

## Bone Mineral Density and Cystic Fibrosis: A Review

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### Abstract

Cystic fibrosis (CF) is a common progressive genetic disorder among children which involves lungs, kidneys, intestine and liver. Apart from the significance of genetic factors, various environmental factors particularly bone mineral density are directly associated with CF. Remarkably, bone disease is appeared as a routine and common trait in long term CF survivors which implies that environmental parameters including calcium and vitamin D intake as well as drug inducement are the most important risk factors causing low bone mineral density.

Conspicuously, absolute and notable treatment of cystic fibrosis associated to bone disorder must involve investigating the risk factors including the reduced intake of certain vitamins and minerals due to pancreatic inadequacy, modified hormone production, severe and chronic lung infection with increased ranges of bone function cytokines for a weak bone health situation. In this review, focus is on these considerable factors alongside the genetic factors in cystic fibrosis.

**Key Words:** Cystic Fibrosis, Low Bone Mineral Density, Genetic Factors, Vitamin D.

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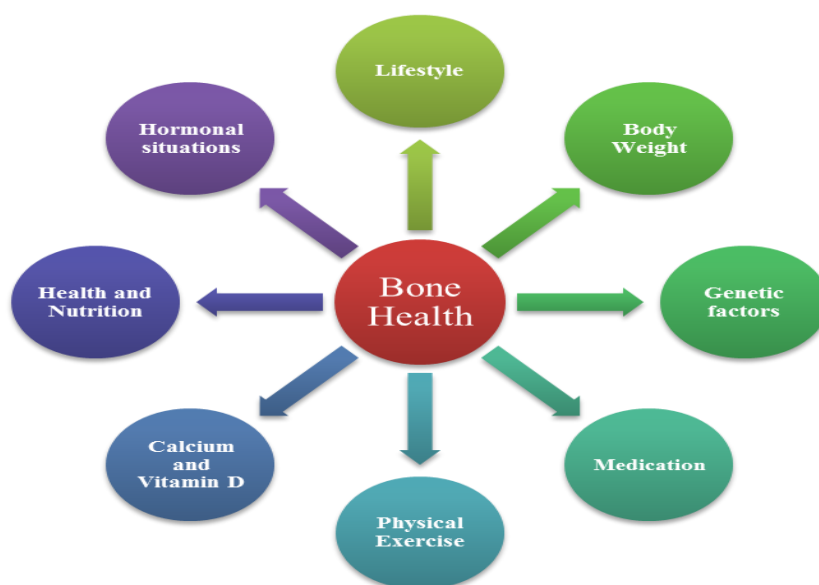
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## 1- INTRODUCTION

Cystic fibrosis (CF) is one of the common lethal autosomal recessive situations affecting the children's population worldwide, and it is inherited in an autosomal recessive function. It results mainly from the presence of certain mutations in both copies of the *CFTR* gene (1, 2). The defective CF regulator gene is

evident in some clinical traits like chronic pulmonary disease, biliary cirrhosis and pancreatic insufficiency (3, 4). Notably, improved treatment age is different in eclectic population and it is approximately about 31 years (5-7). Consequently, different complications of CF disease are emerging and comprise low bone mineral density (**Figure.1**).



**Fig.1:** Main factors that can affect bone density and its chemical combinations.

Patients suffering from CF have many notable risk factors for the progression of low bone mineral density (BMD) including low vitamin D intake, pulmonary disease, glucocorticoid therapy, hypogonadism with diabetes, delayed puberty, decreased levels of physical function and malnutrition. The most important clinical consequence of low bone mineral density is fracture, and patients with CF have increased fracture rate compared to normal people (8-10).

Generally, when the bone density is lower than normal, it may mean that there is a greater chance of getting osteoporosis in the future. There are many factors in CF that may affect bone mineral density and it is important to evaluate these factors. The aim of this investigation was to

discuss the most influential parameters by which CF affects different aspects of bone mineral density. First, we talk over clinical qualifications and the prevalence of bone mineral density in cystic fibrosis and the related factors. Then, we discuss the relationship between bone histomorphometry and CF. Also, density fluctuation and intake fluctuation of bone are taken into account, the pathophysiology of bone disease is elaborated in CF and finally, the inheritance and genetic factors are discussed.

## 2- MATERIALS AND METHODS

In order to find the documents related to the review article, the keywords including "cystic fibrosis, bone mineral

density, vitamin D, fracture, children, and pediatric" were searched on PubMed, Scopus and Science Direct databases from 1975 until now. Over this period, more than 500 documents were examined and the articles were selected according to the following criteria: first, the titles were examined for thematic relationship. After reviewing the titles of the articles, they were evaluated at the next stage in terms of abstract communication with the intended purpose. Selected items were thoroughly studied and the important notes were extracted. Then, the collected materials were classified into two main areas: "environmental factors", and "genetic factors" which were subsequently summarized. In cases where it was required, additional comments and descriptions for the content were provided by the author for better clarity.

### 3- RESULTS

#### 3-1. Role of clinical qualifications of bone mineral density in cystic fibrosis

Many studies and researches have indicated the role of low bone mineral density in cystic fibrosis patients (11-16). Diminished bone mineral density is quite routine in post pubertal kids and adults with cystic fibrosis (17). As a result, the prevalence of bone mineral density is very common. Correspondingly, improved methods can be made for bone evaluation including bone age or size by applying bone mineral density, but, some additional problems will be encountered by the new methods used to evaluate bone size with X-ray absorptiometry. Many studies have focused on the density of bone structure and have indicated the importance of low bone mass fixed after fitting for these factors. This means that some of the alterations in these searches could be illustrated by the patients' situation including age (for instance, children have a better volumetric bone density than adults) (18, 19).

The prevalence of bone disorder tends to increase with the severity of lung problems and malnutrition. Younger people may have normal status of bone mineral density, suggesting that the bone disorder is not originally associated to the *CFTR* gene mutation and remarkably, some mutations in this gene can happen, and diverse mutations cause many structural defects in the *CFTR* protein and, in some situations, diseases (20-24). Clinically, patients with acute pulmonary problem sometimes have a serious and severe bone disease, with a high rate of fractures of vertebrae, ribs and bones and kyphosis (**Figure.2**).

#### 3-2. Role of histomorphometry in cystic fibrosis

Recent findings of bone histomorphometry in adults with cystic fibrosis and low bone mineral density illustrate decreased bone volume and a trend towards reduced connective tissues (25, 26). Notably, in this situation the indexes of bone formation were also significantly decreased. Evaluation of the intake cavities indicated tiny regions, depths and reconstructed lengths of the cavities in CF patients, and this causes the amount of bone formation to be reduced by approximately 50% (27-29). Conclusively, these findings explain that the major reason for low cancellous bone volume seems to be low bone concentration in tissues. Many rare case studies about the autopsy of bone specimens from a mixture with transplantation activity in people with cystic fibrosis illustrated acute osteopenia in bone (3, 30). There was reduced osteoblastic function and increased osteoclastic function at the cellular level. The decrease in osteoblastic function was due to the reduction in osteoblast and also the biosynthetic potential of these cells (13, 31, 32). Remarkably, cellular and cortical bone mass amounts would be lower after transplantation. Moreover,

none of the cystic fibrosis biopsies indicated osteoid items traits of osteomalacia due to vitamin D deficiency (18, 33, 34).

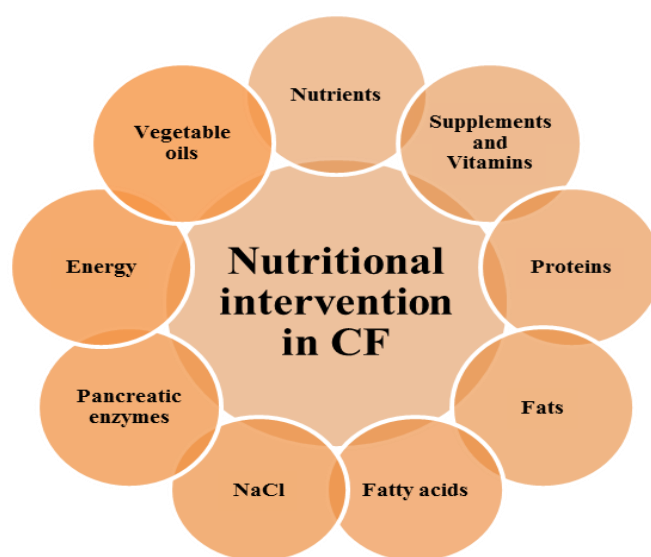
### 3-3. Density fluctuation of bone in cystic fibrosis

There are many important factors for lifetime bone health, which are established during infancy, childhood, and adolescence and require sufficient nutrition, normal body mass, physical exercise and normal hormone production (22, 35). Puberty is a specially required process when growth and mineral accrual are advanced (12, 19). These important factors may be compromised in cystic fibrosis patients who suffer from decreased pubertal growth and delayed puberty. In this account, a study of pubertal children with cystic fibrosis confirmed that insufficient bone mineral amount was found to be lower than the expected bone mineral density and volumetric bone mineral density (36). One study acknowledged this result by illustrating femur, total body, wrist mineral density and spine bone mineral density in children aged 5–10 years with

cystic fibrosis, but total body and distal wrist mineral density in middle-aged people was significantly decreased (11, 37). In fact, these remarkable findings and results must be considered because there is restricted normative bone mineral density data during primary period of life (38, 39). Moreover, the majority of patients with low bone mineral density of cystic fibrosis are adults. The obtained data from the adult and pediatric searches concluded that low bone mineral density results from insufficient bone deposition during puberty stage (16, 40).

### 3-4. Intake fluctuation of bone in cystic fibrosis

Investigations and searches of biochemical markers for bone situation recommend an imbalanced bone intake in cystic fibrosis cases that are clinically stable (41). Accelerated bone intake was initially reported and also the high urinary hydroxyproline levels were also reported (42, 43) (**Figure.2**). The results indicated lower levels of serum osteocalcin in pubertal children and also young adults. Remarkably, there are different formation markers in this case (44-46).

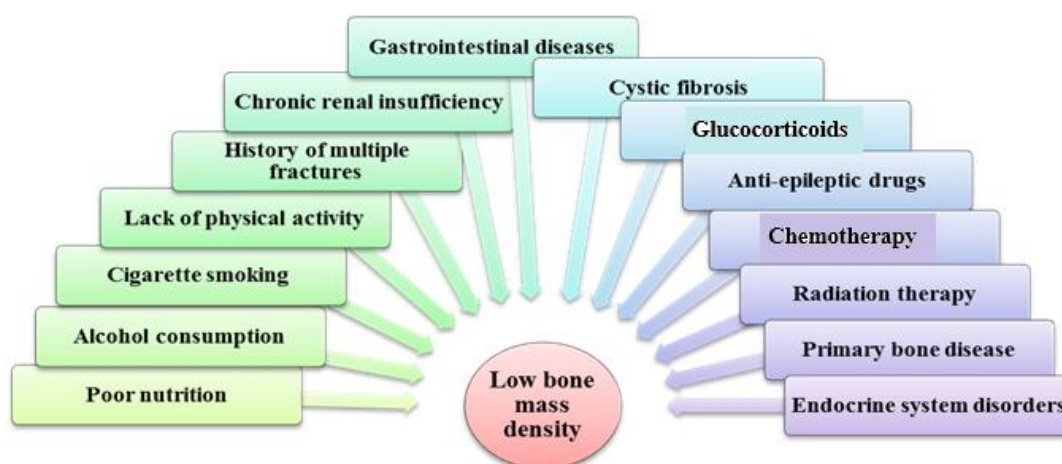


**Fig.2:** Nutritional main factors can also show their effects in cystic fibrosis.

### 3-5. Pathophysiology of bone disease in CF

Besides the genetic factors, major factors that are involved in pathobiology of cystic fibrosis can be environmental factors like pancreatic exocrine insufficiency and also malabsorption, vitamin D insufficiency, pancreatic endocrine insufficiency, physical activity, delayed puberty or early gonadal failure, chronic infection, hormonal alterations like glucocorticoids and lung transplantation and immunosuppressant therapy (47, 48). In pancreatic exocrine insufficiency and

malabsorption, optimal nutrient intake is necessary to maintain sufficient body and bone mass health. Evidently, malnutrition is a common complication of CF (49). This implies that malabsorption is associated with the catabolic process occurring with severe lung infections (25, 50). In this way, one of the most important risk factors that increases the severity of the disease and its complications is BMI. Interestingly, many researches have indicated a correlation between malnutrition and low bone mineral density in cystic fibrosis (**Figure.3**).



**Fig.3:** Risk factors that are involved directly in low bone mass density.

There is considerable evidence that acknowledges and confirms vitamin D insufficiency, both low or low normal 25hydroxyvitamin D levels, is a common event among people with cystic fibrosis (51). Compared to normal people in whom vitamin D concentration is approximately 20 ng ml<sup>-1</sup>, most people with cystic fibrosis have low concentration levels of vitamin D. Evidently, at the final stage of cystic fibrosis, vitamin D deficiency is the most common clinical trait and may happen in 25–35% of patients (52). Nevertheless, the cause of vitamin D insufficiency in patients with cystic fibrosis has not been sufficiently investigated and it seems essential to study the causes and factors responsible for this symptom. For

pancreatic endocrine insufficiency, we can focus on diabetes function. Diabetes mellitus has been associated with decreased trabecular bone mass and it is developed in 10% of people with cystic fibrosis (53). Cystic fibrosis associated diabetes may differ in type I and II diabetes. The abnormalities in glucose metabolism result from chronic infection and the inadequate formation of islet cells. In addition, chronic infection leading to insulin resistance may play a key role in reducing the bone mineral density. Besides the main mentioned factors, physical inactivity is of great importance. Cystic fibrosis may lead to a sedentary life style because of decreased lung function and chronic pulmonary infection (54).

Correspondingly, steroid deficiency due to delayed puberty or early hypogonadism certainly supports cystic fibrosis associated bone disease (55). Pubertal delay in cystic fibrosis was identified many years ago and is associated with disease status. For chronic infection, bone remodeling is under the impact of normal hormones, cytokines, and also localized main growth factors. Many factors in the serum and also respiratory system of people with cystic fibrosis can provoke osteoclastic bone intake, comprising parathyroid hormone (PTH), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and growth factor (10). Apparently, many inflammatory cytokines exist in very high concentrations in infected cystic fibrosis lungs and also serum. For glucocorticoids, a measured range of about 25-50% of people with cystic fibrosis are treated and cured with exogenous glucocorticoids for the progress of pulmonary activity (56). Interestingly, many researches and studies have discovered glucocorticoid therapy to be a main risk factor for low bone mass in cystic fibrosis (57). The relationship between corticosteroid application and bone mineral density is confused with disease severity. Lung transplantation and Immunosuppressive therapy are also of great significance. They are used in people with cystic fibrosis in order to extend the survival rate and improve the quality of life (58). Further, immunosuppression is obligatory after transplantation and will aggravate the former low bone mineral density.

### 3-6. Genetic approach to cystic fibrosis

The specific gene in cystic fibrosis is *CFTR* which was localized to 7q21-34 on the long arm of chromosome 7 (Genomic location) (59-61). The gene encodes a 1480 amino acid protein which has been called the cystic fibrosis transmembrane conductance regulator or, *CFTR* gene (62-64). Remarkably, many cystic fibrosis mutations have been reported

(approximately, 1500) and many are rare, while some may not have any clinical symptoms. Different mutations influence the function and activity of *CFTR* gene in different pathways. This implies that some influence the abnormal *CFTR* gene proliferation and others influence the intracellular processing of *CFTR* gene and cellular activity (65-67). According to the above explanation, there are different mutations in *CFTR* gene and the most common mutation is delta F508 which occurs in approximately 75% of people with cystic fibrosis (68-70). In this way, a mutant *CFTR* protein, which is not able to fold into its proper form, is produced (71-73).

### 3-7. Inheritance and risk of passing on the cystic fibrosis

Cystic fibrosis has a simple Mendelian autosomal recessive inheritance. This implies that people with cystic fibrosis have duplicates of the mutant *CFTR* gene. Noticeably, carriers have different situations (one normal and one mutant *CFTR* gene), and have no health problems, because the *CFTR* gene in normal position produces sufficient protein to permit normal cellular activity. Carriers have a 50% chance of transmitting the mutant *CFTR* gene to their children (74). When parents are carriers, there is about 25% chance in every normal pregnancy that the child will have cystic fibrosis and also a 25% chance that the child will have normal *CFTR* genes and 50% chance that the child will be a carrier.

## 4- CONCLUSION

According to many obtained results and findings, the direct correlation of low mineral bone density in cystic fibrosis is recognized. Low bone mineral density kyphosis and also fragility fractures are the most common and routine complications in adults which are extended from childhood. Inflammation, inactivity, malnutrition, medications, and hormone

deficits have all been implicated as the most common risk factors for decreased bone mineral loss. The presence of these main factors makes it difficult to realize the assistance of each variable. Correspondingly, bone mineral density is significantly decreased in adult patients with CF and is associated with markers of disease severity. Moreover, the level of vitamin D supplementation seems to be insufficient and the differences in bone fluctuation between delta F508 homozygotes and non-homozygotes suggest that there may be a genetic correlation to the cause of low bone mineral density in adults with CF. New studies are required to better define the compatible nutritional supplementation and practical programs necessary to avoid poor bone health condition in CF patients, particularly for people with nutritional deficits and also severe pulmonary problems, who obviously need to decrease the risk of bone problems and also reduce fragility fractures.

**5- CONFLICT OF INTEREST:** None.

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