Cystic Fibrosis

Care Guidelines for CF-Related Bone Disease

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This document is based on a consensus of evidence and/or clinical expert opinion.

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Table of Contents

General Age Range Guide

Infant	Preschool	Child	Adolescent	Adult
0 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years	≥ 18 years

Abbreviation Guide

BMD . . . . Bone Mineral Density
BMI . . . . . Body Mass Index
CF . . . . . Cystic Fibrosis
CFRD . . . . Cystic Fibrosis-Related Diabetes
CFTR . . . . CF Transmembrane Conductance Regulator (protein)
CI . . . . . Confidence Interval
CXR . . . . Chest X-ray
DEXA . . . . Dual-Energy X-ray Absorptiometry
FEV1 . . . . Forced Expiratory Volume in 1 second
GERD . . . . Gastroesophageal Reflux Disease
HRT . . . . . Hormone Replacement Therapy
INR . . . . . International Normalized Ratio (prothrombin)
OR . . . . . Odds Ratio
PEx . . . . . Pulmonary Exacerbation
PI . . . . . Pancreatic Insufficiency
PT . . . . . Prothrombin Time
PTH . . . . . Parathyroid Hormone
SD . . . . . Standard Deviation
SOT . . . . . Solid Organ Transplant
WHO . . . . World Health Organization

Introduction

As people with cystic fibrosis (CF) live longer, it is increasingly apparent that this disease can cause complications other than respiratory and pancreatic disease. One such complication is impaired bone health.

Impaired Bone Health Conditions

a. **Osteopenia** – a bone mineral density Z-score between -1.0 and -2.5 standard deviations (SD) below of sex-matched controls; World Health Organization (WHO) criteria for post-menopausal women and men > 50 years is a T-score between -1.0 and -2.5.

See Diagnosis section for explanation of BMD scores

b. **Osteoporosis** – a bone mineral density Z-score below -2.5 SD; WHO criteria for post-menopausal women and men > 50 years is a T-score below -2.5.

- Reduced bone mineral density (BMD) is commonly seen, particularly in adults. In a meta-analysis of 12 studies (a total of 1055 patients age 18 to 32 years), Paccou and colleagues reported pooled prevalence rates for osteopenia of 38% and for osteoporosis of 23.5% (95% confidence interval 16.6 to 31).[1]
- Cross sectional studies from the UK have reported reduced BMD in 13 to 34% of adults.
- There is a paucity of data specifically addressing bone health in older adults with CF.
- Subgroups of adults with severe lung disease (FEV1 30% predicted or less) have reported mean BMD Z-scores of -2 and osteopenia rates of ~90%.[2]
- Although less common, low BMD has been demonstrated in children and adolescents with even mild pulmonary disease.[3]
- Studies of bone histomorphometry have shown features typical of osteoporosis from other causes in CF patients with reduced cancellous bone and reduced connectivity. Findings suggested that this arises primarily because of reduced bone formation with reduced osteoblastic function and numbers. Augmented osteoclast activity might also play a role in abnormal bone health in CF based on autopsy studies.[4]

c. **Osteomalacia** – characteristic pathologic bone features leading to softening of the bones, typically through a severe deficiency of vitamin D or calcium

- The prevalence is quite low, likely because of the routine attention to vitamin D supplementation and the magnitude of vitamin deficiency required to produce this condition.

Clinical Significance of Impaired Bone Health

- A number of studies have demonstrated higher prevalence of fragility fractures among individuals with CF compared to the general population. In a systematic review, Paccou and colleagues found vertebral fracture rates between 5 to 30% based on studies using plain radiographs. These rates are comparable to those of untreated post-menopausal osteoporotic women. Furthermore, the fracture rates were approximately double those observed among women and men in the general population. More sensitive ways of assessing the vertebrae are likely to show even higher rates. Interestingly, a greater number of fractures occurred at the thoracic vertebral level rather than lumbar and might be expected to have more of a negative impact on thoracic physiology. Non-vertebral fractures were reported to range from 20-40% (predominantly the ribs and forearm). Again, these far supersede age expected rates.1
- Fractures might contribute to negative outcomes in several ways in CF patients. All of these have the potential to contribute to accelerated lung function decline in CF.
  - Pain associated with the acute fracture, particularly rib and vertebral fracture, might inhibit airway clearance and predispose to pulmonary exacerbations.
  - Patients with fractures have higher rates of chronic musculoskeletal pain and consequently might be less physically active and could require more analgesics.
  - Kyphosis rates are higher in CF patients with vertebral fractures and could alter thoracic compliance, reduce lung volumes, and reduce efficiency of ventilatory muscles.
- Severe osteoporosis adds to the morbidity post-transplant. In some transplant programs, severe osteoporosis can be a relative (if not absolute) contraindication for transplant given the expected further bone loss post-transplant with corticosteroid use.

Causes of CF Bone Disease

The etiology of CF bone disease is multifactorial with nutrient deficiencies and chronic inflammations likely being the major contributors.

- Common causes:
  - Malabsorption of key nutrients including calcium, vitamin D, and vitamin K
  - Pulmonary infections and subsequent chronic inflammation
  - Medications (glucocorticoids and proton pump inhibitors)
  - Poor growth secondary to poor nutrition and abnormalities in growth hormone
  - Delayed puberty and decreased sex hormones (hypogonadism)
  - Decreased physical activity due to shortness of breath and fatigue, especially with severe lung disease
  - Genetics - CF transmembrane conductance regulator (CFTR) dysfunction is an independent factor after controlling for severity of lung disease and pancreatic sufficiency
  - CF Related Diabetes (CFRD) and insulin deficiency

- Other contributors not specific to CF:
  - excess alcohol and/or caffeine intake
  - limited sun exposure
  - suboptimal dietary sources of calcium and vitamin
- Groups most susceptible to rapid bone loss:
  - advanced lung disease
  - limited physical activity
  - pancreatic insufficiency (PI)
  - prolonged or frequent use of systemic corticosteroids
  - poor compliance with vitamin/mineral supplementation
  - those with limited finances or access to resources
  - post-transplant
  - prolonged limited sun exposure
  - low Body Mass Index (BMI)

Prevention of Bone Disease

Optimization of bone health requires intervention at an early age given the trajectory of bone accrual prior to adulthood. A failure to achieve proper bone growth by early adulthood can lead to low bone density even without the additional factors that CF patients face.

A multifaceted approach is essential to prevent osteoporosis amongst those with CF. These recommendations should also be considered in those with existing CF bone disease as an adjunct to treatment to optimize bone health.

General Recommendations

- Optimize overall nutrition with appropriate caloric intake and enzyme supplementation. Target normal growth metrics. This requires CF specialist nutritional input on an ongoing basis.
- Optimize mineral and vitamin intake (considering dietary sources and supplements).
- Minimize glucocorticoid use where possible. This applies predominantly to oral steroid use but should also include high dose inhaled steroids.
- Customize physical activity to specifically consider benefits to bone health.
- Consider and treat any endocrinologic or metabolic disorder that might contribute to bone disease (e.g. CFRD, thyroid disease, hypogonadism). If such a disorder is suspected, consider an endocrine referral.
- Prevent and promptly treat CF pulmonary exacerbations (PEx) to reduce the degree of inflammation.
- Advise against excess alcohol and caffeine intake.

Nutritional and Supplement Recommendations

a. General Nutritional and Weight Goals

- Optimize and supplement to provide adequate macro and micro nutrients needed for nutrition repletion and weight gain.
    - Aim to reach and maintain an optimal BMI of:[5]
    - Over 22 in women
    - Over 23 in men
    - Over the 25th to 50th percentile in children

b. Supplement Recommendations for Decreased Bone Density

(Based on current CF guidelines)[6]

Table 1: Supplement Recommendations for Decreased Bone Density

	Supplementation	Serum Reference Values Monitoring Frequency
Vitamin D	Dependent on serum values, which vary with dietary intake and sun exposure. **Vitamin D3 (cholecalciferol) routine dosing*** 0 to 12 months = 400 to 500 IU 1 to 10 years = 800 to 1000 IU 10 to 18 years = 800 to 2000 IU > 18 years = 800 to 2000 IU *Increase dosage when bone density levels remain low following stepwise dosing (see 'Cystic Fibrosis Care Guidelines for Nutritional Management')	Serum 25-hydroxyvitamin D minimum 30 ng/mL (75 nmol/L)[7] When bone density decreases, aim for Serum 25-hydroxyvitamin D of 30 to 60 ng/mL (75 to 150 nmol/L) Monitor annually, preferably at the end of winter Repeat bloodwork 3 to 6 months after initiation or change in therapy
Vitamin K	Supplement based on INR or PT **Vitamin K1** Infants: 0.3 to 1.0mg/day Older children and adults: 1 to 10mg/day	Target normal INR (< 1.2) Repeat bloodwork 3 to 6 months after initiation or change in therapy
Calcium	**Calcium Carbonate** > 10 years 1300 to1500 mg daily in divided doses (up to 500mg/dose)	Repeat bloodwork 3 to 6 months after initiation or change in therapy

Rationale:

- Vitamin D plays a key role in bone formation and calcium metabolism. As it is a fat soluble vitamin, it is not surprising that vitamin D deficiency is common in CF. Wolfenden and colleagues reported low 25OH vitamin D levels in approximately 75% of 185 adults.[8]
- Given the important role of sun exposure in vitamin D metabolism, levels would be expected to be even lower amongst individuals in northern latitudes, such as in Canada.
- European and US guidelines recommend routine supplementation of vitamin D for CF patients, however, there

For more information on Nutritional and Supplement Recommendations related to nutritional deficiencies, see Cystic Fibrosis Care Guidelines for Nutritional Management

has been debate regarding the optimal dose and formulation of vitamin D supplementation in CF. There is evidence that previous 'standard' dosing often underachieves target levels. Experience has shown that personalization of dosing is often required at amounts that may considerably exceed historical suggestions.

- Even without coagulopathy, Vitamin K can still be of benefit to those with CF-related bone disease.
- Calcium is needed both in forming bone as well to maintain bone strength. Consider supplements when calcium intake is insufficient from food sources.
- Magnesium and zinc are also important for bone health and calcium absorption. Current CF vitamin therapy provides appropriate magnesium and zinc supplementation.

Physical Activity Recommendations

- A physical activity prescription should contain recommendations for both weight bearing aerobic and resistance training, to be performed on as many days of the week as possible for that person, with more being encouraged. This must be done in addition to regular respiratory and nutritional therapies to be of optimal use (See Appendix 1).

Rationale:

- Osteoporosis treatment guidelines generally use vague terminology around exercise recommendations, e.g. 'regular weight bearing exercise'. Although this allows for patient-specific program development, such general recommendations offer no guidance as to the frequency, quantity, intensity, and type of exercise required to produce bone-protective effects. This could be the result of the difficulty in interpreting the large volume of studies undertaken in this area, almost none of which are specific to CF.
- A review of the osteoporosis exercise literature does reveal the following trends:
  - Weight bearing aerobic exercise has a positive effect on BMD at the hip, with greater effects (a larger effect size) demonstrated with higher-impact types of exercise (e.g. running is better than walking, walking is better than water exercise, etc.). However, this type of exercise has little to no effect on BMD in the spine.

    Effect size is a simple way of quantifying the difference between the control group and the treatment group.
  - Resistance exercise has a positive effect on BMD in the spine, with high-intensity and progressive loading protocols being the most productive. However, this type of exercise has little impact on bone density at the hip.
  - Multi-modal exercise programs have consistently demonstrated improved bone density at both the hip and the spine.
  - For patients with low BMD who are not able to exercise in traditional ways (e.g. spinal cord-injured patients, exceedingly frail elderly patients), whole-body vibration machines seem to provide benefit over and above medication alone.

  - In studies that examined exercise frequency in osteoporosis, greater exercise frequency is associated with a greater increase in BMD (larger effect sizes).
- Assuming we can extrapolate from these studies, the ideal exercise prescription for a person with CF-related decreased BMD would be tailored to what that person can and will do.

Screening

Regular chest x-rays (CXR) performed for respiratory assessment every 6 months starting at age 2 years can be helpful in identifying early stages of osteopenia and osteoporosis. A loss of vertebral height or a vertebral compression fracture (>20% reduction in the anterior height of a vertebral body compared to the posterior height) can be an indication of osteoporosis.

Regular screening of patients at risk for osteopenia and osteoporosis is recommended, based on current CF recommendations. [9, 10]

Screening Method

- Dual-energy x-ray absorptiometry (DEXA) is the screening tool of choice, however normal BMD is not absolutely reassuring in patients with CF who may suffer from fractures and complications secondary to poor bone quality despite normal bone density measurements.[11, 12] Because of this, the clinical utility of routine screening of BMD by DEXA has been called into question as it provides an inaccurate and imprecise measure of bone quality. Despite this, the DEXA remains the best available test for CF bone disease at this time.
- There has been a significant interest in identifying biomarkers for the screening and assessment of bone disease in CF. Higher rates of markers of bone resorption, including urinary hydroxyproline and urinary N-telopeptide, and lower markers of bone formation such as osteocalcin and bone alkaline phosphatase have been see in in CF patients when compared to controls.[9, 13, 14] To date, these markers have only been employed in research and have not gained clinical traction.

When to Screen

- Start regular focused screening for osteopenia and osteoporosis at age 18 years. (See Table 2: Guidelines for Bone Density Screening)
- In children, osteoporosis screening is controversial as peak bone density has not been reached but experts recommend screening children under any of the following circumstances:
  - FEV1% predicted < 50% (as more severe bone disease correlates with progressive lung disease)
  - frequent or prolonged systemic glucocorticoids
  - < 90 % ideal body weight
  - delayed puberty
  - a history of fracture

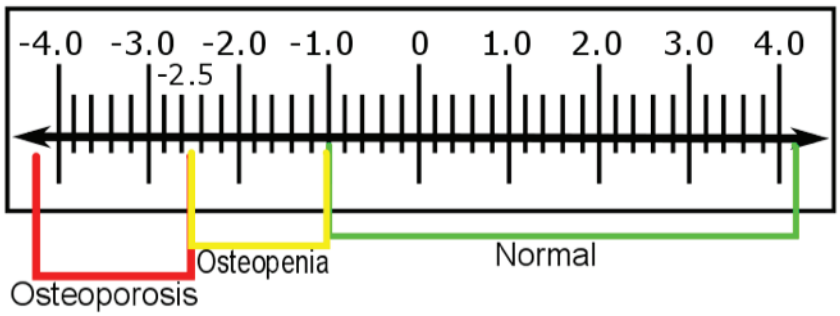
Tabel 2: Guidelines for Bone Density Screening

	Bone Density score*	Ongoing DEXA monitoring
Starting @ 18 years	Z-score > -1.0	Repeat in 5 years
	Z- or T-score between -1.0 and -2.0	Repeat in 2 to 4 years
Children with: ■ FEV1 % predicted < 50% ■ frequent or prolonged systemic glucocorticoids ■ < 90 % ideal body weight ■ delayed puberty ■ a history of fracture	Z- or T-score < -2.0 or a significant decline from prior scores	Repeat annually
Adults > 50 years[9]	T-score > -1.0	Repeat in 5 years
	T-score between -1.0 and -2.5	Repeat every 2 years
	T-score <-2.5 or patient is felt to be at significant risk	Repeat annually
Patients on continuous systemic steroids		Repeat annually

*Use bone density scores based on age:
Z-scores for those < 30 years old
T-scores for those ≥ 30 years old

Diagnosis

- Patients with CF suffer from a decrease in the substrate required to form new bone because of vitamin deficiency, increased bone resorption, and decreased mineralization.
- BMD is a measure of the amount of mineralization in a given area of bone under study. BMD is most commonly quantified using DEXA at the femur and the spine in adults.
- The assessment of BMD (measured in g/cm2) is based on a comparison to a population mean using a:
  - Z-score which compares the individual to an average person of the same age and gender, or
  - T-score (a standard deviation score) which compares the individual to a healthy young adult of the same gender.
- Osteopenia is diagnosed when a T or Z-score is -1 to -2.5.
- Osteoporosis is diagnosed when a T-or Z score below -2.5.



Interventions and Ongoing Monitoring

Treatment Indications

- Consider treating bone disease for any of the following reasons: [9, 15]
  - Z- or T-scores of -2.0 in the spine, hip, and/or femur
  - A significant decline in bone density compared to last DEXA (3% decline in spine and 6% decline in femur)
  - A history of fragility fracture (regardless of chronic systemic steroid intake)
  - Patient is awaiting organ transplant and their BMD Z-score is <-1.5
- Before beginning any bone protective treatment, recent BMD measurements should be taken.

First Line Treatment: Anti-resorptive

a. Bisphosphonates

- Reduces bone resorption by inhibiting the recruitment and function of osteoclasts, reducing osteoclast lifespan.[15]
- Can be administered orally or intravenously.

Table 3: Side effects and Precautions

Side effects[9, 16]	Precautions[9,16]
Esophageal disease and gastroesophageal reflux disease (GERD)	Avoid oral route in patients with esophageal disease due to risk of ulceration
Renal dysfunction	Use oral and IV formulations with caution in patients with chronic renal insufficiency
Bone pain and flu-like symptoms	Consider administering acetaminophen and/or prednisone pre-infusion
Osteonecrosis of the jaw (rare) Higher risk with: ■ IV route ■ recent dental procedure	Some experts recommend stopping bisphosphonates for 3 months around the time of dental procedures
Fetal risk of premature birth [17] (no overt teratogenicity found in small human studies)	Avoid administration in women planning pregnancy within next years. Some experts advocate avoiding bisphosphonates in women of child-bearing age.

Ongoing Monitoring:

- Monitor for side effects
- Check BMD using DEXA annually.
- Monitor for osteonecrosis of the jaw with dental assessments (at least annually).

Evidence:

A recent systematic review of bisphosphonate therapy in CF patients with bone disease evaluated 7 independent trials of at least 6 months duration (n = 237).[18]

Findings summarized:

- No significant reduction in fracture was observed between bisphosphonate and control groups (OR 0.72, 95%CI 0.13 – 3.80).[9]
- However, BMD increased over a six month period after bisphosphonate therapy at:[15]
  - Lumbar spine (OR 4.61, 95%CI 3.90-5.32)
  - Hip or femur (OR 3.35, 95%CI 1.63-5.07)
  - No difference at distal forearm
  - Benefit in BMD observed in lumbar spine and hip/femur persisted to 24 months
  - Bone pain was the most commonly reported adverse effect with IV bisphosphonate; increase in flu-like symptoms were also observed
- In CF patients with solid organ transplant (SOT), IV pamidronate (second-generation bisphosphonate) did not reduce number of fractures.[15]
  - BMD increased with treatment at lumbar spine and femur (both statistically significant).

b. Denosumab

- Prevents osteoclast maturation (a RANKL-protein inhibitor)
- Usual dosing: 60mg subcutaneously every 6 months
- Side effects: muscle aches, arm and/or leg pain (usually mild)

Evidence:

- No specific studies in the CF population.
- A landmark randomized controlled trial of denosumab in post-menopausal females with osteoporosis demonstrated a significantly lower risk of hip or vertebral fracture among those treated with twice yearly denusomab vs placebo over 36 months.[19] Adverse effects were similar between treatment and placebo groups.

c. Hormone Replacement Therapy (HRT)

- Can increase BMD and reduce risk of fractures.
- Might be useful for patients with hypogonadism, delayed puberty, or women in early menopause.[20]
- Side effects:
    1. Estrogen based – increase risk of venous thromboembolism, weight gain, breast cancer, endometrial and/or ovarian cancer[20]
    2. Testosterone based – increase risk of venous thromboembolism, acne, mood changes

Evidence:

- A small cohort study of adolescent males with CF identified 28% as having delayed puberty. Five of those with delayed puberty were treated with testosterone replacement and their growth rate increased from an average of 2.2 cm/year to 7.2 cm/year. Limitations include a lack of placebo control and lack of outcome measures for bone density.[21]
- No specific studies of HRT for bone disease in the female CF population.[20]
- However, literature in non CF patients with osteoporosis and amenorrhea secondary to anorexia recommends focusing on optimal nutrition and weight gain as opposed to hormone replacement therapy.[20]

Second Line Treatment: Anabolic

- If the following bone forming agents are being considered, refer to an endocrinologist for assessment.
- Consider these second line agents when treatment of bone disease is indicated but bisphosphonates are not tolerated or are contraindicated.

a. Teriparatide

- A recombinant form of human parathyroid hormone (PTH) analogue
- Increases new bone formation through osteoblast activity
- Used for severe osteoporosis.
- Usual dosing: 20mg subcutaneously OD (40mg OD considered a high dose)
    - Suggest 2 years of treatment with teriparatide following bisphosphonate treatment (but no consensus opinion).[15]
- Side effects: nausea, headache, dizziness
    - Severe adverse effects similar in treatment and placebo groups, but increases up to 11% in high dose treatment groups.[22]

Evidence:

- Reported to improve BMD in adults with CF in a small case series[23], and reduce fracture rate in general population.[24]

b. CFTR Modulators

- Effective in patients with specific CF gene mutations
- Corrects the function of the defective protein made by the CF gene.
- Currently 2 approved CFTR modulators: ivacaftor and lumacaftor

Evidence:[25]

- In *vitro* data suggests that correction of F508del CFTR mutation decreases RANKL-protein production, which reduces bone resorption.
- A small retrospective study examined the effect of ivacaftor on BMD after 1 to 3 years in 7 patients with G551D mutation. All these patients were naïve to treatment with bisphosphonate or sex hormones. There was an improvement in the average lumbar spine Z-score by 0.9 after a mean of 1.7 years of treatment. Seventy one percent (5/7) had a significant improvement in BMD (Z-score increase > 0.2). One patient had normalization of BMD Z-score from -2.5 to 0 in 12 months.
- Preliminary evidence suggests that CFTR modulator might improve BMD in CF patients. Larger and more robust studies still needed to definitively determine efficacy in bone disease.

APPENDIX

Theoretical Case Study 1

Lisa Simpson is 19 years old, has an FEV_1 75% predicted of 75%, and a BMI 19. She is attending university and working part-time as a waitress. Lisa has just had her first DEXA, and the results have shown that she is osteopenic. Before she started university, she was on her high school swim and soccer teams, but has not found time for exercise in her busy schedule since starting school. She has noted that she is a bit more short of breath with activities such as walking uphill in recent months. Being a bit of a perfectionist, she is not pleased with this development, and is also distressed to learn that she has "the bones of a 60 year old". She would very much like to reverse both of these trends, but has a hard time imagining when she could find the time.

In a highly-motivated and recently fit patient such as Lisa, it would be reasonable to prescribe a fairly high intensity mixed aerobic and resistance program, as this would allow her to do shorter sessions while still achieving the bone-enhancing benefits of exercise. She could start off with 10 to 15 minutes of skipping daily, and add more walking by getting off the bus a couple of stops early when going to school or work (or when going home, if that works better time-wise). Resistance training could start off with body weight squats and lunges, done three times a week at home so she doesn't have to travel to a gym. She can progress these by altering the speed at which she does them, using a more power-type of approach (such as Tabata – a high-intensity interval training workout), and/or super-slow repetitions to maximize time under tension. When neither of these approaches allows her to increase the intensity of the exercises, she could buy a set of adjustable dumbbells to add load.

Theoretical Case Study 2

Brad Simpson is 25 years old, has an FEV1 40% predicted a BMI of 18, and is on disability. He lives with his (and Lisa's) parents. He supplements his disability income by doing some freelance web design. Otherwise, he spends his every waking moment playing World of Warcraft. He has not exercised since the last time PE was compulsory in high school. Over the past 2 years, he has had 8 admissions for IV antibiotics and has had a 1L loss in FEV1, despite being mostly adherent with his prescribed therapies He has been told that transplant is on the horizon, and has decided that he wants to pursue it. He affirms that he despises physical activity and sweating of any sort, but would do it to save his own life. His transplant workup DEXA shows that he has osteoporosis in all areas measured, but a bit worse in the L-spine.

In a patient as deconditioned as Brad, almost any exercise will make some difference. A pulmonary rehab class, where the emphasis is on building participants up to being able to do 30 minutes of continuous aerobic exercise (plus some light resistance training) would be a good place to start with a patient like this. Brad should use the treadmill rather than the stationary bike to maximize the benefit of weight bearing on his bone health. If he could build up the tolerance to do some interval running that would be even more beneficial, but would likely take a long time to develop. The minimal strength training done in these classes is nonetheless more than Brad has been accustomed to doing, so

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