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PREVALENCE OF LOW BONE MASS AND VITAMIN D DEFICIENCY IN PEDIATRIC AND ADULT PATIENTS WITH CYSTIC FIBROSIS IN REPUBLIC OF MACEDONIA

Tatjana Jakovska[1], Jasmina Mecevska-Jovcevska[2], Aleksandar Petlickovski[3], Stojka Fustik[1], Tatjana Zorcec[1]

[1] University Children's Hospital, Medical Faculty, Ss. Cyril and Methodius University, Skopje, R. Macedonia
[2] University Clinic for clinical biochemistry, Skopje, R. Macedonia
[3] Institute for immunology and human genetic, Medical Faculty, Ss. Cyril and Methodius University, Skopje, R. Macedonia

Corresponding Author: Tatjana Jakovska, Vodnjanska 17, 1000 Skopje, R. Macedonia; E-mail: maretti98@yahoo.com

Abstract

Bone disease in cystic fibrosis (CF) has become a topic of widespread interest and impact in the CF community. Recently, some biochemical markers have been proposed to provide information about the dynamics of bone turnover. Only limited information is available for young patients. Imbalance between bone formation and degradation in CF especially in puberty has become an important issue for developing osteopenia. Influence of vitamin D receptor alleles on BMD suggests that these polymorphisms have a greater influence on BMD in childhood. The aim of our study was to assess prevalence of vitamin D deficiency and osteopenia in pediatric and adult CF patients. Methods: The study included 77 clinically stable CF patients (range 5–36 y), who regularly attended CF center at the Pediatric Clinic in Skopje, Macedonia. Serum osteocalcin (OC), βcrosslaps, 25OHD and PTH were determined by electrohemiluminiscent method. BMD was measured via dual energy-ray absorptiometry (DXA) scans with spinal scores recorded. Results: 50% of the CF patients with PI had serum vitamin D > 20 ng (range 10–44 ng/ml) with no difference of age. Osteopenia was determined in 35% of patients. High plasma βcrosslaps values reflect raised osteoclast activity in 50% of patients with osteopenia. We found one CF patient homozygote for Taq1 and Bsm1, one for Taq1 and one for Fok1. These patients have vitamin D deficiency and osteopenia. Conclusions: Bone remodeling in CF patients is impaired. Further investigations are needed to find underlying pathogenesis of low bone mass and vitamin D deficiency.

Key words: cystic fibrosis, osteoporosis, vitamin D deficiency, bone turnover.

Introduction

Cystic fibrosis is the most frequent rare, autosomal recessive and lethal disease in Caucasian population. It is caused by mutation of the gene for cystic fibrosis transmembrans regulator (CFTR). The incidence is 1 : 2500 newborns [1]. Mutation in CFTR gene results in defect chloride transport in epithelial cells in pancreas, gut, liver, lung, renal, bone and testicular canals. Clinical presentations in CF are chronic lung disease with recurrent infections who leads to respiratory insufficiency and eventually lethal end, malapsorption presented with frequent and oily stools, which are manifestation of pancreatic insufficiency and malnutrition which is an important determinant of growth and body development during childhood and adolescence [2]. Attainment of adulthood is now common in CF and survival continues to increase. Major complications emerging with longer survival are failure to maintain body mass, osteoporosis, diabetes mellitus and infertility.

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro

architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk. It was described first time in 1979 in individuals with cystic fibrosis (CF) [3, 4]. Incidence of bone disease in CF in the world is estimated to be 30%. Factors who influence over bone mass are malnutrition and pancreatic insufficiency, deficit of vitamin K, deficit of vitamin D, polymorphism of VDR gene, delayed puberty and hypogonadism, physical inactivity, recidivate respiratory infections and use of corticosteroids [5, 6].

Patients with CF have deficit of liposolubile vitamins (A, D, E, and K). Low levels of 25OHD are found because of malapsorption, low levels of vit. D binding protein, reduced sun exposure or rapid catabolism of 25OHD. Vitamin K is vital in process of decarboksilaton of osteocalcin (protein of bone formation). Malapsorption in CF patients is presented with reduced absorption of calcium because of deficiency of vitamin D and loss of fat free mass (FFM). In most of the studies a normal concentration of calcium in CF patients was reported [7–9].

Imbalance between bone formation and degradation in cystic fibrosis (CF) in childhood has become an important issue for developing osteopenia [6]. Vitamin D, whose activity is determined by VDR gene, has influence over bone mass. The variants of alleles of VDR gene are ApaI (allele A/a), BsmI (allele B/b), FokI (allele F/f), and TaqI (allele T/t) [10, 11]. Risk for fractures in CF patients is higher in late adolescents, especially in female patients. Mostly there are fractures on spine (L2-L4). Prevalence of radiological vertebral and nonvertebral fractures in the world is 14% [12–14].

Aim of the study was to assess prevalence of vitamin D deficiency and osteopenia in pediatric and adult CF patients who regular visit the CF center at the University Pediatric Clinic in Skopje, Macedonia despite the daily supplementation of 800 IU vitamin D and to assess bone formation and resorption process with bone markers in prepubertal, pubertal and young adult CF patients.

Materials and Methods

Patients

The study included 77 clinically stable CF patients (range 5–36 y) who regularly attended the CF center at the Pediatric Clinic in Skopje. The diagnosis of CF was made by the presence of typical clinical characteristics of CF (chronic respiratory disease and/or pancreatic insufficiency) together with abnormal sweat chloride test (> 60 moll/l) and/or the presence of two CFTR gene mutations.

They were divided in 3 groups: prepubertal (5–11 years), pubertal (12–18 years) and young adults (19–36 years). The control group included 60 healthy subjects with similar characteristics. They were investigating for osteocalcin, ßcrosslaps, PTH, 25OHD, calcium, phosphorus and alkaline phosphatase in serum.

Clinical assessment

The nutritional status of CF patients was expressed as Z score of index weight for height (T/V), how many standard deviations (SD) T/V differs from median for appropriate age and sex;

Pulmonary functional tests were measured by Flow Screen-Jaeger Spiro meter. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were analyzed. The values were expressed as percent of predicted values for sex, age, weight and height;

Cystic fibrosis disease severity was assessed using the Shwachman-Kulczycki (S-K) system, which rates general activity level, pulmonary physical findings, growth and nutriation, and chest radiographic findings. Total S-K scores may range from 20 to 100; low scores representing greater illness severity.

Laboratory measurements

Calcium, phosphorus, and alkaline phosphatasis were measured in serum at the University Pediatric Clinic in Skopje. Serum osteocalcin (OC), β crosslaps, 25OHD and PTH were determined by electrohemiluminiscent method on the automatic immune analyzer elecsys 2010 Roche at the University Clinic for Biochemistry in Skopje. Referral values for 25OHD are 15–44 ng/ml. According Cystic Fibrosis Foundation levels for 25 OHD in CF patients below 30 ng/ml are consider insufficient and levels beyond 20 mg/ml for deficiency.

For determining polymorphism for VDR gene the method for restriction fragment lenght polymorphism (RFLP) was used and haplotypes of VDR genetic locus-TaqI (T/t), BsmI (B/b) and FokI (F/f) were determined. Variants of alleles of VDR gene were investigated in

Institute for immunology and human genetic, Medical Faculty, Skopje.

Bone density measurements

BMD was measured via dual energy-ray absorptiometry (DXA) scans with spinal scores recorded. They were expressed by Z or T scores depending of the age of patients.

Densitometry definition of osteoporosis is accepted by the European Foundation for Osteoporosis and World Health Organization (WHO) and is the golden standard for definition for osteoporosis. Osteoporosis is defined as a bone density < 2.5 SD of the mean BMD of a 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.

Statistical analysis

Results are reported as mean value (M) and standard deviations (SD) for each group. Student's *t*-test was used for calculating significant differences between CF and control group. Pearson scores were used to determine correlation analysis between BMD and various clinical variables. Statistical significance was defined as $p < 0.01$.

Results

The study included total 77 patients with cystic fibrosis, who were divided in three groups depending on age and pubertal status.

Table 1

Total number and average age of CF groups of patients

	5–11 years old (prepubertal group)	12–17 years old (pubertal group)	Above 18 years (adult group)
Total number	34	24	19
Average years	8.32 ± 1.89	14.04 ± 1.9	23.6 ± 3.5

50% of the CF patients with PI had serum vitamin D > 20 ng (range 10–44 ng/ml) with no difference of age. In CF group we found 30% < 15 ng/ml.

Mean value 25OHD in CF group is 22.23 ± 9.97 and mean value in control group is 30.32 ± 11.3, which is statistically significant ($p = 0.0001$*) despite daily supplementation in CF patients with 800 IU (Figure 1).

Figure 1 – Mean values of vitamin D in CF and control group

In CF patients we didn't find statistically significant difference for vitamin D between the groups (Table 2).

Table 2

t-test for 25OHD in serum between prepubertal, pubertal and adult CF patients

Age groups	*t*-test	p
Adult/pubertal	0.41	0.68
Adult/prepubertal	-0.76	0.44
Pubertal/prepubertal	-1.31	0.19

We found statistically significance for osteocalcin in pubertal and prepubertal CF group; the levels were higher in these groups what indicates higher turnover (Table 3).

Table 3

t-test for osteocalcin in serum between prepubertal, pubertal and adult CF patients

Groups	*t*-test	p
Adult/pubertal	-5.48	0.000003*
Adult/prepubertal	-5.01	0.000007*
Pubertal/prepubertal	1.99	0.05

**statistically significant*

We found statistically significance in prepubertal and pubertal group for βcrosslaps values, which means that children with CF have abnormal turnover. High plasma βcrosslaps values reflect raised osteoclast activity in 50% of patients with osteopenia (Table 4).

Table 4

t-test for ßcrosslaps in serum between prepubertal, pubertal and adult CF patients

Groups	*t*-test	p
Adult/pubertal	-3.85	0.0004*
Adult/prepubertal	-3.32	0.001*
Pubertal/prepubertal	0.51	0.6

**statistically significant*

There was no statistically significance for PTH in CF groups besides higher bone turnover in younger patients (Table 5).

Table 5

t-test for PTH in serum between prepubertal, pubertal and adult CF patients

Groups	*t*-test	p
Adult/pubertal	-0.29	0.76
Adult/prepubertal	1.54	0.12
Pubertal/prepubertal	1.44	0.15

Average values of vitamin D and bone markers in CF groups are presented on Table 6.

Osteopenia (Z or T score < -1SD) was determined in 35% of patients. We found 2 patients are with osteoporosis (Figure 2).

Table 6

Average values for 25OHD, osteocalcin, ßcrosslaps, PTH, calcium and alkaline phosphatase in serum for prepubertal, pubertal and adult CF patients

Groups	25OHD ng/ml	Osteocalcin ng/ml	ßcrosslaps ng/ml	PTH pg/ml	Ca mmol/l	AF IU
Adult	21.6	28.94	0.68	49.29	2.4	240
Pubertal	20.11	94.31	1.47	53.14	2.3	230
Prepubertal	24.04	71.2	1.37	37.68	2.4	240

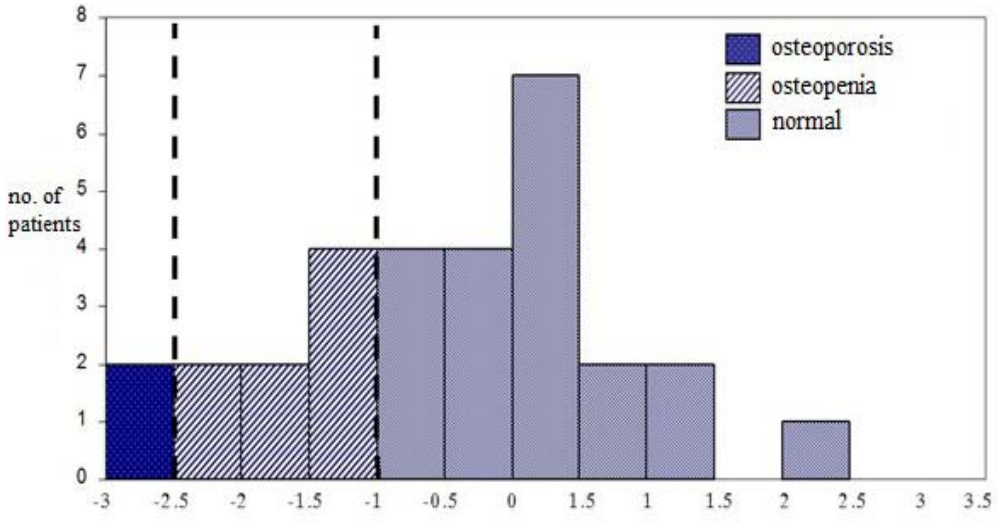

Figure 2 – Distribution for Z or T scores from DXA scans in CF patients

There was one CF patient homozygote for TaqI and Bsml, one for TaqI and one for Fokl. These patients have vitamin D deficiency and osteopenia. Further investigations are needed.

Discussion

Since 1979 when low bone mineral density (BMD) in patients with cystic fibrosis (CF) was firstly described, a lot of studies are performed trying to understand the underlying reason for metabolic disturbance in bones in these patients [1–4]. The term "bone disease" is used to differentiate the bone abnormalities seen in CF from postmenopausal osteoporosis [5, 6]. Adulthood is now common in CF and survival continues to increase, but they face major complications emerging with longer survival including diabetes, liver disease, osteoporosis and infertility [7, 8].

Osteoporosis is systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk.

A lot of risk factors may influence over low bone density including malapsorption of calcium and vitamin D, malnutrition, delayed puberty, hypogonadism, diabetes, reduced physiccal activity, glucocorticoid therapy, frequent antibiotic therapy and chronic pulmonary infection [9, 10]. The origin of the low bone mass in patients with CF is incompletely understood.

Meta analysis from Paccou and al. reports that the mean prevalence of osteoporosis in adults with CF was 23.5% (in different studies from 9–59.1%) [5]. The prevalence of osteopenia ranged from (12.1–70%), with mean value 38%. BMD was lower in patients with malnutrition or in patients who received glucocorticoids [5, 6].

Although more pathological consequences from the bone lose reflects in adulthood, there are many studies about children and pubertal CF patients who cannot achieve half of the bone density compared with their school mates [17]. Puberty is crucial period for gaining adequate peak bone mass accumulation. Decreased peak bone mass accumulation is the result of delayed puberty, chronic pulmonary infections and hormonal disbalance.

Many studies reports that the children and adolescents with CF don't succeed to achieve adequate bone mass, compared with healthy children in time of their quick puberty growth [17, 18]. The International Society for Clinical Densitometry defines low bone density in children and adolescents like Z score equal or lower than -2,5 SD, determined for age, sex and height [24]. BMD values are difficult for interpretation in patients with short stature. In study from France in 114 children and adolescents with CF who had good nutritional status and mild lung disease, 34% had Z score lower than -1 in lumbar part of the spine, including pati-

ents 6 years old. Similar findings in normal prepubertal children with CF are reported in studies from Gronowitz and al., Bianchi and al. [18, 19]. This suggests that the bone disease in youngest CF patients can develop independently from the nutritional or pulmonary status [20].

The risk from fractures in CF patients starts in late adolescence, and is higher in female [21]. In meta analysis from 12 studies with total number of 1055 patients aged 18.5–32 years, the prevalence of radiological vertebral and no vertebral fractures was 14% [5]. On lateral radiography of thorax in 143 adult CF patients 71 fractures in 39 patients (27%) were found. Most studies suggest on higher incidence on vertebral fractures and ribs fractures [12, 13, and 14]. Elkin in 2001 found 17% of CF patients with vertebral fractures, and 8% with rib fractures [13]. Aris, 1998, found 51% of adult CF patients with vertebral fractures [12].

The development of CF bone disease leads to decrease in pulmonary function, caused by inability to cough and pain when they are doing physical therapy. Every vertebral or rib fracture makes difficult the clearance of secret from bronchi's what is necessary for prevention of exacerbations of pulmonary infections.

Studies in children with moderate lung disease with good nutritional status showed higher risk of fractures [13, 15]. In study with 107 children with CF, age 5–16 years who have different clinical status, 14% have fractures [16–18]. Osteopenia and osteoporosis are quite common in the adult CF population. Vertebral fractures in patients with CF may contribute to an accelerated decline in lung function and can be a contraindication to lung transplantation. That is why is particularly important to promote the screening of osteoporosis in these patients. This study presented high prevalence of osteopenia 35% in CF patients who attend our CF center.

The foundation for lifetime bone health is established during infancy, childhood, and adolescence and requires adequate nutrition, body mass, physical activity and hormone production. Puberty is a particularly critical period for mineral accrual, especially for individuals with CF, who often suffer from delayed puberty and lower pubertal growth velocity. Delayed puberty and hypogonadism may impair bone mineral accretion and/or accelerate bone loss. Studies have shown that CF patients have pathological bone turnover, mainly defined with higher bone resorption even in clinical stable patients. That was found first time in study of Grey [15] who found high levels of hydroxyprolin, betacrosslaps and deoxiprolin in urine [18]. Bone turnover markers in CF patients indicate that they suffer from hyperresoption and an inadequate compensation in bone formation even when clinically stable [5, 13, 15]. In this study we show that pubertal patients have significantly lower BMD ($p < 0.01$).

Hahn in 1979 year was first who described the relationship between low bone density and vitamin D deficiency [4]. There is evidence from more than 20 reports that vitamin D insufficiency (low 25 OHD levels) is common among individuals with CF (23–75%), irrespective of season and despite supplementation with 800–1000 IE/day [6–9, 20, 22).

There was suggested that current recommendations for vitamin D supplementation may not be adequate in CF patients [7–9]. Low serum 25 OHD concentrations were associated with lower BMD, suggesting that vitamin D deficiency may play a significant role in the pathogenesis of demineralization in cystic fibrosis [19, 21, 23, 24, 27, 28]. The cause of vitamin D insufficiency can be malapsorption, vitamin D malapsorption, and low levels of vitamin D binding proteins and reduced sunlight exposure. In our study we found that 30% of CF patients have vitamin D deficit, despite supplementation with 800 IE/day. CF patients have significantly lower levels of vitamin D ($p < 0, 001$) than healthy subjects.

Influence of vitamin D receptor alleles on BMD suggests that these polymorphisms have a greater influence on BMD in childhood [10, 11]. We found one CF patient homozygote for TaqI and Bsml, one for TaqI and one for Fokl. These patients have vitamin D deficiency and osteopenia.

Conclusion

- Prevalence of osteopenia and vitamin D deficiency in our study is very high, about 30% from investigated patients.
- CF patients have need of higher doses of vitamin D per day and annually monitoring of 25OHD levels.

- Levels of markers for bone resorption in serum were elevated in prepubertal and pubertal children with CF and this may contribute to impaired bone turnover. There is a possibility of a very early onset of defective bone mineralization in CF independent of severe inflammation and nutritional status.
- Bone remodeling in CF patients is impaired. Further investigations are needed to find underlying pathogenesis of low bone mass and vitamin D deficiency.

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Резиме

ПРЕВАЛЕНЦА НА МАЛА КОСКЕНА МАСА И ДЕФИЦИТ НА ВИТАМИН Д КАЈ ПЕДИЈАТРИСКИ И АДУЛТНИ ПАЦИЕНТИ СО ЦИСТИЧНА ФИБРОЗА ВО РЕПУБЛИКА МАКЕДОНИЈА

Татјана Јаќовска[1], Јасмина Мечевска-Јовчевска[2], Александар Петличковски[3], Стојка Фуштиќ[1], Татјана Зорчец[1]

[1] Универзитетска клиника за детски болести, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Скопје, Р. Македонија
[2] Универзитетска клиника за клиничка биохемија, Скопје, Р. Македонија
[3] Институт за имунологија и хумана генетика, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Скопје, Р. Македонија

Коскената болест кај цистична фиброза (ЦФ) стана тема од голем интерес и влијание кај ЦФ популацијата. Неодамна некои биохемиски маркери беа наведени како важни во динамиката на коскениот метаболизам. Но, постојат само ограничени податоци за тоа кај педијатриски пациенти. Нерамнотежата помеѓу коскеното формирање и разградување кај ЦФ особено во пубертетот стана важно прашање за развој на остеопенија. Влијанието на витамин Д рецепторните алели врз коскениот дензитет укажуваат дека овие полиморфизми имаат големо влијание врз коскениот метаболизам кај децата. Целта на студијата беше да се оцени преваленцата на витамин Д дефицит и остеопенија кај педијатриски и адултни ЦФ-пациенти.

Методи: Студијата вклучи 77 клинички стабилни ЦФ-пациенти (5–36 години), кои редовно го посетуваат Центарот за ЦФ при Клиниката за детски болести во Скопје, Македонија. Остеокалцин, бетакрослапс, 25ОХД и паратхормон беа мерени со метод на електрохемилуминисценција. Коскениот дензитет беше мерен со метод на двојна енергетска апсорпциометрија (ДХА) врз лумбалниот дел од ’рбетниот столб.

Резултати: 50% од ЦФ-пациентите со панкреасна инсуфициенција имаа серумско ниво на витамин Д > 20 нг (10–44 нг/мл) без обѕир на возраста. Високите нивоа на бетакрослапс имаа одраз врз зголемена остеокластна активност кај 50% од пациентите со остеопенија. Најдовме еден пациент хомозигот за TaqI и BsmI, еден за TaqI и еден за FokI. Овие пациенти имаа витамин Д дефицит и остеопенија.

Заклучок: Коскеното ремоделирање кај ЦФ-пациентите е нарушено. Потребни се понатамошни испитувања за да се пронајде основната патогенеза за мала коскена маса и витамин Д дефицит.

Клучни зборови: цистична фиброза, остеопороза, витамин Д дефицит, коскено ремоделирање.