Update on maintaining bone health in cystic fibrosis

Michael P. Boyle

Purpose of review

The high prevalence of decreased bone density in adults with cystic fibrosis is now well recognized, and guidelines for screening and treatment of cystic fibrosis-related bone disease have recently been published. This review summarizes the current best practices for optimizing bone health in cystic fibrosis and highlight recent findings that provide insight into the etiology of cystic fibrosis-related bone disease.

Recent findings

Recent research suggests that cystic fibrosis-related bone disease actually starts during childhood, when individuals with cystic fibrosis fail to demonstrate normal bone calcium accretion. The failure to reach peak bone mass is made worse by increased osteoclast activity and bone resorption. This combination results in decreased bone density and an increased risk of fracture. Recent clinical studies suggest that multiple contributing factors need to be addressed in cystic fibrosis to optimize bone health: malnutrition, vitamin and mineral malabsorption, recurrent infections, inadequate sex hormones, and lack of exercise. Oral bisphosphonates have been demonstrated to be effective in cystic fibrosis and should be used when osteoporosis or progressive osteopenia is present.

Summary

Research suggests cystic fibrosis-related bone disease actually begins during childhood, and guidelines now exist to aid in identifying and treating those with decreased bone density.

Keywords

bisphosphonates, bone disease, cystic fibrosis, osteoporosis, vitamin D

Curr Opin Pulm Med 12:453–458. © 2006 Lippincott Williams & Wilkins.

Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Correspondence to Michael P. Boyle, MD, FCCP, Associate Professor of Medicine, The Johns Hopkins University School of Medicine, 1830 E. Monument Street, 5th floor, Baltimore, MD 21205, USA
Tel: +1 410 502 7044; fax: +1 410 502 7048; e-mail: mboyle@jhmi.edu

Current Opinion in Pulmonary Medicine 2006, 12:453–458

Abbreviations

BMD	bone mineral density
DXA	dual-energy X-ray absorptiometry
25-OHD	25-hydroxyvitamin D

1070-5287

Introduction

The median survival of individuals with cystic fibrosis has climbed steadily over the last 40 years, from early teens in the 1960s to 36.8 years now [1]. One notable effect of the increased survival in cystic fibrosis has been the recognition of medical complications associated with cystic fibrosis that were not easily detectable until individuals began to regularly live longer. Poor bone health is a prime example of a medical complication that has grown in significance in cystic fibrosis as survival has improved [2]. Recent investigations, however, have demonstrated that although poor bone health is most often detected in adults with cystic fibrosis, problems actually begin during childhood, particularly during puberty [3•]. Strategies for optimizing bone health in cystic fibrosis are now being developed and recent guidelines have suggested a multifaceted approach which includes screening, monitoring, and nutritional and pharmacologic interventions [4••].

Epidemiology of cystic fibrosis-related bone disease

Numerous studies have documented the striking prevalence of decreased bone density (both osteopenia and osteoporosis) in the adult population with cystic fibrosis [2,5,6]. Estimates of prevalence in adults with cystic fibrosis range from 40 to 70%. In adults with cystic fibrosis with severe-enough lung disease to be evaluated for lung transplantation, some degree of decreased bone mineral density (BMD) is almost universal, and as many as 45% have significant osteoporosis [7]. After lung transplantation for cystic fibrosis lung disease, the prevalence of osteoporosis may be 70% or more [7].

Most of these studies have utilized standard World Health Organization criteria for evaluating BMD using T-scores (the number of standard deviations that the measured BMD is different from the mean of a population of healthy young adults). These criteria are based on studies in postmenopausal women and define osteopenia as BMD T-scores of −1 to −2.5 standard deviations below the mean. Osteoporosis is defined as a T-score of more than −2.5 standard deviations below the mean for young adults [8]. The areas generally evaluated for BMD are the lumbar spine and hip region. Concern has been expressed that comparison with healthy populations is inappropriate for individuals with cystic fibrosis because they tend to have smaller body mass; however, studies with quantitative computed tomography have suggested that cystic fibrosis-related bone disease is not just related to decreased bone size [9,10]. What is clear, however, is

that the use of T-scores is not appropriate in pediatric populations because they have not accrued their full adult bone mass [11]. Pediatric studies therefore utilize Z-scores (the number of standard deviations that the BMD score is above or below the mean compared with individuals of that age). The current recommendations of the US Cystic Fibrosis Foundation Consensus Committee on Bone Health are to use Z-scores up to age 18, Z- or T-scores between 18 and 30, and T-scores above 30 [4••].

Cross-sectional studies have suggested that BMD in healthy pediatric cystic fibrosis patients during early childhood is comparable to individuals without cystic fibrosis [3•,12]. During early adolescence, however, children with cystic fibrosis begin to demonstrate decreased bone accumulation, and the prevalence of decreased BMD begins to rise [3•,12,13•,14,15••]. The presence of risk factors such as poor nutrition, steroid use, or recurrent infections increases the risk of decreased BMD [4••].

Clinical characteristics of cystic fibrosis-related bone disease

The main reason for concern about decreased BMD in individuals with cystic fibrosis is that it significantly increases the risk of fracture [16,17]. It does not appear that this fracture risk is due just to having cystic fibrosis, as children with cystic fibrosis are not at an increased risk for fracture if they have moderate lung disease and no evidence of decreased BMD [18••]. However, the risk of fracture in even a young adult with cystic fibrosis-related osteoporosis is comparable with that seen in a postmenopausal woman with severe osteoporosis and a history of previous fractures [16]. This fracture risk is of particular importance in the setting of lung transplantation when use of high-dose corticosteroids and immunosuppression can dramatically worsen the bone disease that is already present [7]. The most common fractures are vertebral compression fractures, followed by rib fractures [16]. It has been estimated that when compared to age-matched healthy controls, individuals with cystic fibrosis and osteoporosis have a 100-fold increased risk of vertebral fractures and a 10-fold increased risk of rib fractures [16].

The other common clinical characteristic associated with cystic fibrosis-related bone disease is kyphosis. Studies have estimated the prevalence in individuals with cystic fibrosis to be approximately 10–40% [19], depending on the characteristics of the study group. In the study by Aris and co-workers [16] of 70 adults with cystic fibrosis referred for lung transplantation, over 60% had kyphosis (vertebral angle equal to or greater than 40°). The mean vertebral angle in the group was $44 \pm 14°$, and accounted on average for a decrease in stature of approximately 6 cm [16].

Etiology of cystic fibrosis-related bone disease

The etiology of decreased BMD in cystic fibrosis is multifactorial [4••]. Studies evaluating bone histology in cystic fibrosis-related bone disease are consistent with a multifactorial etiology as the histomorphic changes seen are not consistent with osteomalacia due to vitamin D and calcium insufficiency alone [20]. Numerous contributors to decreased BMD in cystic fibrosis have been identified, including circulating cytokines secondary to recurrent pulmonary exacerbations [21••,22], poor nutrition and low body mass index [23], vitamin D and K insufficiency [4••], inadequate gonadal steroid levels [24], use of exogenous glucocorticoids [16], and decreased frequency of weight-bearing exercise [5].

The etiology of cystic fibrosis-related bone disease has received particular research attention recently. Schulze and co-workers [14,15••] studied prepubertal and pubertal girls with cystic fibrosis and determined that throughout adolescence, and particularly during early puberty, girls with cystic fibrosis demonstrate less calcium deposition in their bones than healthy controls. Shead and co-workers [21••] found that pulmonary exacerbations are accompanied by an increase in the number of circulating osteoclast precursors, and suggested that an increase in osteoclast activity during cystic fibrosis exacerbations may contribute to bone loss in adults with cystic fibrosis. Studies in cystic fibrosis transmembrane conductance regulator (CFTR)-null mice suggest that even in the setting of good nutrition, loss of CFTR expression is associated with both a reduction in bone formation and an increase in bone resorption [25]. Finally, several investigators have identified in individuals with cystic fibrosis-related bone disease low levels of insulin-like growth factor 1 [15••,26•,27•], a peptide thought to play an important role in the differentiation of osteoblasts. All of these findings lead to a picture of cystic fibrosis-related bone disease being caused by a combination of decreased bone formation, particularly during adolescence, and increased bone loss, particularly in individuals with frequent pulmonary exacerbations and poor nutrition [4••].

Screening and monitoring for cystic fibrosis-related bone disease

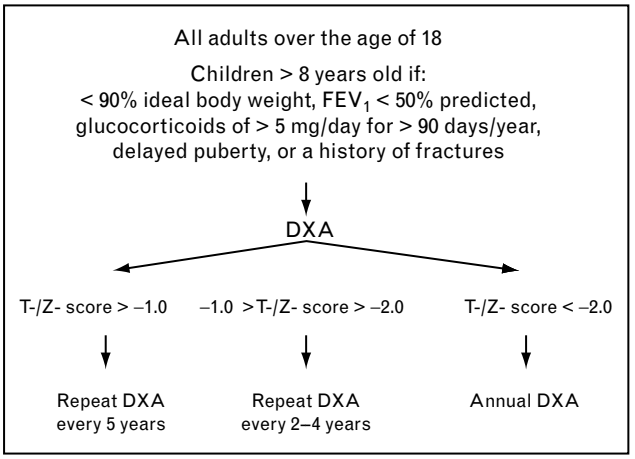
The recommendations of the Cystic Fibrosis Foundation Bone Health Consensus Committee were published in the *Journal of Clinical Endocrinology and Metabolism* in 2005 [4••]. One of the areas stressed in the recommendations was the importance of identifying cystic fibrosis-related bone disease early in its course, to allow nutritional and pharmacologic intervention which might optimize bone health. They recommended determining a baseline BMD in all adults with cystic fibrosis at age 18,

and in children over the age of 8 with risk factors for poor bone health (ideal body weight $< 90\%$, forced expiratory volume in 1 s (FEV_1) $< 50\%$ predicted, glucocorticoids ≥ 5 mg/day for more than 90 days/year, delayed puberty, or history of fractures). Although there have been discussions about the ideal method for determining BMD in individuals with cystic fibrosis, the current recommendation is standard dual-energy X-ray absorptiometry (DXA) of the lumbar spine and hip. Because standards for BMD in children are not well established and Tanner puberty stage can greatly influence BMD, Z-scores should be utilized for individuals below the age of 18. Individuals with T- or Z-scores of -1.0 or better do not need repeat DXA monitoring for 5 years unless there is a change in risk factors. Individuals with T- or Z-scores of -1.0 to -2.0 should have a repeat DXA scan every 2–4 years to monitor disease progression. It is recommended that individuals with T- or Z-scores below -2.0 should have annual DXA scans. Figure 1 summarizes the consensus conference screening DXA scan recommendations.

Prevention and treatment of cystic fibrosis-related bone disease

The other major area stressed in the consensus conference publication was the importance of optimizing vitamin, calcium and nutritional status in all individuals with cystic fibrosis to provide the best opportunity for normal bone health. When needed, antiresorptive agents have been demonstrated to be effective in improving BMD. There has been ongoing research in each of these areas which has helped shape recommendations for best practice (Table 1).

Figure 1 Dual-energy X-ray absorptiometry (DXA) screening protocol



Dual-energy X-ray absorptiometry should include measurements of the lumbar spine and femur. Z-scores should be used up to age 18, Z- or T-scores are nearly equivalent between ages 18 and 30, T-scores should be used above the age of 30. FEV_1, forced expiratory volume in 1 s. Adapted with permission from [4••].

Table 1 Bone health treatment recommendations

Everyone
Vitamin D supplementation to maintain serum 25-OHD > 30 ng/ml
Calcium supplementation to achieve 1300–1500 mg/day
Vitamin K supplementation 0.3–0.5 mg/day
Target BMI > 25th percentile
Encourage outdoor weight-bearing exercise
Aggressive treatment of pulmonary infections
Minimize exposure to corticosteroids
Treat cystic fibrosis diabetes
For delayed puberty or hypogonadism, refer to endocrine specialist
For T-/Z-scores between −1.0 and −2.0
Start oral bisphosphonate* if fragility fractures have occurred, patient is awaiting transplant, or annual BMD loss is > 3% at the spine or 5% at the femur
For T-/Z-scores less than −2.0
Start oral bisphosphonate*
Consider intravenous pamidronate if oral route is not tolerated (risk of infusion related to bone pain)
Consider teriparatide

25-OHD, 25-hydroxyvitamin D; BMD, bone mineral density; BMI, body mass index. Based on [4••].
* Bisphosphonates have not been approved for use in children and should be used with caution.

Vitamin D supplementation

Numerous studies have documented a high prevalence of vitamin D deficiency in individuals with cystic fibrosis, likely due to fat malabsorption. Vitamin D deficiency has the potential to significantly affect bone health by both preventing normal calcium absorption and inducing secondary hyperparathyroidism. The exact prevalence of vitamin D deficiency in cystic fibrosis depends on the serum level used to define 'deficient'. Based on evidence in non-cystic fibrosis individuals that serum parathyroid hormone levels begin to rise with 25-hydroxyvitamin D (25-OHD) levels below 30 ng/ml, the consensus conference committee identified a serum 25-OHD level of 30 ng/ml as the target to optimize calcium metabolism and bone health in cystic fibrosis [4••]. They recommended annual 25-OHD screening and adequate vitamin D supplementation in all individuals with cystic fibrosis to keep their level above 30 ng/ml. Using this threshold, studies suggest that 60–80% of adults with cystic fibrosis may have inadequate serum 25-OHD levels, even when receiving standard vitamin D supplementation of 800 IU of cholecalciferol per day [28,29••].

What is also clear is that when individuals with cystic fibrosis are identified as deficient, standard doses used for vitamin D supplementation are often inadequate. The consensus committee therefore recommended a stepped approach using high-dose ergocalciferol (vitamin D_2) to replete individuals with inadequate 25-OHD levels. Based on data in non-cystic fibrosis populations, they recommended beginning by supplementing with 50 000 IU of ergocalciferol once a week for 8 weeks, followed by twice a week for 8 weeks if needed. A recent study by Boyle and co-workers [29••] found that even this high-dose regimen may be inadequate to correct deficiency in many adults with cystic fibrosis, with

only five of 38 patients treated with the full regimen correcting their 25-OHD to above 30 ng/ml. A subsequent study in the same patient group, not yet published, has suggested that for those who do not respond to the initial course, 50 000 IU of ergocalciferol a day for 30 days is much more successful in correcting serum 25-OHD levels to greater than 30 ng/ml. Other potential methods of successfully providing vitamin D supplementation in cystic fibrosis include more polar analogs such as cholecalciferol and sun exposure/phototherapy.

Calcium supplementation

Given that much of the attention given to maintaining adequate vitamin D levels aims to optimize calcium absorption, the consensus conference committee also acknowledged the importance of adequate calcium supplementation in cystic fibrosis. It has been demonstrated by Schulze and co-workers [14] that increased calcium absorption in young women with cystic fibrosis is associated with increased rates of bone calcium deposition. There are no cystic fibrosis-specific studies evaluating optimal dosing for calcium supplements, so the current recommendation is to follow the non-cystic fibrosis guideline of 1300–1500 mg of elemental calcium per day [4••].

Vitamin K supplementation

The role of vitamin K in cystic fibrosis-related disease has begun to receive more research attention in recent years. Although no cause-and-effect relationship between vitamin K deficiency and low BMD has been established, vitamin K is a necessary co-factor in the posttranslational activation of osteocalcin, a bone protein which plays a role in bone formation and mineralization. Conway and co-workers [30•] studied 93 children with cystic fibrosis and found that 70% showed evidence of suboptimal vitamin K status. In a small study of 20 children with cystic fibrosis, Nicolaidou and co-workers [31•] found that administration of 10 mg of oral vitamin K each week resulted in a decrease in markers of bone turnover. Further cystic fibrosis-specific research will be needed before altering the current recommendation that individuals with cystic fibrosis follow general intake guidelines of 0.3–0.5 mg of vitamin K per day.

Sex hormone-replacement therapy

Delayed puberty and low serum estradiol and testosterone levels are thought to occur more frequently in individuals with cystic fibrosis than in non-cystic fibrosis populations, although study results have varied [17,32,33•]. Delayed puberty may retard bone growth and prevent attainment of peak bone mass, but a direct relationship between low sex hormones and cystic fibrosis-related bone disease has not been established. Current recommendations are to ensure that individuals with low BMD do not have early gonadal failure, but there are currently inadequate data to suggest the use of sex steroids for treatment of osteoporosis unless a deficiency is present [4••].

Bisphosphonates

The effectiveness of bisphosphonates in the treatment of cystic fibrosis-related bone disease is now well established. The recommendations of the Cystic Fibrosis Foundation Bone Health Consensus Committee are to strongly consider the use of bisphosphonates in all adults with cystic fibrosis who have BMD T-scores of -2.0 or less. Individuals with BMD scores between -1.0 and -2.0 should be considered for treatment if they have a history of fragility fractures, are awaiting lung transplant, or experience BMD loss of $> 3–5\%$ per year [4••]. In 2004 Aris and co-workers [34] published a randomized, placebo-controlled, double-blinded trial of 48 individuals with cystic fibrosis and T-scores of less than -1.0 which conclusively demonstrated the benefit of 10 mg of oral alendronate a day. They found that 1 year of treatment with oral alendronate increased spinal BMD by $4.9 \pm 3.0\%$ and femur BMD by $2.8 \pm 3.2\%$. This was significantly more than the placebo controls, which lost $1.8 \pm 4.0\%$ of their BMD at the lumbar spine ($P < 0.001$) and $0.7 \pm 4.7\%$ at the femur ($P = 0.003$). Urine N-telopeptide levels, a marker of bone resorption, also declined in the treatment group ($P = 0.002$), consistent with the known antiresorptive effects of bisphosphonates. Other smaller studies have also confirmed the benefit of oral bisphosphonates in treating cystic fibrosis-related BMD loss [35•].

Whereas oral bisphosphonates are now considered to be the standard of care in individuals with cystic fibrosis-related osteoporosis, concerns still exist about the use of intravenous bisphosphonates in cystic fibrosis. A study of the intravenous bisphosphonate pamidronate in cystic fibrosis patients after lung transplantation found that it significantly improved BMD without causing side effects [36]. However, the use of intravenous bisphosphonates in individuals with cystic fibrosis who are not post-transplant has been complicated by a high rate of severe infusion-related bone pain. Haworth and co-workers [37,38] reported that while pamidronate did improve BMD in the lumbar spine by an average of 4.1% at 6 months, 11 of the 15 individuals receiving pamidronate in their study experienced significant bone pain in the 48 h after infusion. Recently, a randomized trial in adults with cystic fibrosis of the potent intravenous bisphosphonate zoledronate had to be stopped after three of the first five participants experienced bone pain with infusion severe enough to require emergency-room visits [39]. It has been noted by investigators that the infusion-related pain seen with intravenous bisphosphonates tends to be less severe with subsequent doses [38]. However, given that oral bisphosphonates have been demonstrated to be effective in cystic fibrosis and are much better tolerated, they should be considered as first-line therapy.

Recombinant human growth hormone

There is growing interest in the use of recombinant human growth hormone to improve bone mineral content in children and adolescents with cystic fibrosis. Recent studies have focused on children and adolescents who have experienced impaired longitudinal growth and poor weight gain. Hardin and co-workers [40••] studied 32 poorly growing prepubertal children with cystic fibrosis between the ages of 7 and 12. Sixteen were randomized to treatment with a daily subcutaneous injection of growth hormone at a dose leading to a total of 0.3 mg/kg per week. The growth hormone treatment group demonstrated significantly greater increase in height, weight, and bone-mineral content than the nontreatment group (bone-mineral content gain: 281 ± 34 g compared with 58 ± 23 g for the treatment and control groups, respectively; $P = 0.03$) [40••]. The same research group also demonstrated the benefit of growth hormone treatment in prepubertal children with cystic fibrosis receiving enteral nutritional supplementation [41•]. The 18 children in the study were divided into two groups: one received no growth hormone for 1 year, followed by treatment for 1 year; the other received a consecutive 2 years of treatment. At the end of the first year the growth hormone treatment group again demonstrated a significantly greater increase in height, weight, and bone-mineral content than the nontreatment group [41•]. The one study not in young children was a retrospective evaluation of 25 pubertal adolescents with cystic fibrosis between the ages of 13 and 16 who had been referred to endocrinology for evaluation of poor growth [42•]. It demonstrated that 1 year of treatment with a daily subcutaneous injection of growth hormone for a total of 0.3–0.35 mg/kg per week resulted in a significantly greater increase in height, weight, and bone-mineral content than a nonrandomized control group (bone-mineral content gain: 650 g compared with 75 g for the treatment and control groups, respectively; $P < 0.05$) [42•]. The control group was 12 adolescents with cystic fibrosis with poor growth who were not treated with growth hormone.

All of these studies suggest that the use of growth hormone in cystic fibrosis in prepubertal children and pubertal adolescents with poor growth and weight gain results in improvement in height, weight, and bone mineral content. To date there have been no studies of growth hormone as a treatment for decreased BMD in adults with cystic fibrosis, nor have there been conclusive data for the use of growth hormone for treatment of osteoporosis in adult populations without cystic fibrosis.

Teriparatide (1–34 human parathyroid hormone)

Teriparatide is a synthetic polypeptide that consists of the 34 amino acids from the N-terminal region of human parathyroid hormone, which account for much of its biologic activity. It is given as a daily subcutaneous injection and has been demonstrated to increase BMD and decrease the risk of fracture in men and postmenopausal women with osteoporosis [43,44]. Although continuous exposure to parathyroid hormone results in increased bone resorption, intermittent exposure like that experienced with a daily injection results in increased osteoblast formation and bone growth. There have not been any published studies of teriparatide use in cystic fibrosis yet, but it has potential to be a promising therapy in the future, particularly for individuals with severe osteoporosis or previous fractures.

Conclusion

Whereas low BMD, kyphosis and vertebral fractures are most often recognized in the adult cystic fibrosis population, it is now becoming increasingly clear that cystic fibrosis-related bone disease is a process that starts in childhood and adolescence. Decreased calcium accretion during puberty, poor nutrition, and recurrent infections are among the multiple factors which cause an imbalance between bone formation and resorption that leads to decreased BMD. Guidelines for screening and treatment of cystic fibrosis-related bone disease are now available, and they suggest that close attention to nutrition, vitamin and mineral supplementation, aggressive treatment of infection, and use of antiresorptive agents may help prevent the development of cystic fibrosis-related osteoporosis. Newer therapies, including recombinant human growth hormone in children and teriparatide in adults, provide the promise of even better treatment in the future.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 475).

1 Cystic Fibrosis Foundation. Patient Registry 2005 Annual Report. Bethesda, MD: Cystic Fibrosis Foundation; 2006.

2 Conway SP, Morton AM, Oldroyd B, *et al.* Osteoporosis and osteopenia in adults and adolescents with cystic fibrosis: prevalence and associated factors. Thorax 2000; 55:798–804.

3 • Buntain HM, Schluter PJ, Bell SC, *et al.* Controlled longitudinal study of bone mass accrual in children and adolescents with cystic fibrosis. Thorax 2006; 61:146–154.
This 2-year study in 85 children and adolescents with cystic fibrosis showed that they had less bone-mass accrual than 100 age- and sex-matched controls.

4 •• Aris RM, Merkel PA, Bachrach LK, *et al.* Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 2005; 90:1888–1896.
A summary of the screening and treatment recommendations of an international consensus committee on bone health in cystic fibrosis.

5 Elkin SL, Fairney A, Burnett S, *et al.* Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study. Osteoporos Int 2001; 12:366–372.

6 Haworth CS, Selby PL, Webb AK, *et al.* Low bone mineral density in adults with cystic fibrosis. Thorax 1999; 54:961–967.

7 Aris RM, Neuringer IP, Weiner MA, *et al.* Severe osteoporosis before and after lung transplantation. Chest 1996; 109:1176–1183.

8 Kanis JA, Melton LJ III, Christiansen C, *et al.* The diagnosis of osteoporosis. J Bone Miner Res 1994; 9:1137–1141.

9 Henderson RC, Madsen CD. Bone mineral content and body composition in children and young adults with cystic fibrosis. Pediatr Pulmonol 1999; 27:80–84.

10 Salamoni F, Roulet M, Gudinchet F, *et al.* Bone mineral content in cystic fibrosis patients: correlation with fat-free mass. Arch Dis Child 1996; 74:314–318.

11 International Society for Clinical Densitometry Position Development Conference. Diagnosis of osteoporosis in men, premenopausal women, and children. J Clin Densitom 2004; 7:17–26.

12 Buntain HM, Greer RM, Schluter PJ, *et al.* Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. Thorax 2004; 59:149–155.

13 • Bianchi ML, Romano G, Saraifoger S, *et al.* BMD and body composition in children and young patients affected by cystic fibrosis. J Bone Miner Res 2006; 21:388–396.
A total of 136 individuals with cystic fibrosis, age 3–24, were studied and low BMD was found in 66%. Impaired pulmonary function and total steroid dose had the greatest negative influence on BMD.

14 Schulze KJ, O'Brien KO, Germain-Lee EL, *et al.* Calcium kinetics are altered in clinically stable girls with cystic fibrosis. J Clin Endocrinol Metab 2004; 89:3385–3391.

15 •• Schulze KJ, Cutchins C, Rosenstein BJ, *et al.* Calcium acquisition rates do not support age-appropriate gains in total body bone mineral content in prepuberty and late puberty in girls with cystic fibrosis. Osteoporos Int 2006; 17:731–740.
A study comparing girls with cystic fibrosis with non-cystic fibrosis controls. Results demonstrate that during prepuberty and late puberty bone calcium accretion rates in girls with cystic fibrosis falls below rates in healthy girls, even with adequate calcium intake.

16 Aris RM, Renner JB, Winders AD, *et al.* Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. Ann Intern Med 1998; 128:186–193.

17 Rossini M, Del Marco A, Dal Santo F, *et al.* Prevalence and correlates of vertebral fractures in adults with cystic fibrosis. Bone 2004; 35:771–776.

18 •• Rovner AJ, Zemel BS, Leonard MB, *et al.* Mild to moderate cystic fibrosis is not associated with increased fracture risk in children and adolescents. J Pediatr 2005; 147:327–331.
The investigators administered a lifetime fracture-history questionnaire to 186 young cystic fibrosis patients with mild to moderate lung disease and 427 healthy controls. A fracture was reported by 24% of subjects with cystic fibrosis and 23% of controls, suggesting children and adolescents with cystic fibrosis and mild to moderate lung disease are not at an increased risk of fracture.

19 Henderson RC, Specter BB. Kyphosis and fractures in children and young adults with cystic fibrosis. J Pediatr 1994; 125:208–212.

20 Haworth CS, Webb AK, Egan JJ, *et al.* Bone histomorphometry in adult patients with cystic fibrosis. Chest 2000; 118:434–439.

21 •• Shead EF, Haworth CS, Gunn E, *et al.* Osteoclastogenesis during infective exacerbations in patients with cystic fibrosis. Am J Respir Crit Care Med 2006; 174:306–311.
Blood samples from cystic fibrosis before, during and after pulmonary exacerbations demonstrated an increase in the production of osteoclast precursors in peripheral blood during cystic fibrosis infective exacerbations.

22 Aris RM, Stephens AR, Ontjes DA, *et al.* Adverse alterations in bone metabolism are associated with lung infection in adults with cystic fibrosis. Am J Respir Crit Care Med 2000; 162:1674–1678.

23 Grey AB, Ames RW, Matthews RD, *et al.* Bone mineral density and body composition in adult patients with cystic fibrosis. Thorax 1993; 48:589–593.

24 Bhudhikanok GS, Wang MC, Marcus R, *et al.* Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study. J Pediatr 1998; 133:18–27.

25 Dif F, Marty C, Baudoin C, *et al.* Severe osteopenia in CFTR-null mice. Bone 2004; 35:595–603.

26 • Gordon CM, Binello E, Leboff MS, *et al.* Relationship between insulin-like growth factor I, dehydroepiandrosterone sulfate and proresorptive cytokines and bone density in cystic fibrosis. Osteoporos Int 2006; 17:783–790.
In this study of 32 individuals with cystic fibrosis, serum insulin-like growth factor 1 concentrations were found to be below the age-adjusted mean in 78%. Multivariate analysis also identified insulin-like growth factor 1 as an independent predictor of BMD.

27 • Street ME, Ziveri MA, Spaggiari C, *et al.* Inflammation is a modulator of the insulin-like growth factor (IGF)/IGF-binding protein system inducing reduced bioactivity of IGFs in cystic fibrosis. Eur J Endocrinol 2006; 154:47–52.
This study, comparing cystic fibrosis subjects with controls, demonstrated significantly lower insulin-like growth factor 1 levels in individuals with cystic fibrosis.

28 Ott SM, Aitken ML. Osteoporosis in patients with cystic fibrosis. Clin Chest Med 1998; 19:555–567.

29 •• Boyle MP, Noschese ML, Watts SL, *et al.* Failure of high-dose ergocalciferol to correct vitamin D deficiency in adults with cystic fibrosis. Am J Respir Crit Care Med 2005; 172:212–217.
This study of 109 adults with cystic fibrosis demonstrated that 81% had 25-OHD levels below 30 ng/ml. Only five of the first 38 completing the recommended ergocalciferol repletion protocol corrected to above 30 ng/ml, suggesting that alternative treatment strategies should be considered.

30 • Conway SP, Wolfe SP, Brownlee KG, *et al.* Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover. Pediatrics 2005; 115:1325–1331.
In this study, 65 of 93 children with cystic fibrosis tested showed suboptimal vitamin K status on the basis of either low serum vitamin K levels or increased vitamin K-deficient prothrombin levels.

31 • Nicolaidou P, Stavrinadis I, Loukou I, *et al.* The effect of vitamin K supplementation on biochemical markers of bone formation in children and adolescents with cystic fibrosis. Eur J Pediatr 2006; 165:540–545.
In this study of children with cystic fibrosis, vitamin K intake was associated with an increase in serum markers of bone formation and a decrease in markers of bone turnover and parathyroid hormone.

32 Leifke E, Friemert M, Heilmann M, *et al.* Sex steroids and body composition in men with cystic fibrosis. Eur J Endocrinol 2003; 148:551–557.

33 • Buntain HM, Greer RM, Wong JC, *et al.* Pubertal development and its influences on bone mineral density in Australian children and adolescents with cystic fibrosis. J Paediatr Child Health 2005; 41:317–322.
This study in 85 children with cystic fibrosis suggested there was no evidence in cystic fibrosis of clinical pubertal delay or low BMD (after adjustment for short stature and lean tissue mass).

34 Aris RM, Lester GE, Caminiti M, *et al.* Efficacy of alendronate in adults with cystic fibrosis with low bone density. Am J Respir Crit Care Med 2004; 169:77–82.

35 • Cawood TJ, McKenna MJ, Gallagher CG, *et al.* Oral bisphosphonates improve bone mineral density in adults with cystic fibrosis. Ir Med J 2005; 98:270–273.
A small observational study demonstrating the efficacy of oral bisphosphonate use in cystic fibrosis.

36 Aris RM, Lester GE, Renner JB, *et al.* Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. Am J Respir Crit Care Med 2000; 162:941–946.

37 Haworth CS, Selby PL, Webb AK, *et al.* Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis. Lancet 1998; 352: 1753–1754.

38 Haworth CS, Selby PL, Adams JE, *et al.* Effect of intravenous pamidronate on bone mineral density in adults with cystic fibrosis. Thorax 2001; 56: 314–316.

39 Boyle MP, Lechtzin N, Watt S. Zoledronate therapy for decreased bone density in adults with cystic fibrosis. Pediatr Pulmonol 2005; S28:458.

40 •• Hardin DS, Ahn C, Prestidge C, *et al.* Growth hormone improves bone mineral content in children with cystic fibrosis. J Pediatr Endocrinol Metab 2005; 18:589–595.
A randomized trial demonstrating that growth hormone treatment in cystic fibrosis children results in a significant increase in the rate of height, weight, and bone-mineral content gain.

41 • Hardin DS, Rice J, Ahn C, *et al.* Growth hormone treatment enhances nutrition and growth in children with cystic fibrosis receiving enteral nutrition. J Pediatr 2005; 146:324–328.
A study demonstrating the benefit of growth hormone in children with cystic fibrosis who had documented growth failure and were receiving enteral nutrition.

42 • Hardin DS, Ferkol T, Ahn C, *et al.* A retrospective study of growth hormone use in adolescents with cystic fibrosis. Clin Endocrinol 2005; 62:560–566.
The only study of growth hormone in cystic fibrosis that does not include younger children. Results suggest a benefit of growth hormone in adolescents with cystic fibrosis and inadequate growth.

43 Neer RM, Arnaud CD, Zanchetta JR, *et al.* Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; 344:1434–1441.

44 Finkelstein JS, Hayes A, Hunzelman JL, *et al.* The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 2003; 349:1216–1226.