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Low Bone Mineral Density and Associated Factors in Patients with Cystic Fibrosis: A Cross-Sectional Study

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Abstract

Background: Failure to maintain bone mass density is a major complication in patients with cystic fibrosis (CF). This study was conducted to evaluate the prevalence of low bone mineral density (BMD) and also identifying associated risk factors in CF patients.

Materials and Methods: Present study conducted on 59 CF patients aged 5-35 years referred to respiratory clinic of Masih Daneshvari Hospital, Tehran-Iran. BMD was measured using dual energy X-ray absorptiometry (DXA) scan. Patients were divided in two groups: cases aged 5-18 years as group A and cases over 18 years as group B. Anthropometric variables, corticosteroid usage, pulmonary function test, serum calcium, phosphate and 25-OH vitamin D were assessed and correlation of them with BMD was investigated.

Results: Low BMD (Z score < -2 standard deviation) was found in 72.8% (44) of patients. There was a positive correlation between malnutrition, Forced Expiratory Volume 1 (FEV1) and BMD (r=59 and 0.47, P<0.01, respectively). Steroid therapy and Pseudomonas aeruginosa colonization correlated significantly inversely with BMD (r = -0.34 and -0.32, P<0.05). Vitamin D deficiency was found in 36.7% (18) CF patients. No significant correlation was found between 25-OH vitamin D levels and BMD (r = 0.17; P=0. 23).

Conclusion: In present study, the prevalence of low BMD was about 72.8% with significant correlation with low weight, BMI (poor nutritional status), FEV1, Pseudomonas aeruginosa colonization and the use of glucocorticoids.

Key Words: Bone mineral density, Children**,** Cystic fibrosis, Dual-energy X-ray absorptiometry.

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1- INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder that occurs in about 1 of 3,500 *white newborns (1).* New therapeutic approaches, based on the function of cystic fibrosis transmembrane conductance regulator (CFTR), lead to increase of the patients survival with CF to more than 30 years (2). Therefore with survival increment, the complications including diabetes, liver disease, infertility and impaired bone mineralization also increase. Multiple studies well documented that CF is associated with an increased risk of fracture in patients due to low bone mineral density (BMD) (3-5).

Malabsorption of calcium and vitamin D, pancreatic insufficiency, malnutrition, corticosteroids, inactivity, male sex and delay puberty are involved in low BMD condition. It has been shown that several inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease and cystic fibrosis are associated with bone resorption. The negative bone mass balance is mostly mediated by inflammatory cytokines that activate osteoclasts, impeding simultaneously osteoblast function (6, 7).

BMD is commonly measured by dual energy X-ray absorptiometry (DXA) scans as a gold standard (8). Low BMD using the International Society for Clinical Densitometry definition is considered Z-score equal or lower than -2.0 standard deviation (SD), determined for age, sex, and height (9). In order to offer a new insight into the correlation between low BMD and CF, present study was conducted to determine the prevalence of low BMD in both children and adults with cystic fibrosis.

2- PATIENTS AND METHODS

2-1. Study design and population

This cross sectional study was conducted on Fifty-nine patients with CF aged 5-35 years who regularly referred to the Pediatric Respiratory Disease Research Center (NRITLD) affiliated in Masih Daneshvari Hospital, Tehran- Iran. The study has started from December 2013 to March 2015.

2-2. Methods

Convenience sampling was used for recruitment of the patients. In all patients, diagnosis of CF was confirmed by a specialist, patients were divided in two groups: cases aged 5-18 years as group A and cases over 18 years as group B.

2-3. Laboratory measurements

All patients were investigated about CF onset age, diabetes mellitus and current use of glucocorticoids. The nutritional status of CF patients was expressed by weight, height, and body mass index (BMI). Blood was sampled for the measurement of serum calcium, phosphorus, and 25 (OH) vitamins D (10-12). Spirometry was utilized to measure forced expiratory volume in first second (FEV1) at the time of bone density scan. BMD was measured by DXA using a Hologic 4500 bone densitometer. In group B, BMD values were also expressed as a Z- score and a T- score. Osteopenia is defined according to the World Health Organization (WHO) if the T- score was between -1.0 and -2.5 and osteoporosis is diagnosed if the T- score was -2.5. Sputum culture was analyzed for the presence of Pseudomonas aeruginosa *(P. aeruginosa*) (13).

2.4-Ethical consideration

The Ethics committee of the National Research Institute of Tuberculosis and Lung Disease (NRITLD) approved the study (ID number: 93/12/21/963).

2-5. Inclusion and exclusion criteria

Patients aged 5-35 years who was diagnosed CF and have filled the informed consent form were enrolled to study.

Patients were excluded if they have severe respiratory failure or hemodynamic instability.

2-6. Data Analyses

Results are reported as mean ±SD. Pearson test were used to determine correlation analysis between BMD and various clinical variables. Statistical significance was defined as $P < 0.05$.

3- RESULT

Of the 59 cases were assessed in present study, 24 cases (40.6 %) were female and 35 cases (59.4 %) were male. **Table.1** summarizes baseline demographic, anthropometric, and other clinical characteristics.

In present study thirty six CF patients (61 %) were younger than 18 years and 23 (39 %) were 18 years or older. The mean age was 18.03±5.9 years (results were shown in **Table.2**). Age at diagnosis was sub-divided into < 1 years (n: 24) and ≥ 1 years (n: 35). Also, six patients (10 %) were diagnosed with diabetes mellitus.

The mean of BMI was 17.78 ± 2.2 kg/m2 for group B. Thirteen patients (56.52%) in group B had malnutrition based on BMI measurements (BMI<18.5 kg/m^2). In group A, five patients (13.9%) showed mild, 9 (25%) moderate and 18 (50%) severe malnutrition based on weight-for-age Z- score.

Malnutrition had a significant positive correlation with BMD (r=0. 595; P<0.001). Weight, BMI, and malnutrition significantly correlated with BMD (P<0.05).

The Z- score less than -2 was present in 27 (79.4%) patients in group A, and 16 (69.6%) patients in group B. The prevalence of total reduced BMD in present study was about 72.8%. The T-score median of total body was available for 16 patients aged over 18 years. Six patients (37.5 %) had a T-score <−2.5, 9 cases (56.3 %) had a T-score between −1 and −2, and 1 case (6.3 %) had a normal T-score. Twenty three males (53.5%) and 20 females (46.5%) had Z- scores < -2.0 SD, but male gender was not correlated with bone density Z- score (r= 0.04; P=0. 766).

No significant difference was observed between the two groups regarding Z-scores (-2.37± 1.14 and -1.82±1.37) (P=0. 712). Serum calcium and phosphorus levels were within the normal range. There was no significant correlation between bone density Z- score and age, serum calcium and phosphorus (P>0.05) (**Table.2**).

Thirty six patients (63.2%) had severe, 14 (24.6%) moderate, and 3 (5.3%) mild lung diseases. FEV1 was significantly and positively correlated with BMD Z- score (r=0. 475, P<0.001).

25 OHD level was available in 51 individuals (86.4%) with CF. Vitamin D deficiency (<10 ng/ml) was present in 18 (36.7%) subjects, vitamin D insufficiency (10-29 ng/ml) occurred in 26 (53.7%) subjects and only 7 (10.2%) subjects had normal vitamin D levels (≥ 30 ng/ml).

No correlation was observed between bone parameter BMD and vitamin D levels (r= 0.171; p=0. 230). Oral corticosteroid administration (none: 40, short time: 10, continuous: 7) had a negative correlation with BMD (r= -0.336; P= 0.009). Forty two CF patients (71.2%) were colonized with *P. aeruginosa*.

There was a negative correlation between BMD and *P. aeruginosa* colonization (r= -0.000 317; P=0. 015). **Table.2** shows the correlation of different factors with BMD Z scores.

Table 1: Demographic characteristics and clinical parameters of studied patients

Parameters	Group A (age <18 years)	Group B (age ≥ 18years)
Subjects, n (%)	36(61%)	23(39%)
BMD, Z- score	-2.37	-1.82
BMD, T- score		-2.11
Gender		
Male, n (%) Female, n (%)	24 (66.7%) 12(33.3%)	11(47.8%) 12(52.2%)
Age at diagnosis (<12 month), n (%)	18 (75%)	6 (25%)
BMI (kg/m2), (Mean ±SD)	14.62±2.85	17.78±2.2
Weight (kg), (Mean ±SD)	31.86±10.9	47.26±8.6
Height (cm), (Mean ±SD)	145.64±16.9	162.48±7.9
Underweight, n (%)	32 (88.9%)	13 (56.52%)
FEV1 (Liter), (Mean ±SD)	50.7±24.67	50.82±16.8
25-OH vitamin D (ng/ml), (Mean ±SD)	23.9±31.2	13.18±10.9
Serum calcium (mg/dl), (Mean ±SD)	9.4±0.46	9.2±0.82
Serum phosphorus (mg/dl), (Mean ±SD)	4.55±0.68	3.77±0.66
Pseudomonas (positive), n (%)	24(57.1%)	18(42.9%)

BMI: body mass index; 25-OH-D: 25-hydroxy vitamin D; FEV1: Forced expiratory volume in 1second; SD: standard deviation.

Table-2: The relationship between patient demographic and clinical parameters with bone density Z scores

Parameters	Mean ± SD n (%)	Correlation with bone density Z scores	P- value
Bone density Z-scores	-2.15±1.25		
Age (year)	18.03± 5.9	0.047	0.725
BMI (kg/ m^2)	15.85±3	0.365	0.004
Weight (kg)	37.86±12.5	0.33	0.011
Height (cm)	152.2±16.3	0.19	0.149
FEV1(Liter)	50.76±21.7	0.475	<0.001
25-OH vitamin D (ng/ml)	19.49±25.3	0.171	0.23
Serum calcium (mg/dl)	9.32±0.6	0.041	0.759

Serum phosphorus (mg/dl)	4.25±0.8	-0.102	0.442
Pseudomonas (positive), n (%)	42 (71.2%)	-0.317	0.015
Malnutrition	45 (76.2%)	0.595	<0.001
Gender Male (%) Female (%)	35 (59.3%) 24(40.7%)	-0.04	0.766
Use of glucocorticoids (%)	17 (29.8%)	-0.336	0.009

BMI: Body mass index; FEV1: Forced expiratory volume in 1second.

4- DISCUSSION

The prevalence of decreased bone mineralization in adolescents and adults with CF is well documented (14). Previous studies described the incidence of osteopenia and osteoporosis which ranged 32% -79% (3, 4, 14-17). Few studies have reported normal bone mineral status in well-nourished children with mild disease (18, 19). This difference *is* most likely due to population studies. Previous studies have involved patients with mild disease, which might underestimate the degree of osteopenia in a general CF population. In addition, clinical condition, treatment regimens and duration of measurement could be considered as the main factors associated with bone loss. Several risk factors have been associated with bone mass including BMI, malnutrition, FEV1, decreased physical activity and use of medication such as glucocorticoids (20).

The mean percent predicted FEV1 in our population was 51%; although, other studies reported between 33% and 51% (21). In addition, our findings revealed a positive correlation between BMD and pulmonary function that is in agreement with previous studies (14). Donadio et al. (22), reported a positive correlation between BMD and pulmonary function and negative correlation with chronological age and age at diagnosis. A significant relationship between reduced Z- score and percent of FEV1 was noted by Buntain et al. (23) and Sheikh et al. (24). On the other hand, in a recent study by Dennison and coworkers (25), no significant correlation between BMD and lung function was reported. The absence of relationship in Dennison and coworkers' study can be due to sampling method and range of lung function. Vitamin D plays a main role in bone health by regulating small intestinal calcium absorption and renal tubular calcium loss. No significant association was found between low serum 25(OH) D levels and low BMD in the present study. According to present study 10.2% of our patients had 25 (OH) D levels ≤ 30 ng/ml.

This finding is comparable with Conway's et al. study reported 25 (OH) D deficiency in 7% of cases (26). Our study is in contrast with two previous studies by Sheikh et al. and Abdul Wahab et al. (24, 27) who reported a high prevalence of vitamin D deficiency and high supplementation doses in CF patients. Suboptimal 25 (OH) vitamin D levels were noted in 76.9% and 78% of patients, respectively.

Several studies evaluated the relationship of gender with bone mass in patients with CF, but the results are contrasting. In present study, no significant correlation was observed between BMD and gender. In contrast to present study, Sheikh et al. (24), revealed that Z scores were significantly lower in males and concluded

that male gender is a significant independent variable correlating with low Z scores. Corticosteroids reduce osteoclast function and sex hormone secretion, and inhibit intestinal calcium absorption. In children and adolescent, the use of corticosteroids has a negligible effect on bone formation and growth rates (28). Inconsistent results about the effects of corticosteroid use have been reported in previous studies (17, 26, 29). This study showed a clear relationship between corticosteroid use and reduced BMD. Therefore, our findings recommended the use of prescribed glucocorticoid with caution. In the present study, the assessment of malnutrition in patients with CF revealed a significant decrease in weight and BMI, which may be attributed to several factors. The mean of BMI in our population was 17.8 and related to decreased bone mineralization. Similarly, the BMI mean in other studies varied between 18 and 21 (21, 30).

A strong positive correlation was found between malnutrition and BMD. These results were in agreement with previous studies in which authors proved that weight, height and BMI were significantly lower in subjects with CF which were related to decreased bone mineralization (24, 26, 29, 31). *P. aeruginosa* is the most common respiratory pathogen in cystic fibrosis. According to present study infection with *P. aeruginosa* was detected in 71% of cases. Our results were in accordance with those of Sermet et al. (5) and Li et al. (32), reported that children with *P. aeruginosa* had significantly lower BMD Z scores. As reported by Abdul Wahab et al. (27), significant negative correlation was observed between BMD and chronic *P.aeruginosa* colonization.

4-1. Limitations of the study

The main limitation of present study was that the effect of corticosteroid in daily and total dose of administration didn't evaluate and also the body fat didn't analyzed by DXA. Finally, the cross-sectional design of this study cannot capture the dynamic changes that occur in the skeleton nor risk of future fractures. In spite of these limitations, our study provides useful information on Bone density in patients with cystic fibrosis.

5- CONCLUSION

In present study, the prevalence of low BMD was about 72.8% with significant correlation with low weight, BMI (poor nutritional status), FEV1, *P. aeruginosa* colonization and the use of glucocorticoids. Small sample size was a limitation in present study. It is nesssary to note that if study was conducted on larger size, it was more probability for reporting significant cases and also more generalizability.

6- CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

7- ACKNOWLEDGMENTS

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8- REFERENCES

1. Parker-McGill K, Nugent M, Bersie R, Hoffman G, Rock M, Baker M, et al. Changing incidence of cystic fibrosis in Wisconsin, USA. Pediatric pulmonology 2015;50(11):1065-72.

2. MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, et al . Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the cystic fibrosis foundation patient registry. Annals of internal medicine 2014;161(4):233-41.

3. Caldeira RJdA, Fonseca VdM, Junior G, Chaves CRMdM. Prevalence of bone mineral disease among adolescents with cystic fibrosis. Jornal de pediatria 2008;84(1):18-25.

4. Baker JF, Putman MS, Herlyn K, Tillotson AP, Finkelstein JS, Merkel PA. Body composition, lung function, and prevalent and progressive bone deficits among adults with cystic fibrosis. Joint Bone Spine 2016;83(2):207-11.

5. Sermet-Gaudelus I, Souberbielle JC, Ruiz JC, Vrielynck S, Heuillon B, Azhar I, et al. Low bone mineral density in young children with cystic fibrosis. American journal of respiratory and critical care medicine 2007;175(9):951-7.

6. Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. Nature reviews Drug discovery 2012;11(3):234-50.

7. Gensburger D, Boutroy S, Chapurlat R, Nove-Josserand R, Roche S, Rabilloud M, et al. Reduced bone volumetric density and weak correlation between infection and bone markers in cystic fibrosis adult patients. Osteoporosis International 2016;27(9):2803-13.

8. Roux C, Briot K. Current role for bone absorptiometry. Joint Bone Spine 2017;84(1):35-7.

9. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi M-L, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone 2008;43(6):1115-21.

10. Hall WB, Sparks AA ,Aris RM. Vitamin D deficiency in cystic fibrosis. Int J Endocrinol. 2010; 2010:218691

11. Aris RM, Lester G, Dingman S, Ontjes D. Altered calcium homeostasis in adults with cystic fibrosis. Osteoporosis international 1999;10(2):102-8.

12. Lee JY, So T-Y, Thackray J. A review on vitamin d deficiency treatment in pediatric patients. The Journal of Pediatric Pharmacology and Therapeutics 2013;18(4):277-91.

13. Goeminne PC, Vandendriessche T, Van Eldere J, Nicolai BM, Hertog ML, Dupont LJ. Detection of Pseudomonas aeruginosa in sputum headspace through volatile organic compound analysis. Respiratory research 2012;13(1):87.

14. Legroux-Gérot I, Leroy S, Prudhomme C, Perez T, Flipo RM, Wallaert B, et al. Bone loss in adults with cystic fibrosis: prevalence, associated factors, and usefulness of biological markers. Joint Bone Spine 2012;79(1):73-7.

15. Jakovska T, Fustik S, Zorcec T. Genetic Markers Of Low Bone Mineral Density In Patients With Cystic Fibrosis. Journal of IMAB–Annual Proceeding Scientific Papers 2015;21(1):722-7.

16. Neri A, Lori I, Festini F, Masi L, Brandi M, Galici V, et al. Bone mineral density in cystic fibrosis patients under the age of 18 years. Minerva pediatrica 2008;60(2):147-54.

17. Lucidi V, Bizzarri C, Alghisi F ,Bella S, Russo B, Ubertini G, et al. Bone and body composition analyzed by Dual-energy X-ray Absorptiometry (DXA) in clinical and nutritional evaluation of young patients with Cystic Fibrosis: a cross-sectional study. BMC pediatrics 2009;9(1):61.

18. Street ME, Spaggiari C, Ziveri MA, Volta C, Federico G, Baroncelli GI, et al. Analysis of bone mineral density and turnover in patients with cystic fibrosis: associations between the IGF system and inflammatory cytokines. Horm Res. 2006;66(4):162-8.

19. Hardin D, Arumugam R, Seilheimer D, LeBlanc A, Ellis K. Normal bone mineral density in cystic fibrosis. Archives of disease in childhood 2001;84(4):363-8.

20. Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Guide to bone health and disease in cystic fibrosis. The Journal of Clinical Endocrinology and Metabolism. 2005; 90(3):1888-96.

21. Rossini M, Del Marco A, Dal Santo F, Gatti D, Braggion C, James G, et al. Prevalence and correlates of vertebral fractures in adults with cystic fibrosis. Bone 2004;35(3):771-6.

22. Donadio MV, Souza GCd, Tiecher G, Heinzmann-Filho JP, Paim TF, Hommerding PX, et al. Bone mineral density, pulmonary function, chronological age, and age at diagnosis in children and adolescents with

cystic fibrosis. Jornal de pediatria 2013;89(2):151-7.

23. Buntain H, Greer RM, Schluter P, Wong J, Batch J, Potter J, et al. Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. Thorax 2004;59(2):149-55.

24. Sheikh S, Gemma S, Patel A. Factors associated with low bone mineral density in patients with cystic fibrosis. Journal of bone and mineral metabolism 2015;33(2):180-5.

25. Dennison E, Dhanwal D, Shaheen S, Azagra R, Reading I, Jameson K, et al. Is lung function associated with bone mineral density? Results from the Hertfordshire Cohort Study. Archives of osteoporosis 2013;8(1-2):1-6.

26. Conway SP, Oldroyd B, Brownlee KG, Wolfe SP, Truscott JG. A cross-sectional study of bone mineral density in children and adolescents attending a Cystic Fibrosis Centre. Journal of Cystic Fibrosis 2008;7(6):469-76.

27. Abdul Wahab A, Hammoudeh M, Allangawi M, Al-Khalaf F, Chandra P. Bone mineral density in cystic fibrosis patients with the CFTR I1234V mutation in a large kindred family is associated with pancreatic sufficiency. Int J Rheumatol. 2014;2014:465395.

28. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height of children with asthma. Ugeskrift for laeger 2001;163(48):6746-50.

29. Vanacor R, Raimundo FV, Marcondes NA, Corte BP, Ascoli AM, Azambuja AZd, et al. Prevalence of low bone mineral density in adolescents and adults with cystic fibrosis. Revista da Associação Médica Brasileira 2014;60(1):53-8.

30. Elkin S, Fairney A, Burnett S, Kemp M, Kyd P, Burgess J, et al. Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study. Osteoporosis International 2001;12(5):366-72.

31. Kelly T, Buxbaum J. Gastrointestinal manifestations of cystic fibrosis. Digestive diseases and sciences 2015;60(7):1903-13.

32. Li Z, Kosorok MR, Farrell PM, Laxova A, West SE, Green CG, et al. Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children with cystic fibrosis. JAMA. 2005;293(5):581-8.