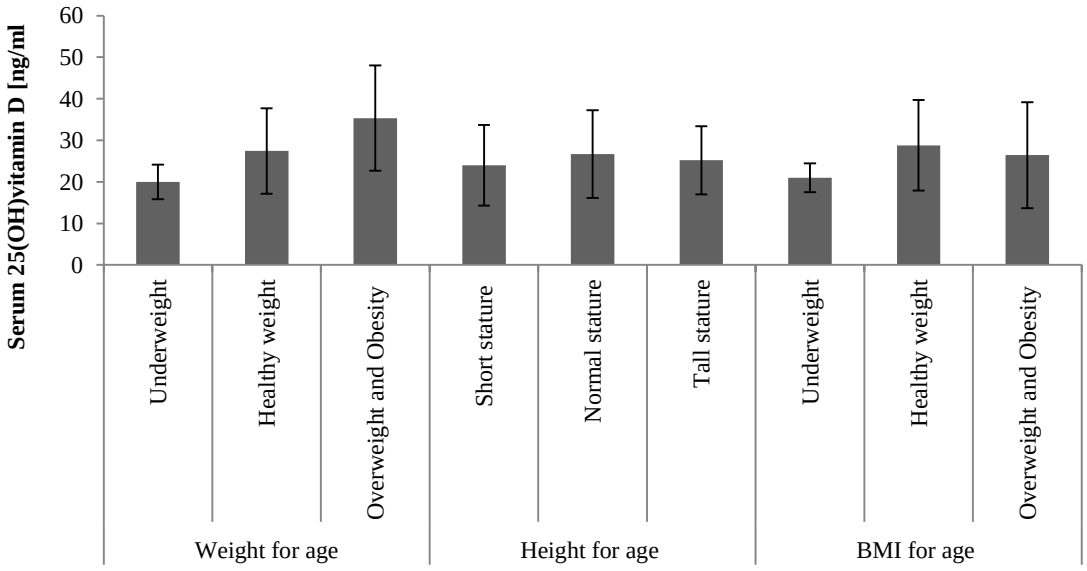


Figure 6. Vitamin D levels in various classifications based on the growth indices

Discussion

Dietary sources for vitamin D are limited and unable to meet the body needs, especially in winters when the sun exposure is not high enough to trigger vitamin D synthesis in the skin. Therefore, vitamin D deficiency has been a major threat to public health even in healthy people [17]. In this cross-sectional study, majority of patients with CF (78.9%) were reported to have vitamin D deficiency and insufficiency. Similar to the current study, other studies on CF patients have shown that vitamin D deficiency/insufficiency is a prevalent phenomenon, ranging 23–95% [18-21]. Grey et al. showed that the prevalence of inadequate 25(OH)D status in the North American pediatric CF population was 95% [22].

The present findings revealed that participants without supplementations had lower levels of vitamin D (21.4 ±3.3) in contrast to those with insufficient (24.8 ±9.3) and sufficient (30.5 ±12.1) supplementations. In this study, correlations were detected between serum vitamin D levels and vitamin D supplementation statuses. Rates of sufficient vitamin D (> 30 ng/ml) in CF participants without supplementations and with insufficient and sufficient supplementations included 0, 25 and 36%, receptively. Another study reported that even with appropriate supplementation (800 IU/d), 90% of CF participants represented insufficient levels of vitamin D. In the current study, rate of insufficient levels of vitamin D in participants with sufficient supplementation was 64%. Brodlie et al. demonstrated that even with increasing vitamin D supplementation by > 450%, 50% of CF patients did not reach vitamin D sufficient levels [20]. Hence, a majority of CF patients in the present study had vitamin D deficiency and insufficiency. Although supplementation could increase vitamin D levels, it was not adequate to guarantee optimal levels of vitamin D in these patients.

Studies have verified that patients with CF have inappropriate growth rates [23]. A study by Henderson et al. showed that the mean ±SE (standard error) weight Z-score was -0.70 ±0.11 and the mean height Z-score was -0.66 ±0.15. Their study represented deficits in bone minerals for the CF patients [24]. In the present study, WAZ and HAZ were similar to those reported by Henderson et al. Based on a study by Lai et al. mean weight and height percentiles for patients with CF in the United States were 23.3 and 27%, respectively. Proportions of underweight and short height patients with CF were 32.2 and 30.3%, respectively [25]. In the current study, the median weight and height percentiles included 22.3 and 40.7%. Moreover, it was investigated that proportions of underweight and short height patients with CF were 26.3 and 18.4%, respectively. Rates of underweight and short height were lower in the present study than that in Lei et al. study. Differences might be due to the time of study. Their study was carried out on CF patients, 1992–1994. However, treatment and supplementation approaches have been changed since that time.

A major finding of the current study was that serum vitamin D levels were correlated with WAZ based on WHO and WAZ based on CDC for patients with age under ten years old. Vitamin D levels were significantly higher in healthy weight and obese CF patients than underweight CF patients. In contrast, no differences were observed in CF patients with short, normal and tall heights. Ongaratto et al. could not detect correlations between serum vitamin D and nutritional status (BMI Z-score, H/A Z-score)[26]. Due to the low number of participants with CF and lack of screening program in West Azerbaijan Province for identifying new patients, the present study sample size was small. Another limitation included use of ELISA instead of gold standard measurement method of vitamin D or high performance liquid chromatography (HPLC). In general, number of studies assessing associations of vitamin D with nutritional and growth indices are limited. Further studies with larger sample sizes are needed to generalize the current findings.

Conclusions

This cross-sectional study revealed that a majority of CF participants (78.9%) had serum vitamin D deficiency and insufficiency. The highest rate of vitamin D deficiency was observed in CF patients, who did not receive supplementations. Although no participants with appropriate supplementation were reported to have deficient levels of vitamin D, rate of vitamin D insufficiency was 64.2%. Positive correlations between the serum vitamin D and BAZ and WAZ, based on WHO and CDC recommendations in CF patients (age < 10 years old). Healthy-weight CF patients represented higher levels of serum vitamin D in contrast to under-weight participants based on CDC recommendations. The present study revealed that CF patients with sufficient supplementation did not reach the target value of serum vitamin D (> 30 ng/ml). However, supplementation significantly decreased the number of vitamin D deficient participants. In conclusion, appropriate supplementation and maintaining desired levels of vitamin D may include beneficial effects on growth of CF patients.

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