

# Hypervitaminosis D: case report of pediatric osteoporosis secondary to cystic fibrosis

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## Summary

**The objective of the study is to evaluate alterations of bone metabolism in adolescence and adult CF, determining the rate of osteoporosis, osteopenia and vertebral and non-vertebral fractures. We took into account the clinical case of a child who right from the age of seven years has presented joint pain.**

**The little girl was diagnosed with osteopenia with the rapy of calcium and vitamin D; after few years despite treatment nephrocalcinosis and osteoporosis take over.**

**It was examined a cohort of patients with cystic fibrosis of the southern Italy, 24 patients aged between 12 and 44 years, 12 females and 12 males with BMD assessment methods like dual energy X-rays (DXA) and calcaneal ultrasound densitometry in a few cases, ultrasonography was used jointly.**

**From this case study we tried to establish the relationship between cystic fibrosis and osteoporosis etiopathogenetic, the adoptive therapy and the impact of therapies on patients.**

**It was concluded that, given the high number of unrecognized patients with impaired bone mineralization, we must implement and integrate a more aggressive treatment with bisphosphonates and prevention programs that can combat the lifestyle and new eating habits of our young people that facilitate the loss of bone mass.**

*KEY WORDS: cystic fibrosis; osteoporosis; hypercalciuria.*

## Introduction

Cystic fibrosis is an autosomal recessive disease, occurring the most frequently in Caucasians with a frequency of 1:2500-3000 born. The gene encodes a chloride channel protein that transports across cell membranes, called CFTR (cystic fibrosis transmembrane regulator) and is an abnormal protein that is responsible for the particularly dense secretions produced by esocrine glands.

From discovery of gene other 1000 mutations have been identified and with the exception of the most frequent Delta F 508, the other mutations are rare or very rare and variously distributed geographically and ethnically. Cystic fibrosis is a complex disease with multiple organ failure that may occur and develop differently in different periods of life. The organ most affected by the disease is the lung, but we will deal with the correlations with bone mass.

## The case

A 12 years old girl suffering from cystic fibrosis who is hospitalized for nausea, refusal of food, periumbilical and epigastric pain. Along with these symptoms are those of a bronchial cough, sometimes productive, purulent sputum and mild fever.

*Past history:* born out by childbirth and pregnancy at term without complications.

At the second week of life are present gastrointestinal and respiratory symptoms and hence the identification of cystic fibrosis in the first months of life.

At the second year of life: onset of persistent fever with normal inflammatory markers associated with bone and joint pain.

At the seventh year of life: running a bone densitometry with Z-score of -1.5, -5 T-score, then the patient begins a treatment with 2200 IU vitamin D/day and 1000 mg of calcium per week followed by 1000 mg of calcium per day for about one year.

*Family history:* mother, maternal grandmother and maternal great-grandmother suffering from kidney stones, all heterozygous for cystic fibrosis.

*Next anamnesis:* presence of a framework type of pulmonary fibrosis and bronchiectasis, chronic colonization with Staphylococcus a and intermittent Pseudomonas a. The cycles of intravenous antibiotics used for respiratory exacerbations improved joint and bone pain.

From about 10 months occurrence of abdominal pain with greater involvement of the upper quadrants.

*Clinical course:* the abdominal pain was initially relieved by proton pump inhibitors at high doses. The imaging techniques showed a slow intestinal transit and a gastrectasia that was accentuated after the meal and blood tests showed increased alkaline phosphatase, serum calcium to normal but higher limits, altered renal tubular function indices, detection of hypercalciuria (6 mg/kg/24 h-212 mg/24 hour urine) and values of 25 OH vitamin D increased (75ng/ml). Also in the kidney was found a nephrocalcinosis with minute gallstone calcification. Withholding the dose of calcium, reducing the intake of vitamin D at 400 U/day and taking a water cure normalized values of calciuria (3 mg/Kg/24h-110 mg/24 h urine), tubular index, vitamin D 25 OH (19.7 ng/ml) and slightly altered values of parathyroid hormone. You add in the citrate therapy.

Subsequently, the abdominal pain became remittent administering Ketorolac, it improved by a better distribution of the meals, and it took turns to free renal colic with expulsion of small concretions stone formers. DXA values were found in the survey L1-L4 T-score of -4.0 and -3.3 Z-score values, while the femur T-score of -2.4 and -1.9 Z-score.

After eighteen months the gastrointestinal symptoms were significantly attenuated by merely mild and tolerable nausea and

abdominal cramps, and kidney colic disappeared while persisting nephrocalcinosis.

The patient has continued treatment with citrate, the dosage of vitamin D has been adapted while the calcium has not been given.

### **Cystic fibrosis and osteoporosis**

In literature data that correlate alterations of bone metabolism in adult CF show a 23.5% prevalence of osteoporosis, 38% of osteopenia, 14% of vertebral fractures and 19.7% of non-vertebral fractures (1-8). Also the data regarding the pediatric population revealed a deficit of heterogeneous mineralization both of the spine and of the skeleton in its entirety with the prevalence of osteoporosis from 20% to 28% and osteopenia from 33% to 47% (9-13).

The demineralization is quite early, from the age of 5 years, even in children with mild forms of respiratory disease and longitudinally there is a loss of a standard deviation every 6-8 years.

The frequency of osteopenia increases in adolescence therefore a fair number of young people have a peak of reduced bone mass.

Rib fractures and vertebral fragility fractures are the most frequent in cystic fibrosis with a 10 times greater risk of rib fractures and 100 times more of vertebral fractures compared to healthy peers.

With reference to children and adolescents there are limited data on fractures, but the frequent presence of kyphosis (from 10% to 40% of cases) could be misunderstood to imply vertebral fractures (14).

As with many chronic diseases, the low bone density can be caused both by factors related to the disease itself and to therapies that could interfere with the necessary complex processes of bone remodeling and reaching the peak of bone mass.

The presence of malabsorption, malnutrition, delayed puberty, hypogonadism, corticosteroid therapy, low oxygen and reduced physical activity, and a possible liver damage are all factors of osteopenia.

In these subjects there is also a chronic inflammatory state interrupted by more or less frequent exacerbations of the disease that cause the activation of T lymphocytes and release of markers of inflammation, including interleukin (IL-6) and Tumor necrosis factor (TNF-alpha) that affect bone and a high turnover loss of bone mass.

Recent studies show the importance of CF gene on bone mass as Delta F508 homozygous genotype have a reduced density compared to other genotypes and heterozygotes to confirm this (15).

### **Materials and methods**

It was considered a cohort of patients with cystic fibrosis in southern Italy, 24 patients aged between 12 and 44 years, 12 females and 12 males with methods of assessment of BMD type dual-energy X-rays (DXA) and calcaneal ultrasound densitometers, and in many cases phalangeal ultrasound has been used.

### **Results**

The prevalence of osteoporosis patients is 6 out of 24, including 3 females and 3 males, 3 adult and 3 pediatric patients. The average BMI of the subjects tested was 29.2 while the average FEV1 was 64.6%.

The spinal district was the most affected, 6 cases out of 6 (Z-score between -2.7 and -3.3) and (T-score between -2.9 and -3.8), while the femur was involved in a pediatric patient (Z-score -2.6) and in an adult patient (T-score -2.5).

Only one subject was diagnosed with a vertebral fracture, but some

of these have a history of back pains, spinal deformity and especially kyphosis.

The frequency of osteopenia is instead of 5 out of 24 patients with a prevalence of female cases, 4 out of 5, two of which are younger than 20 years.

In all osteopenic/osteoporotic patients there are additional risk factors for bone loss including: diabetes or glucose intolerance 6/11, the frequent use of cortisone 4/11, multiple allergies 3/11, liver disease 3/11, thyroid disease 2/11, celiac disease 2/11, malnutrition, 2/11, finally hyperlipidemia, cryptorchidism, arthralgia, tachycardia and vertigo 1/11.

### **Conclusions**

The clinical history of patients with this autosomal recessive disease has greatly changed in recent years. The most aggressive therapies towards respiratory exacerbations, greater attention to nutrition issues, new treatments and the use of lung transplantation have increased the survival of these patients.

So cystic fibrosis from being exclusively a pediatric pathology has become a disease of interest also for the physicians of the adults and hopefully in the future it will become a disease of interest also for geriatrics.

Although in the last 30 years there have been reports of osteoporosis in CF, studies on the skeletal involvement are quite recent. Given the high percentage of patients – both pediatric and adult – with reduced bone mineralization it is necessary to make a careful assessment of the health status of the bones so that you can activate, by early recognition of bone damage, a targeted prevention. In this small number of subjects it has been observed (many studies support our thesis) that in patients with cystic fibrosis, and especially in female subjects, there is a greater risk of vertebral fracture, resulting in a further deterioration of lung injury (16). Another consideration is the association between cystic fibrosis and nephrolithiasis in the case considered.

In these patients the risk of kidney stones is higher even if it is not yet clear which are the causes including poor urine output, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, in any case a supersaturation of urine (17).

Finally, in the treatment of osteoporosis in cystic fibrosis it is necessary to maximize the intake of vitamin D and calcium individualizing the dosage, to assess any drugs that can increase bone density improving the resistance, and to take appropriate physiotherapy techniques and gymnastic exercises.

More extensively for the pediatric area, given the large number of subjects with reduced bone mineralization misunderstood, we must implement integrated prevention programs that can counter the new lifestyle and eating habits of our young people that facilitate the loss bone mass.

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