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The Relationship between Bone Mineral Density and Serum Vitamin D Levels in Cystic Fibrosis Children

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Abstract

Background: Cystic fibrosis is a multisystemic disorder. It is the most common autosomal recessive disorder in whites that causes complications such as changes in bone density. Therefore, evaluating bone densitometry and serum levels of vitamin D in children with cystic fibrosis is the aim of our study.

Methods: This study was performed on 54 children with cystic fibrosis. After recording demographic information, bone densitometry and serum levels of vitamin D were recorded. Chi-square and Pearson correlation tests were used to compare data.

Results: Based on our study 53.7% of patients with CF had vitamin D less than 20 nmol / l. It was also found that based on lumbar BMD, 20.3% had a BMD less than 2.5 - Based on femoral BMD, 18.5% had a BMD less than -2.5. And our results demonstrated that there is no relation between BMD with vitamin D, calcium and phosphorus but it is significantly correlated with age, height, weight, and BMI.

Conclusion: Decreased BMD is high in patients with CF; on the other hand there is a deficiency of vitamin D in more than 50% of these patients to whom vitamin D supplements should be prescribed along with the standard treatments. Further studies are also required to investigate the effect of other factors on BMD.

Key Words: Bone densitometry, Cystic fibrosis, Vitamin D.

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1- INTRODUCTION

Cystic fibrosis (CF (is the most frequent genetic disease among Caucasians. The cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a transmembrane glycoprotein, is mutated (1). Over the previous three decades, life expectancy for cystic fibrosis (CF) has increased from about 2 to 32 years (2). Patients with cystic fibrosis (CF) experience a high prevalence of low bone mineral density as their life expectancy increases (3, 4). Low bone density is associated with bone fractures which affect the patients' quality of life (5). Many studies have indicated a decline in bone mineral density (BMD) in children and young adults with cystic fibrosis. Osteopenia is reported to have occurred in 28 to 47 percent of this population and osteoporosis in 20 to 34 percent (5).

Children and adults with cystic fibrosis are increasingly being diagnosed with osteoporosis and fractures (6, 7). Fractures of the ribs and vertebrae can cause severe morbidity in CF patients (8).

Although the exact cause of CF-related bone disease is unknown, patients with CF are at risk for low bone density due to a number of factors, including pancreatic insufficiency, malabsorption, poor nutritional status, vitamin D deficiency, delayed puberty, glucocorticoid use, inflammation, and physical inactivity (9, 10). Vitamin D deficiency is one of the major nutritional factors associated with poor skeletal health in CF patients. The level of 25 (OH) D in the serum is used to evaluate vitamin D status (11). In CF patients, serum 25-hydroxyvitamin D [25(OH)D] levels begin to drop in adolescence (12) The Cystic Fibrosis Foundation and the Endocrine Society established criteria for vitamin D sufficiency (25(OH) D>9 30ng/mL), deficiency (25(OH)D< 20ng/mL), and insufficiency (20 to 29.9ng/mL) (13, 14). The etiology of vitamin D deficiency in CF is multifactorial, including reduced intake, pancreatic insufficiency, poor body fat stores, reduced sunlight exposure, reduced absorption, and decreased vitamin D binding protein (15). According to recent studies, the frequency of vitamin D deficiency in the CF population is as high as 90%. (16). Despite routine supplementation, 7 percent of CF patients had vitamin D deficiency (25(OH) D<11 ng/ml) and 90% had vitamin D insufficiency (25(OH)D<30 ng/ml), based on one study on children (10, 17, 18). Some studies were known about the daily practice of vitamin D intake, vitamin D supplementation, and its connection with serum 25(OH) D in pediatric CF patients (19).Therefore, the aim of this study was to evaluate bone densitometry and serum levels of vitamin D in children with cystic fibrosis.

2- MATERIALS AND METHODS

The participants in this cross-sectional study were 54 children diagnosed with cystic fibrosis, aged between 8 to 18 years who were admitted to Imam Hossein Children's Hospital, affiliated to Isfahan University of Medical Sciences, Iran. Clinical symptoms and two increased sweat chloride tests, as well as CFTR genotyping, were used to confirm the diagnosis of CF. Digital scales were used to record weight, and a stadiometer was used to measure height. Body mass index (BMI) was calculated.

Non-fasting blood samples were drawn for measurement of serum concentrations of 25-hydroxyvitamin D [25(OH)D] by electrochemiluminescence. Also calcium and phosphorus were measured. Dual energy-ray absorptiometry (DXA) scans (The cost of these measurements was borne as part of their routine care) used to determine BMD, and spinal scores were obtained. DXA results were expressed in T-scores, and Z-scores. The T-score was defined as the number of standard

deviations above or below the mean for a healthy 20-year-old adult of the same sex and ethnicity.

Pediatric osteopathy usually is defined on the basis of BMD Z-scores (which are identical to BMD-SDS). We classified our patients on the basis of BMAD-SDS, differentiating the following categories: patients with $-2 \leq$ BMAD-SDS < -1 were classified as osteopenia patients and those with BMAD-SDS < -2 were considered to suffer from osteoporosis. The Z-score was defined as the number of standard deviations a patient's BMD differs from the average BMD of their age, sex, and ethnicity. Osteoporosis is defined as a bone density lower than -2 SDs of the mean BMD of the gender-matched, young healthy population. Osteopenia is an intermediate category of reduced bone density defined as a Z or T score within -1 SD and -2 SD.

2-1. Inclusion and Exclusion Criteria

Inclusion criteria were a clinical diagnosis of CF, age range of 8-18, Exclusion criteria were the use of oral or intravenous glucocorticoids (chronically taking oral glucocorticoids for more than 6 weeks), lung transplantation, severe respiratory failure, immobilization for more than 1 week, cystic fibrosis-related diabetes mellitus (CFRD), liver disease (defined here as either known/proven cirrhosis or portal hypertension).

2-2. Statistical Analysis

Statistical analysis was done by using the Statistical Package for Social Sciences (SPSS) version 24. Both independent samples t-test and paired t-tests were used to compare means depending on the situation. Associations between two or more qualitative or categorical variables were assessed using the chi-square test. Pearson tests were used to determine the correlations between BMD and various clinical variables. Statistical significance was defined as $P < 0.05$.

3- RESULTS

Fifty-four children with CF were enrolled in this study. And 38 were male (70.4%). The average age of the 54 patients was 11.69 ± 3.06 years (range, 8-18 year). Baseline characteristics of the participants are shown in **Table 1**.

Table-1: Characteristics of the patients with cystic fibrosis (CF)

parameter	N=54 (Mean ± SD)
Age(year)	11.69 ± 3.069
Weight(kg)	31.15 ± 11.258
Weight z score	-1.84 ± 1.868
Height(cm)	137.85 ± 17.049
Height z score	-1.41 ± 1.342
BMI	15.88 ± 2.162
BMI z score	-1.25 ± 1.64
Lumbar z score	-1.37 ± 1.416
Femur z score	-1.34 ± 1.318
Phosphorus (mg/dl)	4.52 ± 0.788
Calcium level (mg/dl)	8.64 ± 1.625
25[OH]D levels(ng/ml)	23.5 ± 21.33

Nutritional status was within normal ranges for most subjects (mean BMI Z-score: -1.25 ± 1.64). Mean (SD) serum calcium and phosphate were 8.64 (1.625)

mg/dL and 4.52 (0.788) mg/dL, respectively.

Vitamin D levels were grouped into two classes: sufficient (25(OH)D ≥20ng/mL) and hypovitaminosis (25(OH)D <20ng/mL). The mean serum concentrations of 25(OH) D were 23.5 ± 21.33 ng/ml in the CF patients. Sufficient (25(OH)D ≥20ng/mL) was observed in 46.3% of the sample. Twenty-nine subjects (53.7%) showed 25(OH)D hypovitaminosis (25(OH)D <20ng/mL).

The mean (± SD) BMD z scores of femur and lumbar are listed in **Table 1**. 20.3% of the measured lumbar BMD and 18.5% of the measured femur BMD were less than -2.5. Weight, BMI, and malnutrition significantly correlated with BMD (P<0.05). There was a positive correlation between L1-L4 Z-score and BMI (r = 0.68, P, 0.0001).

Table-2: Comparing the lumbar and femoral BMD z score according to vitamin D levels

parameter	Vitamin D	f	mean	SD	P-value
Lumbar z score	25(OH)D <20ng/mL	29	-1.36	1.545	0.925
	25(OH)D ≥20ng/mL	25	-1.39	1.282	
Femur z score	25(OH)D <20ng/mL	29	-1.35	1.245	0.982
	25(OH)D ≥20ng/mL	25	-1.34	1.424	

No correlation was observed between bone parameter BMD and vitamin D levels (P>0.05).

According to **Table 3**, there was no association between nutritional status of subjects measured by BMI Z-score and vitamin D levels (P>0.05). Weight, height, and BMI significantly correlated with BMD (P<0.05). There was a negative correlation between BMD and age.

4- DISCUSSION

The purpose of this study was to evaluate bone densitometry and serum vitamin D levels in pediatric cystic fibrosis patients with 8 to 18 years of age. In the present study we analyzed 54 CF patients from Isfahan province, center of Iran, Imam Hossein Children's Hospital. 70.4% male and 29.6% female children with the mean age of 11.69±3.06 participated in the study.

According to the results, 53.7% had 25(OH) D concentration <20ng/ml and 46.3%≥ 20ng/ml. In addition, mean lumbar Z-score was -1.37 ± 1.41 and mean femur Z-score was -1.34 ± 1.31.; and it presented no association between vitamin D and BMD.

This study and previously published research data showed that CF patients have low concentrations of vitamin D, indicating that vitamin D is not sufficiently absorbed, even without pancreatic insufficiency, or the current dose of supplementation is not enough to reach the goal of 25 (OH) D concentration. For example, Brodlie et al. (20) measured 25(OH)D in children ≥1 in 2008. They demonstrated an increasing vitamin D3 by >450% and a repeat audit performed in 2010. The increase in supplementation resulted in significant increase in 25(OH)D level but still about half of the participants failed to reach the desired serum level(20). This was also confirmed by our study that 53.7% of children with CF had 25(OH) D less than 20ng/ml.

In another study, Lansing et al. retrospectively evaluated vitamin D deficiency in CF children for 2 years. They concluded that the targeted interventions are needed for pediatric CF patients living in the northern United States to prevent vitamin D deficiency (21). We achieved the same results in Iran, Isfahan province.

Table-3: Correlations between different factors

Variables	Z-score													
	Weight		Height		Femur		BMI		Lumbar		25(OH)Vit D		Phosphorus	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
age	-0/399**	0/003	-0/215	0/119	-0/343*	0/011	-0/348**	0/010	-0/469**	0/000	0/171	0/217	-0/082	0/588
Calcium	-0/020	0/889	-0/014	0/920	0/001	0/994	-0/008	0/954	-0/067	0/635	0/094	0/505	0/528**	0/000
Phosphorus	0/354*	0/016	0/368*	0/012	0/070	0/646	0/160	0/288	0/193	0/198	0/090	0/551	1	1
weight	1	1	0/786**	0/000	0/596**	0/000	0/840**	0/000	0/646**	0/000	0/221	0/109	1	1
Height	1	1	1	1	0/543**	0/000	0/379**	0/005	0/616**	0/000	0/259	0/058	1	1
BMI	1	1	1	1	1	1	0/448**	0/001	0/448**	0/001	0/167	0/228	1	1
Femur	1	1	1	1	1	1	1	1	0/793**	0/000	0/023	0/868	1	1
Lumbar	1	1	1	1	1	1	1	1	1	1	-0/026	0/850	1	1

Several studies have indicated BMD deficiency in children. For instance, Gupta et al. measured BMD in the groups of patients and controls by dual X-ray energy absorptiometry plus 25 (OH) D. They found that children with cystic fibrosis have significantly lower bone density than the control group; most of them were vitamin D deficient. So intervening in the early stage of disease and providing best medical care in all factors affecting bone health and bone densitometry may be beneficial (22).

Sharma et al. highlighted, in their retrospective research, that although children and adolescents may have normal growth in height, bone mineral density is low in those with the poorest nutritional regime and lung function (23, 24).

In our study, lumbar BMD and femur BMD were 20.3% and 18.5% less than -2.5, respectively. And there is no correlation between BMD and vitamin D. Since the cause of bone disease in CF patients is probably multifactorial, further research is needed to assess other effective factors on BMD, and define the optimal nutritional supplementation in CF patients.

4-1. Limitations of the study

The present study contained limitations. One of them was not being able to record compliance of supplementation. The lack of calcium intake data from calcium was the second limitation, because Calcium plays a key role in vitamin D absorption.

5- CONCLUSION

Our study demonstrated that low BMD is highly prevalent in CF patients and more than 50% are vitamin D deficient. Extra works are expected to focus on the importance of improving the nutritional status and vitamin D supplementation of the patients with cystic fibrosis, and assess other factors on BMD and bone health of these patients.

6- ETHICAL CONSIDERATIONS

Written informed consent was obtained from the patients or legal guardians of those less than 18 years of age. The study was approved by the local Ethics committee of Isfahan University of Medical Sciences.

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