REVIEW

Prevention of osteoporosis in cystic fibrosis

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Purpose of review
The increased life span of patients with cystic fibrosis has lead to the detection of new complications. Osteopenia is present in up to 50% of adult patients with cystic fibrosis, and osteoporosis in 10–34% and can cause a difficult management problem.

Recent findings
In children, defects in bone health become apparent generally at adolescence because of suboptimall bone peak mass achievement. Malnutrition, inflammation, vitamin D and vitamin K deficiency, altered sex hormone production, glucocorticoid therapy, and physical inactivity potentiate poor bone health.

Summary
Monitoring bone mineral density and preventive care of osteoporosis are necessary from childhood to minimize cystic fibrosis-related bone disease in adult cystic fibrosis patients.

Keywords
bisphosphonates, bone mineralization, cystic fibrosis, dual-energy X-ray absorptiometry, vitamin D

INTRODUCTION

Cystic fibrosis affects over 70 000 patients worldwide. It is related to mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene, which, in turn, leads to dysfunction of the multifunctional CFTR protein – a cyclic AMP-dependent ion channel that is one of the main regulators of the transepithelial solute flow. The main clinical consequence is a chronic infected obstructive bronchopathy. The increased life span of patients with cystic fibrosis has lead to the detection of new complications. Defect in mineral content can cause a difficult management problem. This study will review current strategies for preventing cystic fibrosis-related osteoporosis.

EPIDEMIOLOGY OF CYSTIC FIBROSIS OSTEOPOROSIS

Adult studies

Low bone mass and fractures in individuals with cystic fibrosis has been described in more than 70 reports. The most recent studies report T-scores less than −2.5 (defining osteoporosis) between 10 and 20% of the adults with cystic fibrosis [1,2], whereas the prevalence of osteopaenia defined by a T-score between −1 and −2.5 standard deviations (SDs) ranges from 34 [3] to 45% [4], and up to 58% [5]. Annualized losses in bone mineral density (BMD) average 0.1–0.5% at lumbar spine and 1–1.8% at total hip BMDs, for example, approach those experienced by women following menopause [6]. Comparative studies highlight improvement in bone defect in the past 10 years, as assessed by a decrease between 2000 and 2012 in prevalence of osteoporosis from 18 to 6% and osteopenia from 48 to 33% [2,7]. This improvement is consistent with improvement in respiratory and nutritional status.

Pediatric studies

Most of the prepubertal children with mild disease do not display low BMD. Defects become apparent from adolescence [8–10]. Longitudinal pediatric studies report an inadequate bone mass accrual, which is half that of healthy children with failure to achieve optimal bone peak mass [11▪,12,13]. Low BMD is mainly observed in children with the poorest nutritional status and lung function [11▪].

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KEY POINTS

- Decreased bone mineralization is present in 1/3 to 50% of cystic fibrosis adult patients.
- Osteoporosis prevention in cystic fibrosis relies on early monitoring of bone health.
- Osteoporosis prevention in cystic fibrosis relies control of risk factors, such as chronic infection, abnormal nutritional status, adequate calcium and vitamin D low intake, decreased muscle mass and physical activity, and hormonal deficiencies including hypogonadism.

SCREENING FOR BONE MINERAL CONTENT IN CYSTIC FIBROSIS-RELATED BONE DISEASE

Measurements of bone mineral content

Detecting low bone mineralization is the first and mandatory step in prevention of osteoporosis. Bone mineral content (BMC) is measured by dual-energy X-ray absorptiometry (DXA), based on BMD by surface area of the whole body (excluding the head), lumbar spine or femoral neck [14]. DXA measurements have been shown to predict a fracture risk in postmenopausal women, which is multiplied by 2.6 for each missing SD, regardless of clinical manifestations. In this population, and also in men over the age of 50 years with cystic fibrosis, osteoporosis is defined by a BMD T-score ≤ -2.5 and osteopenia by a BMD between 1 and 2.5 T-scores.

The above result is in contrast to children and young adults, because the predictive value of a low BMD for the risk of fracture is uncertain [15]. In this population, osteoporosis is based on fracture history [16]: either at least one vertebral fracture without significant trauma regardless of the BMD values; and/or clinically significant long bone fractures with BMC and/or BMD Z-score less than -2. Clinically significant long bone fractures are defined by their mechanism (fractures secondary to mild to moderate trauma) and number ($\geq$two long bone fractures before age 10 and $\geq$three fractures before age 19), excluding fractures of the nose, fingers, and toes. In cystic fibrosis children, adolescents or young adults, BMD must be scored by Z-scores (e.g. compared to an age and sex-matched population). Demineralization is classed as moderate for a Z-score between -1 and -2, and severe for a Z-score below -2.

A major caveat for areal BMD measure is that it fails to distinguish between changes in mineral density and bone size in growing children. This leads to artifactual overestimation of the BMD defect when the defect in growth (and bone size) is relatively more important than the BMC defect [16]. Therefore, BMD values in children and adolescents must be interpreted according to bone size (influenced by the child's height), bone maturation (influenced by pubertal stage), and body composition [17]. Correction for height or bone size of DXA measurements using bone mineral apparent density (BMAD) may improve the accuracy of the measurement. Other techniques such as peripheral quantitative computerized tomography (pQCT) or high-resolution pQCT (HRpQCT) can be used to assess the BMC reported to volume, differentiate cortical and trabecular bone, and also evaluate biomechanical properties of bone [18]. However, these measures are not readily available in all centers and most used for research than osteoporosis screening.

The DXA measurement must be associated to fracture risk assessment (FRAX) in the most severe adults to target those patients necessitating initiation of pharmacologic treatment [19]. The FRAX algorithms have been developed in adults to give the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). It is based on individual patient models that integrate clinical risk factors and BMD at the femoral neck.

There is no consensus for vertebral fracture screening. The most frequently used is the frontal and lateral radiograph of the thoracolumbar spine, with a less irradiating EOS system (4–10 times less than a standard radiograph), or spinal fracture detection software with DXA [20]. Genant's semiquantitative assessment allows to quantify the degree of severity of a compression [21].

Monitoring bone mineral density in cystic fibrosis patients

It is important to screen for bone health early, as recommended by the European and French guidelines. A first baseline assessment should be made at 8 years and if Z-scores is at -1 or above, it is recommended to monitor DXA every 5 years. If Z-score is between -1 and -2, DXA should be repeated every 2–4 years, and every year for those below -2. American guidelines recommend a baseline BMD at age 18. This is extended to children over the age of 8, only if risk factors of low BMD are present, such as ideal body weight below 90%, forced expiratory rate less than 50% predicted, glucocorticoids more than 5 mg/day for more than 90 days/year, and delayed puberty or history of fractures.

RISK FACTORS FOR CYSTIC FIBROSIS-RELATED BONE DISEASE AND PREVENTION STRATEGIES

All patients with cystic fibrosis are at risk of low bone mineralization. Prevention of cystic fibrosis-related

disease relies on a multifaceted approach which includes control of chronic infection, satisfactory nutritional status, adequate calcium and vitamin D intake, maintenance of muscle mass and physical activity, and correction of a possible hormonal deficiencies including hypogonadism.

Bone toxic medications should be limited as far as possible such as oral and even inhaled steroids [22▪▪,23]. Tobacco must be avoided because it alters trabecular microarchitecture [24], and also excessive alcohol consumption and high dose of caffeine which both negatively impact on the mechanism of bone remodeling, osteoblastic proliferation, and activity [25,26].

Inflammation control

Systemic inflammation is linked to chronic pulmonary infection. It alters bone remodeling and accelerates osteoclastic bone resorption. This is at least partially due to elevated level of proinflammatory cytokines. This is reflected by the association between serum concentrations of proinflammatory cytokines, bone resorption markers, and annualized declines in BMD [27]. As proinflammatory cytokine levels normalize upon antibiotics [28], management of bone-cystic fibrosis-related disease should focus to limit as much as possible bronchial exacerbations. The evaluation of bone resorption markers (CrossLaps, CTX) and formation (osteocalcin and bone alkaline phosphatases) may provide information about pathophysiology; however, these markers are variable and are not correlated with BMD. They are of little use in the diagnosis of bone fragility.

Nutrition status optimization

Low BMD is significantly associated with low BMI [29]. Importantly, patients with normal weight can have altered bone mineralization. In these situations, several studies have shown a correlation with lean body mass decrease [30]. This may be due to a defect or resistance to insuline-like growth factor (IGF)-I – an anabolic factor implicated in regulation of osteoblast proliferation and differentiation [31]. The objective of nutritional management is to maintain a BMI and lean body mass within the normal range [15,32,33].

Physical activity

Physical activity has a beneficial effect on bone health, particularly weight-bearing activities [34]. Physical activity generates site-specific mechanical constraints which induce microcracks and synthesis of new bone. This effect is more pronounced in prepubescent children or those in early puberty [35]. In postmenopausal women, walking, weight-bearing activity, or exercise against resistance is effective to prevent osteoporosis, mainly at proximal femur [22▪▪].

Therefore, European and French guidelines recommend exercise for 30–45 min three times a week including high-impact weight-bearing activities and resistance such as jumping or skipping [15,33].

Calcium metabolism

There is an increased risk of negative calcium balance in cystic fibrosis. On one hand, calcium can be less available because of deficiency of vitamin D and low calcium intake [36]. On the other hand, calcium loss may be increased in feces because of maldigestion and intestinal permeability [37]. This may be associated with low calcium accretion, possibly related to a defect or resistance in IGF-1, and inadequate osteocalcin and leptin level. Hypercalciuria is frequently observed and is related to the high natriuresis because of high-salt diet [38]. This is the reason why European and French guidelines recommend to monitor calciuria annually, aiming for an optimal ratio of urinary calcium/creatinine between 0.1 and 0.5 [15,33]. A calcium-rich diet is imperative (based, as a minimum, on dietary reference intake by the European Food Safety Authority) in conjunction with enough pancreatic extract replacement therapy (PERT) to maintain lipolysis and avoid feces calcium loss in soaps [38]. In case of suboptimal calcium intakes, food intake and high calcium content mineral water drinks should be proposed as they are better absorbed than oral tablets.

Vitamin D

The prevalence of vitamin D insufficiency [serum 25-hydroxyvitamin D (25(OH)D less than 30 ng/ml (75 nmol/l)] and deficiency [serum 25(OH)D less than 20 ng/ml (50 nmol/l)] is high in cystic fibrosis [39]. The definition of optimal vitamin D levels for bone health is still under discussion. Indeed, there is no relation between seric vitamin D level correction and BMD improvement [38]. In adults, the threshold of 30 ng/ml was suggested because levels below 30 ng/ml increase the risk of fractures, cause parathyroid stimulation, decrease intestinal calcium absorption, induce bone resorption, and impair nonskeletal functions, such as muscle strength, lung function, insulin secretion, and innate antimicrobial defense [40,41]. This was recently also suggested in cystic fibrosis by a pilot study which reported that high dose of vitamin D may increase the number of

patients returning to their pre-exacerbation forced expiratory volume in 1 s (FEV_1) values in comparison with placebo controls, in association with decreases in inflammatory markers [42]. This benefit is less clear in children and young adults where attenuation of parathyroid hormone (PTH) levels is observed above 20 ng/ml [43]. This may be detrimental in children and young adults in whom PTH is needed to stimulate bone formation and modeling with the risk to give rise to an 'adynamic' bone disease [44]. Moreover, serum concentrations above 30 ng/ml can be associated with hypercalciuria and increased risk of nephrolithiasis, and less certainly, cardiovascular events as reported in the postmenopausal women.

The US Cystic Fibrosis Foundation recommends levels above 30 ng/ml [32]. The European and French guidelines, and also the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommend a minimum 25(OH)D threshold of 20 ng/ml (50 nmol/l), arguing that the 30-ng/ml cut-off is mainly beneficial in cases where bone defect is due to increased bone resorption, as in postmenopausal women, but is not demonstrated in other population [15,33,45].

Vitamins D3 oral intake is preferred over D2 [46]. The recommended doses are 800 IU in infants, 800–1200 IU a day in children older than 1 year, or 50 000 IU once a month, or 100 000 IU every quarter [15,32–34]. In case of low levels, there is still debate between increase in the daily dose, use of loading doses ('Stosstherapie') (50 000 IU weekly for 8 weeks or 100 000 UI weekly twice), or prescription of more polar compounds, better absorbed, such as calcifediol or calcitriol [47,48]. 'Biological efficacy' of this treatment must include monitoring of 25(OH)D, and also PTH, which must stay in the normal level, and calcemia and calciuria to detect too high dosage.

Assessment of vitamin D status includes serum 25(OH)D, preferably at the end of winter, and also 3–6 months after a dosage change [33]. This should be associated with PTH, and seric and urinary calcium [15,32,33].

Vitamin K

A deficiency in carboxylated osteocalcin is associated with low BMD and reduced bone formation markers [49]. Vitamin K is a carboxylase cofactor transforming the inactive noncarboxylated osteocalcin into gamma-carboxylated active form. Vitamin K supplementation increases carboxylated osteocalcin level after 1 month of daily supplementation [50]. The rational for vitamin K supplementation is, however, only theoretical, because the only study published thus far shows an increase in carboxylated serum osteocalcin, without any effect on bone mineralization [50].

Vitamin K status can be evaluated by serum concentrations of vitamin K, PIVKA-II (protein induced by vitamin K absence) or carboxylated/undercarboxylated osteocalcin ratio, or more routinely, prothrombin time – a much less insensitive marker [15,32,33].

A supplementation of 1 mg/day or 10 mg/week, increased to 1–5 mg/day in case of low vitamin K level, is recommended because these doses have been shown to improve bone biochemical markers leading to reduced bone resorption [15,32,33].

Puberty and sex hormone deficiency: endocrine disorders

Puberty is a crucial period for the development of bone density because peak bone accrual occurs during the time of peak growth velocity and is influenced by both sex steroids and growth hormone [51]. Pubertal delay (lack of breast development in girls after 13 years of age and no increase in testicular volume in boys after 14 years of age) is common in all chronic diseases and is accompanied by a delay in the acquisition of peak bone mass. In cystic fibrosis, a delay in the peak of height velocity by 9–10 months in boys and 10–14 months in girls has been documented. This leads to suboptimal peak bone mass acquisition and ultimately risk for osteoporosis in these patients [52,53].

Systematic screening is therefore important to detect pubertal delay in cystic fibrosis. No studies with hormone replacement therapy have been conducted thus far to determine the benefits on bone mass content. This would be useful, as suggested by physiological estrogen supplementation benefit in anorexic girls associated with an increase in BMD [54].

Similarly, testosterone levels should be measured in adult men to detect hypogonadism. Low testosterone levels occur frequently in cystic fibrosis patients, and an endocrinology opinion should be sought to determine a potential impact on bone health [55].

Proinflammatory cytokines affect the hypothalamic-pituitary-gonadal axis and may induce resistance to growth hormone [56]. Indication of this anabolic treatment goes beyond the scope of this review.

CONCLUSION

Decreased bone mineralization is present in 1/3 to 50% of cystic fibrosis adult patients. Efforts to obtain and maintain normal bone status is clearly one of

the corner stone for a good quality of life in this population. Osteoporosis prevention in cystic fibrosis relies on a multifaceted strategy addressing early monitoring of bone health and detection of risk factors. The opportunity to influence bone mineralization appears to be greatest during childhood and adolescence.

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- ■ of special interest
- ■■ of outstanding interest

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