Bone mineral density and its contributing factors in Egyptian children with cystic fibrosis

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Background Cystic fibrosis (CF) is an autosomal recessive disorder that, despite advances in medical care, continues to be a life-limiting disease. With increase in life expectancy of the CF population, bone disease has emerged as a common complication.

Aim The aim of the study was to determine bone mineral density (BMD) and total body composition (TBC) in a sample of Egyptian children with CF and assess the contributing factors that might be related to BMD deficits.

Materials and methods This was a cross-sectional case–control study that included 15 children with CF who were of a mean age of 6.3±3.68 years (2.5–15 years) and were diagnosed by sweat chloride testing. All CF children were subjected to detailed history taking, thorough clinical examination, laboratory investigations, and pulmonary function tests. They also underwent growth, puberty, and nutrition evaluation. BMD and TBC were evaluated using dual-energy X-ray absorptiometry.

Results CF children had significantly decreased mean BMD and TBC compared with the control group. An overall 26.66% of these patients had osteopenia and one patient was 3 years old. They also showed delayed growth when compared with Egyptian standards, and most of them (>80%) presented with recurrent chest infections, malabsorption, undernutrition, and treatment with inhaled steroids for more than 6 months.

Conclusion We demonstrated the presence of osteopenia in our CF patients that presented early in life. Improving nutritional status, correcting malabsorption, and limiting chest infections are necessary for prevention. Annual assessment of BMD and body composition should be initiated early in life to target those who need preventive treatment against osteoporosis and reduce the risk for fractures later in life.
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Introduction

Cystic fibrosis (CF) is the most common inherited disorder and results from mutation of the cystic fibrosis transmembrane regulator (*CFTR*) gene. It occurs in approximately one in every 2500 live births in the White population [1] and is characterized by abnormal thick viscous secretions in the respiratory, gastrointestinal, and genitourinary tracts, together with chronic suppurative endobronchial infection [2], resulting in death or lung transplantation in more than 500 patients every year in the USA [3]. Incidence of CF is lower among African Americans (one in 15000) [4] and Asians (one in 32000) [5].

However, the incidence in people of other ethnic backgrounds including Egyptians has not been fully established, with very little published information available concerning the prevalence of CF in Egypt. Previously thought to be extremely rare, its true frequency may be masked by more common conditions such as respiratory infections, diarrhea, and malnutrition, as well as by other genetic or metabolic disorders, in addition to the limited genetic analysis of the disease [6].

Medical advances including proper antibiotics and anti-inflammatory therapy as well as adequate nutritional support have dramatically increased the life span of CF patients to 40 years over the past two decades, but have also led to the emergence of other problems like reduced bone mineral density (BMD), which becomes apparent as CF patients grow old [7].

Deficient BMD is an increasingly important clinical problem in adult patients with CF but its pathogenesis still remains uncertain. However, many contributing factors can be claimed, such as malnutrition, chronic infection, and excess circulating proinflammatory cytokines, vitamin D deficiency, delayed puberty, and reduced physical activity [8].

There is a paucity of literature on bone status in growing children with CF [9]. Appropriately

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defining and early recognition of bone mineral status in this category of patients may give new insight into the underlying pathogenesis of BMD defects in CF, and one can optimize preventive treatment strategies during this critical period of development to sustain bone health and help maintain the quality of life in many children with CF [10].

The aim of the present study was to determine BMD and total body composition (TBC) in a sample of Egyptian children suffering from CF and highlight the factors contributing to BMD deficits.

Materials and methods

Participants

The present study is a cross-sectional case–control study that included 15 children with CF of a mean age of 6.3±3.68 years (2.5–15 years). The sex ratio (female-to-male) was 0.875. They were recruited from the Pulmonology Unit of New Children's Hospital, Cairo University, where the pulmonary and laboratory assessments were carried out.

The study was conducted on well-diagnosed children with CF who had been suspected clinically and had been confirmed by laboratory tests such as a quantitative sweat chloride test (positive test if chloride>60 mEq/l) [11].

Clinical, nutritional, and growth evaluation, as well as the study of BMD, bone mineral content (BMC), and TBC using dual-energy X ray absorptiometry (DXA), was done in the Pediatric Clinic, National Research Centre (NRC), Cairo, Egypt.

Twenty-four age-matched and sex-matched healthy Egyptian children with a mean age of 7.3±3.74 years [3–17] and sex ratio (female-to-male) of 1.0 were also included in the study and they served as the control group. They underwent assessment of BMD, BMC, and TBC by DXA. They were also subjected to growth evaluation (weight, height, and BMI).

Ethical clearance

Written informed consent was obtained from the patients' parents according to the guidelines of the ethics committee of NRC and that of New Children's Hospital, Cairo University.

Methods

CF patients were subjected to a detailed history taking with special emphasis on cough, expectoration, dyspnea, steatorrhea, recurrent chest infections, inhaled corticosteroids for at least 6 months, pancreatic enzyme supplementation, history of playing outdoors, sun exposure (h/week), and exercise activity, including walking or cycling (h/week).

Diet history and diet analysis

A questionnaire on the patients' dietary habits using a 24 h dietary recall for 3 successive days was used to estimate their daily intake of calories, proteins, calcium, vitamins, and minerals. The diet intake of each patient was analyzed according to the Food composition tables of the National Institute of Nutrition, 2006, and the daily intake of calories, proteins, calcium, vitamins, and minerals was compared with the international standards of recommended daily intake (RDI) [12].

A thorough clinical examination was conducted, focusing on the presence of respiratory distress, clubbing, cyanosis, abdominal distension, hepatomegaly, rectal prolapse, and the presence of wheezing and/or crepitation.

Children with CF underwent anthropometric measurement of body weight in kg using a Seca Scale (http://www.seca.com), which was taken to the nearest 0.1 kg. Body height in cm. was also measured using a Harpenden Standiometer to the nearest 0.1 cm, and finally BMI was calculated according to the known formula:

$$\mathrm{BMI} = \frac{\mathrm{Weight\,(kg)}}{\mathrm{Height\,(m^2)}}$$

Body weight (kg), body height (cm), and BMI measurements were plotted on the Egyptian growth charts (2002).

Pubertal assessment was done using Tanner staging [13].

Laboratory investigations

Presence or absence of *Pseudomonas aeruginosa* (*P. aeruginosa*) on at least one sputum culture.

(1) Estimation of C-reactive protein (CRP) as a marker of inflammation.
(2) Measurement of serum level of total and ionized calcium, as a reflection of vitamin D status.

Pulmonary function tests

Children with CF below 6 years of age were tested with impulse oscillometry and those aged 6 years and above were tested with spirometry. In both methods pulmonary function was tested before and after bronchodilator therapy.

Bone mineral density, bone mineral content, and total body composition

BMD and BMC measurements from two sites, and TBC including total BMD and BMC, as well as fat mass (FM) and free-fat mass (FFM), were checked by DXA in the same patients using a Norland densitometer (XR-46, USA) Rev. 3.9.6/2.3 (http://www.bonedensitymachines.com/norland.../norland-xr-4) and compared with controls. Oral sedation was required in some unstable children. BMD for each patient was expressed in g/cm^2 and BMC was expressed in g; both measurements were taken from the lumbar vertebrae (L2–L4) and femoral neck, and total body measures were also calculated. Results were expressed as *Z*-score, the SD from normal mean BMD for an age and sex-matched Egyptian pediatric population. The expected BMD *Z*-score for a healthy population is 0. An abnormal DXA was defined as more than one SD below the normal mean, expressed as *Z*-score less than −1. Low BMD (osteopenia) was defined as *Z*-score from −1 to −2, very low BMD (severe osteopenia) as a score ranging from −2 to −2.5, and osteoporosis as *Z*-score less than −2.5 or episodes of spontaneous fracture [14,15].

FM and FFM were measured in grams and all readings were compared with those of the control group. The FFM and FM indices (FFMI and FMI) are equivalent concepts to the BMI, with the advantage being that only one component of body weight, that is, FFM or FM, is related to the height squared [16], as shown in the following definition:

$$\mathrm{FFMI} = \frac{\mathrm{Fat-Free\ \ mass}}{\mathrm{Height}^2}\left(\frac{\mathrm{kg}}{\mathrm{m}^2}\right),$$

$$\mathrm{FMI} = \frac{\mathrm{Fat\ \ mass}}{\mathrm{Height}^2}\left(\frac{\mathrm{kg}}{\mathrm{m}^2}\right).$$

Statistical analysis

The results were computerized and analyzed statistically using SPSS, version 20.0 (Armonk, NY: IBM Corp, USA). Results were expressed as means ±SD. The independent *t*-test was used to compare between two groups. The paired *t*-test was used to detect the changes in quantitative data before and after bronchodilator therapy. One-sample *t*-test was used to compare the average nutritional daily intake with the international standards of RDI.

Categorical data were summarized as percentages. The χ^2-test was used to compare the diseased and control groups with respect to categorical data. Pearson's correlation coefficient was used to determine the relationships between the quantitative variables. The level of significance was considered at *P* value less than 0.05.

Results

This study was carried out on 15 patients with CF with a mean age of 6.3±3.68 years who were diagnosed by sweat chloride testing and comprised eight (53.3%) male and seven (46.7%) female patients.

Consanguineous marriage was observed in 60% of parents, and history of affected siblings was noted in 26.6% of patients. Chest infection and steatorrhea were major findings in our CF children, with productive cough in 80% of cases, colored sputum in 73.3%, and steatorrhea in 86.7% of children.

Concerning drug therapy, we found that 66.7% of CF patients had been taking inhaled steroids for at least 6 months, and most of them (86.7%) had taken pancreatic enzyme replacement therapy for steatorrhea.

According to data obtained from the parents, sun exposure for at least 1 h/day was prevalent in 86.7% of cases. Physical activity such as walking or cycling less than five times/week was prevalent in 46.7% of cases and 53.3% had an exercise schedule at least five times/week [13].

Infection with *P. aeruginosa* was detected in 60% of cases and CRP was positive in 73.3% of them. The mean total serum calcium level was 9±1.17 mg/dl and ranged from 6.5 to 11.7 mg/dl. In addition, the mean ionized serum calcium level was 3.6±1.2 mg/dl and ranged from 1.26 to 5.1 mg/dl (Table 1 and Figs 1 and 2).

Table 1 Pulmonary function in CF patients (according to Naguib *et al.* [6])

Impulse oscillometry		Spirometry	
Total respiratory resistance (R5)	% of prediction	FVC	% of prediction
Proximal respiratory resistance (R20)	% of prediction	FEV_1	% of prediction
Distal capacitive reactance (×5)	% of prediction	FEV_1/ FVC	% of prediction
AX		FEF 25,50,75	% of prediction
Resonant frequency			

AX, area of reactance; CF, cystic fibrosis; FEF, forced expiratory flow; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity.

With reference to the Egyptian growth percentiles (Table 2), CF children showed a statistically significant growth delay compared with normal peers. It was also striking that 80% of CF patients had a body weight below the 10th percentile.

Table 3 demonstrates bone health status in our studied patients compared with the control group. BMD and BMC at two sites (femoral and lumbar) were markedly lower in CF patients than in the control group, with a highly significant statistical difference. Assessment of TBC in children with CF as shown in Table 4 revealed a significant decrease in FM, FFM, total BMD, and total BMC in patients compared with controls.

Low BMD (osteopenia) was detected in four patients with CF (26.66%) with femoral and/or lumbar *Z*-score less than −1. Two cases had femoral osteopenia, one case had lumbar osteopenia, and the last one was a 3-year-old patient with both femoral and lumbar osteopenia (−1.94 and −1.5, respectively) denoting that osteopenia in CF starts early in life.

We recorded a significant decrease in the fat content variables such as FFM, FM, and FFMI (P=0.01) in CF children compared with the control group. Although the FMI was also lower than that of controls, it did not reach statistical significance (P=0.06) (Table 4).

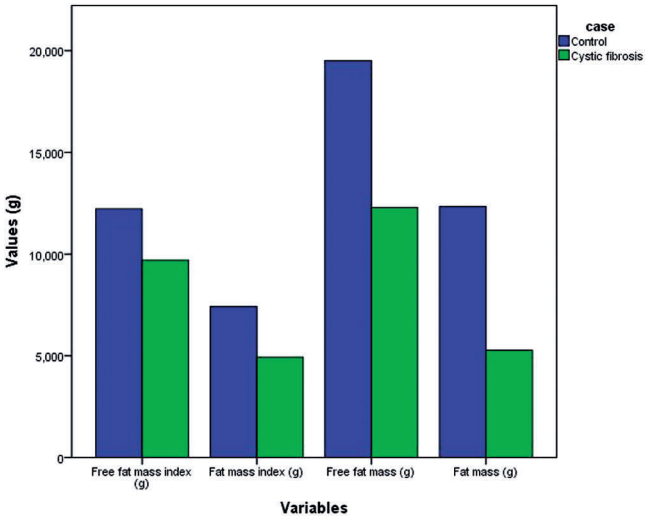
BMD and BMC of the two sites, as well as total BMD and BMC, did not show any sex-related difference in CF children (P>0.1).

Pubertal assessment was done using Tanner staging. Thirteen patients (86.6%) (six girls and seven boys; aged 2.5–9.1 years) had not reached puberty (Tanner stage 1) and two other patients (13.3%) [one boy (12 years) and one girl (15 years)] had reached puberty (Tanner stage 3). None of our patients had delayed puberty.

On the basis of the patients' subjective data collected by history taking, the daily intake of minerals in children with CF as shown in Table 5 was compared with the international standards of RDI, and we found a significant decrease in the intake of zinc compared with the RDI in the age groups 1–3 and 11–15 years. Daily intake of iron in CF patients was nearer to the RDI, with no statistical significance. Calcium intake was generally lower than the RDI, with statistical significance only in the age group 4–6 years.

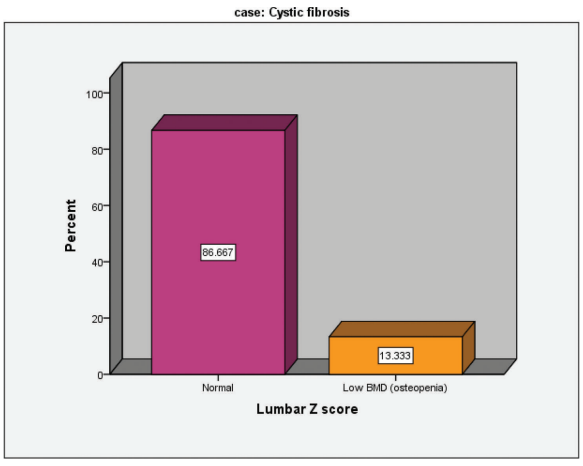
Daily intake of vitamins in children with CF was also compared with the international standards of RDI. It was found that there was a significant decrease in the intake of riboflavin compared with the RDI in the age groups 4–6 and 11–15 years (P=0.01). Regarding thiamin, CF patients in the age group 4–6 years had a statistically significantly lower daily intake than the RDI (P=0.02). Vitamin C intake was extremely lower than the RDI in the age groups 1–3, 4–6, and 7–10 years but it reached statistical significance in the first two groups (P<0.001). Vitamin C intake was higher than the RDI in the age group 11–15 years but with no statistical significance. Daily vitamin A intake in CF patients was extremely lower than the RDI with a high statistical significance in all age groups.

Figure 1



Femoral *Z*-score in cystic fibrosis patients. BMD, bone mineral density.

Figure 2



Lumbar *Z*-score in cystic fibrosis patients. BMD, bone mineral density.

Table 2 Egyptian growth percentiles in patients and controls

	≤10 percentile [*n* (%)]	11th–50th percentile [*n* (%)]	>50th percentile [*n* (%)]	Total [*n* (%)]	*P* value
Egyptian weight percentile					
Control					
Count (% within case)	1 (4.2)	4 (16.7)	19 (79.1)	24 (100)	0.000*
Cystic fibrosis					
Count (% within case)	12 (80)	3 (20)	0 (0.0)	15 (100)	
Egyptian height percentile					
Control					
Count (% within case)	1 (4.2)	7 (29.1)	16 (66.7)	24 (100)	0.001*
Cystic fibrosis					
Count (% within case)	7 (46.7)	8 (53.3)	0 (0.0)	15 (100)	
BMI percentile					
Control					
Count (% within case)	2 (8.3)	5 (20.8)	17 (70.8)	24 (100)	0.003*
Cystic fibrosis					
Count (% within case)	6 (40)	7 (46.7)	2 (13.3)	15 (100)	

*Statistically significant.

Table 3 BMD in patients and controls

	N	Mean±SD	*P* value
Femoral BMD (g/m^2)			
Control	24	0.73±0.12	0.000*
Cystic fibrosis	15	0.55±0.13	
Femoral BMC			
Control	24	2.57±1.08	0.000*
Cystic fibrosis	15	1.39±0.55	
Lumbar BMD (g/m^2)			
Control	24	0.58±0.13	0.000*
Cystic fibrosis	15	0.42±0.10	
Lumbar BMC			
Control	24	18.26±8.52	0.002*
Cystic fibrosis	15	9.88±5.61	

BMC, bone mineral content; BMD, bone mineral density.
*Statistically significant.

Table 4 Total body composition in patients and controls

	N	Mean±SD	*P* value
Fat mass (g)			
Control	24	12333.17±9900.21	0.01*
Cystic fibrosis	15	5272.73±3482.48	
Fat free mass (g)			
Control	24	19505.29±8986.94	0.01*
Cystic fibrosis	15	12289.67±7648.48	
Total bone mineral density (g/cm^2)			
Control	24	0.65±0.11	0.000*
Cystic fibrosis	15	0.50±0.12	
Total bone mineral content (g)			
Control	24	1170.17±552.58	0.006*
Cystic fibrosis	15	700.27±361.62	

*Statistically significant.

The average daily protein intake of CF patients was significantly lower than the RDI in all age groups (Table 6); however, as a result of their malabsorptive state their daily energy intake was increased mainly from fat consumption, followed by carbohydrates, and the average daily caloric intake of CF children was nearer the RDI for all age groups with no significant statistical difference.

A strong positive correlation was detected between femoral and lumbar BMD and BMC and FFM (lean body mass) which reached high statistical significance. However, no correlation was found between femoral and lumbar BMD and BMC and FM (Table 7).

On conducting pulmonary function testing using impulse oscillometry in the 9 cases younger than 6 years one patient was found to have an obstructive pulmonary airway disease and another one was found to have a borderline reversible obstructive airway disease. Improvement in all cases was detected after bronchodilator therapy, with statistical significance in total respiratory resistance (R5) ($P<0.05$). On using spirometry in six cases older than 6 years two patients were found to have combined obstructive and restrictive airway disease. There was improvement in some lung functions after bronchodilator administration – namely, forced vital capacity (FVC), forced expiratory volume in first second (FEV_1), forced expiratory flow (FEF) 25, and FEF 50, but only FEF 25 reached statistical significance.

No correlation was found between FEV_1 and BMD and BMC at the two sites, as well as with the total BMD and BMC both before and after bronchodilator therapy ($P>0.6$).

Table 5 Daily mineral intake of patients with CF

	Age group	RDI	*N*	Mean±SD	*P* value	Mean difference
Zinc (mg)	1–3	10	4	7.17±1.21	0.02*	–2.83
	4–6	10	6	7.70±2.15	0.1	–2.29
	7–10	10	3	8.83±3.03	0.5	–1.16
	11–15	15	2	9.82±0.21	0.019*	–5.17
Iron (mg)	1–3	10	4	8.10±2.45	0.2	–1.89
	4–6	10	6	8.81±2.91	0.4	–1.18
	7–10	10	3	10.20±5.43	0.9	0.20
	11–15	12	2	12.87±0.80	0.3	0.87
Ca (mg)	1–3	500	4	602.59±122.55	0.1	102.59
	4–6	800	6	561.66±60.32	0.004*	–238.33
	7–10	800	3	537.93±155.23	0.1	–262.07
	11–15	1300	2	663.42±98.49	0.06	–636.57

CF, cystic fibrosis; RDI, recommended daily intake.
*Statistically significant.

Table 6 Daily protein and energy intake of patients with CF

	Age group	RDI	*N*	Mean±SD	*P* value	Mean difference
Protein (g)	1–3	16	4	11.25±0.95	0.002*	–4.75
	4–6	24	6	16.25±2.6	0.01*	–7.75
	7–10	28	3	23.00±1.00	0.01*	–5.00
	11–15	45	2	32.50±3.54	0.12	–12.5
Energy (kcal)	1–3	1300	4	1417.54±390.26	0.5	117.54
	4–6	1800	6	1526.59±410.95	0.2	–273.40
	7–10	2000	3	1935.93±873.23	0.9	–64.06
	11–15	2500	2	2021.50±334.66	0.2	–478.49

CF, cystic fibrosis; RDI, recommended daily intake.
*Statistically significant.

We recorded a high statistically significant correlation between age, body weight, and height of CF children and the femoral and lumbar BMD and BMC as well as total BMD and BMC ($P<0.001$).

Discussion

New aggressive therapeutic plans for lung disease with attention to nutritional status have increased the life span of CF patients. However, long-term sequelae, such as CF-related bone disease, are often observed. This study was planned to assess bone health status in patients with CF and to show the possibly contributing factors that may affect BMD in these patients, which is important in planning preventive strategies.

We recorded significant undermineralization in our CF cases. Among those patients 80% had recurrent chest infection, 80% had productive cough, and 66.7% presented with dyspnea. Infection with *P. aeruginosa* was detected in 60% of cases, and CRP was positive in 73.3%. Our results were in accordance with those of Wahab *et al.* [17] who recorded 61.5% of CF patients colonized with *P. aeruginosa*. El-Falaki *et al.* [18] found the following: chronic cough, 84%; history of recurrent hospital admission, 77.8%; crepitation, 77.7%; and wheezing, 66.6%.

Moreover, Haworth *et al.* [19] concluded that chronic pulmonary infection and its associated inflammation is a potential factor in the development of nutritional complications in CF patients, especially in those with low muscle mass (FFM), more frequent exacerbations of respiratory symptoms, and a lower response to antibiotic treatment, resulting in decreased BMD *Z*-scores with high prevalence of undermineralization.

The results of this study were also commensurate with those of Sermet *et al.* [10] and Conway *et al.* [20] who proved that children with *P. aeruginosa* colonization and CF children who had received intravenous antibiotic treatment for chest infection in the previous 12 months had significantly lower BMD *Z*-scores.

In our series 66.7% of CF children were taking inhaled steroids for at least 6 months, which was in agreement with the results of Sermet *et al.* [10] and Conway *et al.* [20], who found a significant high risk for low BMD

Table 7 Correlation between BMD and many variables in CF patients

Correlation	Weight (kg)	Fat mass (g)	Fat free mass (g)	FEV_1
Femoral BMD (g/m^2)				
Pearson's correlation	0.668**	–0.348	0.686*	0.176
P value	0.007	0.204	0.005	0.739
N	15	15	15	6
Femoral BMC				
Pearson's correlation	0.857**	–0.228	0.757*	0.070
P value	0.000	0.413	0.001	0.896
N	15	15	15	6
Lumbar BMD (g/m^2)				
Pearson correlation	0.936**	–0.236	0.808*	0.067
P value	0.000	0.397	0.000	0.900
N	15	15	15	6
Lumbar BMC				
Pearson's correlation	0.980**	–0.289	0.863*	0.053
P value	0.000	0.295	0.000	0.921
N	15	15	15	6

BMC, bone mineral content; BMD, bone mineral density; CF, cystic fibrosis; FEV_1, forced expiratory volume in first second.
*Statistically significant.
**Significant.

among children receiving inhaled corticosteroid for longer than 6 months. Further, Ross *et al.* [21] do not support its routine use as an anti-inflammatory therapy in CF patients who do not have asthma, despite widespread use.

Most of the CF cases in the current study (86.7%) had taken pancreatic enzyme replacement therapy in an attempt to decrease steatorrhea. However, pancreatic enzyme formulations for CF are not readily available in the Egyptian markets and thus their intake by patients may not be consistent. This was nearly similar to its incidence reported by Walkowiak *et al.* [22] (81.5%), Baker [23] (85%), Weintraub *et al.* [24] (85%), and El-Falaki *et al.* [18] (66.7%).

Children with CF exhibited a delayed physical growth in all parameters (weight, height, and BMI), which may be attributed to several factors such as the degree of exocrine pancreatic insufficiency, lack of a proper method in taking enzyme replacement therapy, and also severity and frequency of chest exacerbations with subsequent undernutrition. Buntain *et al.* [25], Ujhelyi *et al.* [26], Conway *et al.* [20], Kelly and Buxbaum [27], and Sheikh *et al.* [28] reported that weight, height, and BMI were all significantly lower in subjects with CF and are related to decreased bone mineralization, especially BMI, which has significant influence on bone mineralization.

Many authors found that BMD in the lumbar spine and proximal femur in CF patients younger than 18 years was significantly reduced and that BMD declines rapidly with age. Similar to our findings, they also found that the regional BMD correlated strongly with body weight [10,26,27,29,30]. Gronowitz *et al.* [31] also recorded lower BMD in children with CF compared with reference values matched for chronological age. Similarly, Binachi *et al.* [32] found a mean reduction in lumbar spine BMD in 55 children aged 3 years to puberty. Our results were in agreement with previous studies in which we found BMD and BMC from two sites (lumbar and femoral) as well as total BMD and BMC to be markedly lower than those of controls, and a significant correlation of regional and total BMD and BMC with age and body weight ($P<0.001$).

Femoral and lumbar *Z*-scores of our CF children revealed low BMD *Z*-scores (osteopenia) in 26.66% of cases that presented early in life, but none of them showed osteoporosis or gave a history of fracture throughout the study period. Javier and Jacqout [33] found that the fracture risk is increased from late adolescence onward and can cause severe respiratory complications, an issue that necessitates long-term follow-up in CF children.

An important parameter in the assessment of disease severity is a pulmonary function test evaluating FEV_1 and FVC expressed as a percentage of predicted values for age and sex. Hardin *et al.* [30] reported no correlation between BMD values and pulmonary function test results in children with CF. We also did not find such a correlation. However, many investigators have found a strong association between BMD and FEV_1 and FVC [10,20,25,28,29]. Such an association was not found

in our study, which may be attributed to the small number of the studied cases as only six patients were candidates for spirometry.

In the present study, assessment of TBC in children with CF revealed a significant decrease in FM, FFM, and FFMI. A strong positive correlation was found between the FFM (lean body mass or muscle mass) and regional (femoral lumbar) BMD and BMC. These results were in agreement with previous studies in which authors proved that lean tissue mass is a very important factor in bone development and BMD increase in normal individuals [34]. In CF, FFM greatly influences lumbar spine BMD *Z*-scores [30], and muscular mass is predictive of bone mass accrual in children and adolescents [25,29,32].

Furthermore, Sermet *et al.* [10] found that lumbar spine *Z*-score was strongly correlated with FEV_1, FVC, and FFM *Z*-score in the univariate analysis, and when these positive correlations were evaluated in a stepwise multiregression analysis, only the FFM *Z*-score remained correlated with the lumbar spine *Z*-score. These findings imply that maintenance of correct FFM is a cornerstone of bone health in CF and confirm the relationship between nutritional status and BMD of CF patients.

In the present study, we were trying to study a large cohort of Egyptian CF patients plus the additive risk factors for bone metabolism in Egyptian children. Our CF children exhibited poor growth and suboptimal nutrition. Daily intake of vitamins (riboflavin, thiamin, vitamin C, and vitamin A) and minerals (zinc and calcium) by CF patients was markedly lower than the RDI.

The average daily protein intake of CF patients was significantly lower than the RDI for all age groups. However, as a result of their malabsorption, they increased their daily energy with an average caloric intake nearer the RDI with no statistical difference.

Stettler *et al.* [35] at the start of their study reported that energy intake by CF children was higher than that of controls but was insufficient to maintain normal growth over the 4 years of follow-up. Salamoni *et al.* [36] found normal BMC in well-nourished patients with CF as compared with controls, and suggested that osteopenia in CF patients has a nutritional origin rather than a primary defect in BMD. Similarly, Hardin *et al.* [30] and Sood *et al.* [37] concluded that osteopenia and osteoporosis in CF may be caused more by malnutrition than by a CF-related genetic defect in BMD. They suggested that overall good health and nutritional status of CF subjects might allow normal bone mass acquisition during childhood and adolescence.

Conversely, when BMD analysis was limited to well-nourished patients with mild pulmonary disease, other investigators found reduced lumbar spine *Z*-scores less than −1 in their cohort of normally growing prepubertal CF children with mild lung disease. They concluded that the origin of CF bone disease may not be related to nutritional status or disease severity, and thus some patients with CF might have a genetic background prone to osteoporosis from birth onward and aggravated by contributing factors such as low FFM, excessive inflammation, and poor nutrition [10,31,32]. This is an issue that really deserves further long-term studies.

The catabolic state and high level of circulating proinflammatory cytokines associated with acute respiratory exacerbations and chronic severe infection would stimulate osteoclast-induced bone resorption and decreased bone formation, which could explain the low BMD in our CF children. Deficiency of fat-soluble vitamin D due to exocrine pancreatic insufficiency may also be claimed, and hence supplementation with special vitamin D formulations in addition to pancreatic enzyme replacement may potentially improve BMD in these patients.

Conclusion

Our CF children had reduced BMD and TBC than did the control group. They also showed suboptimal growth when compared with Egyptian standards. Many contributing factors could be claimed, as most of them presented with recurrent chest infections, malabsorption, undernutrition, and treatment with inhaled steroids for more than 6 months. Treatment to prevent osteopenia in these patients is directed toward improving nutritional status and accentuating energy intake, correcting malabsorption, limiting chest infections, and avoiding steroids as much as possible. Also regular BMD monitoring is recommended.

We suggest further large-scale studies including a more representative population of Egyptian children with CF. All these patients must undergo annual assessment of BMD and body composition early in life to target those who need preventive treatment in an attempt to prevent osteoporosis and reduce the risk for fractures later in life. We also highly recommend screening the complete CFTR gene in CF patients to define the spectrum and distribution of CFTR mutations in

Egypt to determine whether there are certain mutations that could be associated with the development of osteopenia

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Conflicts of interest

There are no conflicts of interest.

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