Advances in Medical Sciences 60 (2015) 315–320

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original Research Article

# Evaluation of factors related to bone disease in Polish children and adolescents with cystic fibrosis

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ARTICLE INFO

*Article history:*
Received 22 May 2014
Accepted 20 May 2015
Available online 3 June 2015

*Keywords:*
Cystic fibrosis
Nutritional status
Bone mineral density
Adolescents
Vitamin D

ABSTRACT

*Purpose:* The aim of the study was to evaluate factors related to bone formation and resorption in Polish children and adolescents with cystic fibrosis and to examine the effect of nutritional status, biochemical parameters and clinical status on bone mineral density.
*Materials and methods:* The study group consisted of 100 children and adolescents with cystic fibrosis with a mean age 13.4 years old. Anthropometric measurements, included body height, body mass and body mass index (BMI); bone mineral densitometry and biochemical testing were performed. Bone mineral density was measured using a dual-energy X-ray absorption densitometer. Biochemical tests included serum calcium, phosphorus, parathyroid hormone and vitamin D concentrations, as well as 24-h urine calcium and phosphorus excretion. Pulmonary function was evaluated using $FEV_1$%, and clinical status was estimated using the Shwachman–Kulczycki score.
*Results:* Standardized body height, body mass and BMI were significantly lower than in the reference population. Mean serum vitamin D concentration was decreased. Pulmonary disease was generally mild, with a mean $FEV_1$% of 81%. Multivariate linear regression revealed that the only factors that had a significant effect on bone marrow density were BMI and $FEV_1$%. There were no significant correlations between bone mineral density and the results of any of the biochemical tests performed.
*Conclusions:* Nutritional status and bone mineral density were significantly decreased in children and adolescents with cystic fibrosis. In spite of abnormalities in biochemical testing, the factors that were found to have the strongest effect on bone mineral density were standardized BMI and clinical status.


## 1. Introduction

Cystic fibrosis (CF) is the most common inherited monogenic autosomal recessive disorder in the Caucasian population. According to the latest data, the incidence of CF in Poland on the basis of newborn screening is 1:4394 [1].

Modern therapies for bronchopulmonary disease and intensive nutritional care prolong survival in CF patients. In developed countries, patients with cystic fibrosis born during the 1980s and 1990s now have a 50% higher chance of living to 40 years old [2]. Nevertheless, comorbidity may be present, including bone disease.

The etiology of bone disease in CF patients has not been fully elucidated [3]. Potential risk factors include poor nutritional status, pulmonary infection, chronic inflammation, severe lung disease, pancreatic insufficiency, vitamin D and K deficiencies, negative calcium balance, hypogonadism, delayed puberty, CF-related diabetes, glucocorticosteroid treatment, reduced weight-bearing activity, organ transplant and immunosuppressive therapy [4–7].

Decreased bone mineral density and the risk of low-trauma fracture may contribute to increased morbidity and reduced quality of life in patients with CF. Fractures may lead to accelerated deterioration of lung function, affect normal chest physiotherapy and be a contraindication for lung transplant [8–10].

The aim of the present study was to evaluate factors related to bone formation and resorption in Polish children and adolescents

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http://dx.doi.org/10.1016/j.advms.2015.05.002
1896-1126/

with cystic fibrosis, and to examine the effect of nutritional status, biochemical parameters, pulmonary function and clinical status on bone mineral density.

## 2. Materials and methods

### 2.1. Study population

Between 2007 and 2009, one hundred patients with cystic fibrosis between 10 and 18 years old took part in the study. The study group included 51 boys and 49 girls. Mean age was, $13.4 \pm 2.7$. There was no significant difference in age between boys and girls, with a mean age of $13.5 \pm 2.6$ years for boys, and $13.4 \pm 2.9$ years for girls.

Sixty of the children were examined at the Cystic Fibrosis Center of the Institute of Mother and Child in Warsaw. Fifteen were examined at the Department of Pediatric Gastroenterology and Hepatology of the Children's Memorial Health Institute in Warsaw. Twenty-five were examined at the Department of Gastroenterology and Metabolic Disease of the University of Medical Sciences in Poznań.

All patients were in stable clinical condition. Diagnosis of CF was confirmed by sweat chloride concentration and genetic analysis before candidates were included in the study group. *CFTR* genotype was F508del/F508del in 57 of the children, F508del/Mt in 23 of the children, and Mt/Mt in 19 of the children, where Mt represents any mutation other than F508del.

Candidates were included in the study on the basis of the following criteria:

- at least ten years of age;
- severe pancreatic insufficiency (stool concentration of elastase-1 less than 100 μg/g and pancreatic enzyme supplementation); and
- compliance with vitamin supplementation.

Candidates were excluded on the basis of the following criteria:

- long-term treatment with systemic steroids;
- hepatic cirrhosis; and
- dependence on supplied oxygen.

All of the children selected had pancreatic insufficiency and were receiving appropriate enzyme supplementation. All were taking oral vitamin D at a dose of 400–800 IU in multivitamin supplements in accordance with national and European guidelines [11,12].

On all of the children included in the study, anthropometric measurements, bone mineral densitometry and biochemical testing were performed. Signed informed consent was obtained from the parents of each child. The study was approved by the Bioethics Committee of the Institute of Mother and Child (No. KBET/29/2006).

### 2.2. Anthropometric measurements

Body height, body mass and body mass index (BMI) were recorded to one decimal place. Standardized values were calculated and expressed in terms of standard deviations away from the means reported in national growth charts [13].

### 2.3. Bone mineral densitometry

Bone mineral density in the lumbar spine (L2–L4) was measured using a Hologic Explorer dual-energy X-ray absorption densitometer and expressed in terms of the BMD *Z*-score. In accordance with Polish and European guidelines, bone mineral density was considered normal for *Z*-scores greater than −1, moderately low for scores between −1 and −2, and very low for scores less than −2 [14,15].

### 2.4. Biochemical testing

Fasting serum was sampled to measure calcium, phosphorus, parathyroid hormone (DiaSorin, Liaison), and 25-hydroxy vitamin D (DiaSorin, Liaison). The reference range was from 2.2 to 2.8 mmol/l for calcium, from 1.0 to 2.3 mmol/l for phosphorus, and from 15 to 65 pg/ml for parathyroid hormone. In accordance with the manufacturer's recommendations, vitamin D insufficiency was defined as a serum 25-hydroxy vitamin D concentration of less than 30 ng/ml [4,14].

24-h urine testing was performed to determine urine calcium and phosphorus excretion. Results were expressed in milligrams per kilogram body mass per 24 h. Calcium excretion was considered normal for values under 4 mg/kg/day. Phosphorus excretion was considered normal for values under 25 mg/kg/day.

### 2.5. Pulmonary function and clinical status

Pulmonary function was evaluated on the basis of forced expiratory volume during the first second ($FEV_1$%) measured using a Lung Test 1000 spirometer. Pulmonary disease was considered mild for values over 70%, moderate for values between 40% and 70%, and severe for values under 40% [16]. Clinical status was estimated using the Shwachman–Kulczycki scale, with 0 representing the worst clinical status, and 100 representing the best [14].

### 2.6. Statistical analysis

Anthropometric parameters were expressed in terms of standard deviations from the age-specific and sex-specific reference values published in Polish national growth reference charts [13].

Differences between the children examined and the reference population were evaluated using Student's *t*-test for single samples. Asymmetry of distributions was evaluated using the Shapiro–Wilk test. Relationships between bone mass density and selected clinical and biochemical factors were evaluated using Spearman's correlation method.

The effect of selected factors associated with the course of the disease on bone mass density was determined using multivariate regression analysis. The dependent variable was the BMD *Z*-score. Independent values included BMI, $FEV_1$% and selected biochemical parameters. Standardized beta cofactors were used to facilitate comparison of the strength of the correlation of individual independent values with those dependent variables recorded using different units.

Differences were considered significant at $p < 0.05$. All analyses were carried out using the STATISTICA 10.0 software package.

## 3. Results

Results for anthropometric measurements are presented in Table 1. Standardized body height, body mass and BMI were significantly lower than in the reference population.

BMI was more than one standard deviation above the reference mean in 4% of the children, within one standard deviation in 63% of the children, from one to two standard deviations below the mean in 30% of the children, and more than two standard deviations below the mean in 3% of the children.