

CHAPTER 13 BONE HEALTH

N. Saxby, A. Kench & J Grunert

Building strong and healthy bones from childhood helps people with cystic fibrosis (CF) live active and independent lives. For people with CF, completing simple preventative measures such as getting enough vitamin D and calcium, and exercising regularly are known to positively affect bone health⁷⁸. Health practitioners also play an important role in recognising CF-related bone disease early and intervening promptly⁶⁴⁴. Prompt intervention can optimise bone mineral accretion during childhood and adolescence and minimise bone losses in adulthood⁶⁴⁴.

Disease Aetiology

Chronic illness and low bone mineral density can result in pubertal delay; in turn, low bone mineral density can be associated with osteoporotic or minimal impact-fractures in people with CF⁶⁴⁴. Fractures such as those in vertebrae and/or ribs can impair sputum clearance, pulmonary function, quality of life and working capacity^{78,645}. Reduced bone accretion and accelerated bone loss are thought to contribute to reduced bone mineral density⁶⁴⁴. Causes of suboptimal bone health are complex and multifactorial. The following should be considered:

NUTRITION

- Undernutrition^{230,646-649}
- Low lean body mass^{262,646}
- Micronutrient deficiencies^{78,650}
 - Calcium** [Chapter 9](#)
 - An important component of bone infrastructure⁶⁵⁰
 - Deficiency may result in bone calcium mobilisation to maintain serum calcium (calcium homeostasis)
 - Vitamin D** [Chapter 8](#)
 - Helps with calcium absorption
 - Vitamin K** [Chapter 8](#)
 - Necessary for posttranslational activation of osteocalcin, which in turn is important for bone formation and mineralisation
- Essential fatty acid deficiency [Chapter 7](#)^{651,652}

MEDICATIONS

- Corticosteroid use – oral, inhaled and nebulised^{230,445,646,647,649,653,654}
 - Commonly used in the management of allergic bronchopulmonary aspergillosis (ABPA)
 - High doses may cause functional hypogonadotropic hypogonadism in both males and females⁶⁵⁵

CF GENOTYPE & COMORBIDITIES

- Complications of CF such as pancreatic insufficiency, CF-related diabetes, and chronic liver disease⁶⁴⁴
- Ongoing effect of inflammation caused by CF lung disease and pulmonary exacerbations, and advanced lung disease^{646,656}
- CFTR gene
 - Contributes to reduced bone mineral density, via defective osteoblast maturation^{657,658}
 - Particular link with Delta F508 genotype²⁶²

PUBERTY

- Pubertal delay may cause osteoporosis^{222,646,649,659}

OTHER described risk factors/correlates

- Sex (gonadal) hormone deficiency⁶⁴⁴

- Sub optimal levels of exercise and physical activity – both cardiovascular and weight bearing ^{648,653,656,660}
- Male gender ²⁶²
- Lung transplant (Chapter 16)
- Pregnancy and lactation ⁶⁶¹
 - Pregnancy can place additional stresses on the skeletal system. However this does not normally result in fractures or persistent osteoporosis
 - Prolonged breast feeding is associated with increased risk of osteoporosis at menopause in the general population

MEDICAL DIAGNOSTIC CRITERIA

The World Health Organization diagnostic criteria of bone mineral densities in adults are listed below (Table 13a) ^{662,663}.

T-SCORES

- Represents the number of standard deviations of an individual's bone density in comparison to the peak bone density of healthy young adults of the same sex (i.e. at 30 years of age) ^{662,663}.
- Not used in children and adolescents as peak bone mass has not been reached.

Z-SCORES

- Represents the number of standard deviations above or below what is normally expected from a child/adolescent of the same age, sex and ethnicity.
- Low bone mineral density is classified as a z-score ≤ -2 ¹⁴⁹.
- In children and adolescents of short stature, use of height or stature age z-score adjustments will help avoid over-estimating deficits in bone mineral density ¹⁴⁹

Table 13a. Diagnostic criteria of bone mineral densities in adults ^{662,663}

Category	t-score
Normal bone density	>-1
Osteopaenia	-2.49 to ≤ -1
Osteoporosis	≤ -2.5

Prevalence of CF-related bone disease is known to increase with age ^{644,645}. A systematic review found that less than 5 percent of children with CF have bone disease, however prevalence increases to around 20 percent in adolescence and up to 65 percent in adults aged 45 years and over ⁶⁴⁵.

Assessment

DIET

Review dietary intake with particular focus on the adequacy of dietary calcium, vitamin D and vitamin K sources. Additional points to consider during the dietary assessment:

- Intake of calcium, vitamin D and vitamin K from oral and/or enteral nutrition support
- Dietary quality

Recent studies in the general population show that a more nutrient dense dietary pattern is associated with higher bone mineral density ^{664,665}.

Consider additional sources of calcium, vitamin D and vitamin K including the following:

- Prescribed supplements
- Over the counter preparations



CLINICAL

GENERAL CONSIDERATIONS

Review an individual's lung function (FEV₁ and FVC) and nutritional status

- Low bone mineral density is correlated with lower lung function and suboptimal nutritional status^{646,647,656,660,666}.
- Sup-optimal nutrition exerts its effects through potential delayed pubertal progression⁶⁶⁶.

Monitor pubertal progression

- Measuring height and Tanner stage every six months in children and adolescents.
 - Tanner pubertal staging information can be found on current Australian growth charts. Available through the [Australian Paediatric Endocrine Group](#).
- If height velocity is compromised, bone age should be assessed to look for evidence of constitutional delay
- If growth is poor (both weight and height percentiles) or if there is no progression of Tanner staging, a referral should be made to a paediatric endocrinologist.
 - Aiming for early intervention to optimise final height and bone density

Explore the use of anabolic steroids, which may be used by adolescent and young adult males who are trying to increase muscle mass⁶⁶⁷.

- Anabolic steroids suppress testosterone levels. Adverse effects on bone density may occur if prolonged androgen suppression occurs following cessation of anabolic steroids⁶⁶⁷.
- Testosterone is an anabolic steroid which can have positive effects on bone mineral density but should only be used under the supervision of an endocrinologist⁶⁵⁰.

Consider CFTR modulators

- Therapeutic options which are targeted at correcting the underlying cellular defect in CF (e.g. CFTR modulator C18) show promise as future therapies for CF-related bone disease⁶⁴⁴.

BONE MINERAL DENSITY SCREENING

How and when should bone mineral content and density be assessed for people with CF? PICO 13.1.1

[Ungraded] Insufficient evidence to make a recommendation specific to CF. Health professionals should follow consensus document recommendations for assessing bone mineral density for people with CF.¹⁴⁹

The only evidence to guide practice for the assessment of bone health in CF comes from consensus based guidelines and recommendations. From 8 years of age, there should be proactive monitoring of bone mineral density. If reduced bone density is identified, treatment intervention should be considered^{1,149,391}. Frequency of follow-up scanning is dependent on previous bone mineral density results, type of treatment that was initiated to improve bone mineral density and the emergency of additional risk factors of bone disease. When clinical status is stable, follow up scanning should be conducted at least:

- Every three to five years if bone mineral density was normal; z or T-scores > -1
- Every two years if bone mineral density was moderately reduced; z-score between -1 and -2; or T-score between -1 and -2.5
- Annually if bone mineral density was severely reduced; z-score <-2 or T-score <-2.5.

More frequent scanning is suggested if significant new risk factors emerge (e.g. prolonged corticosteroid exposure)^{1,149,391}. The current gold standard for measuring bone mineral densities is dual energy X-ray absorptiometry (DEXA)^{1,149,391}. These recommendations are in line with the 2006 version of this guideline¹. There is no significant new evidence.

Additional points of interest regarding DEXA scans:

- Unnecessary to conduct bone mineral density screening in children less than eight years¹.
 - Low prevalence of CF-related bone disease in children
 - Lack of meaningful normative data
- In adults, measurements are to be taken of the lumbar spine and femoral neck with or without the forearm. In children, the usual measurement sites are the lumbar spine and whole body.
- Monitoring and management decisions are usually based on the site with the lowest bone mineral density¹.
 - It may be appropriate to use a weight adjusted density rather than age adjusted one, particularly where pubertal delay is present.

BIOCHEMICAL AND LABORATORY DATA

Annual assessment of key biochemical markers is recommended. Additional information regarding vitamin D and K testing can be found in [Chapter 8](#).

VITAMIN D

Is there an ideal serum 25-hydroxyvitamin D level to aim for in people with CF? PICO 13.1.2

[Ungraded] Insufficient evidence specific to CF for the ideal serum 25-hydroxyvitamin D level. It is suggested that the general Australian and New Zealand goal of ≥ 50 nmol/L be used with a caveat for the time of year at which testing occurs.

Given the lack of any available evidence in the CF literature or otherwise showing improved clinical outcomes in bone health with an increased target of 75nmol/L, it is suggested that the general Australasian goal of ≥ 50 nmol/L be used. In addition, consider the impact of season on monitoring and measurement of vitamin D.

- Aim to measure 25-hydroxyvitamin D at the end of winter months or in early spring ⁶⁶⁸
- If end of winter testing is not feasible, it has been suggested to aim for 10 to 20 nmol/L ⁶⁶⁸ above the range of ≥ 50 nmol /L to allow for the seasonal decrease in winter (i.e. ≥ 60 -70nmol/L)

Discuss any change in serum 25-hydroxyvitamin D targets and higher dose vitamin D supplementation with an endocrinologist. Long term outcomes have not been extensively studied in CF population, particularly in children and adolescents.

VITAMIN K

Serum vitamin K levels are unreliable and should not be used to assess vitamin K status in CF ^{202,408,411}. PIVKA-II (protein induced vitamin K absence-II) and uc-OC (undercarboxylated osteocalcin) are considered the most accurate measures of vitamin K status ^{365,408}. Measures of coagulation are typically used as surrogate measures of vitamin K status, but are not ideal. See [Chapter 8](#) for additional information.

Intervention

Optimal bone health and management is best achieved by utilising the full expertise of the interdisciplinary CF team. In particular, the following members should be engaged and liaise with the endocrinologist as required:

- Respiratory physician
- Dietitian
- Physiotherapist
- Pharmacist

PREVENTION

Throughout the whole of the lifespan promote:

- Optimisation of nutritional status and growth
- A varied diet sufficient in energy, balanced in fatty acids, and high in sources of calcium, vitamin D and vitamin K;
 - Adequate calcium, vitamin D and K intake is especially important pre and during pubertal growth spurts
 - Vitamin D and K should be proactively supplemented for all patients with pancreatic insufficiency [Chapter 8](#)
- Good adherence with routinely prescribed vitamin and mineral supplements
- Ongoing exercise inclusive of weight bearing physical activity ^{669,670}
- Safe sun exposure



NUTRITION SUPPORT

What are the calcium requirements in CF to reduce the risk of low bone mineral density? ^{PICO 13.1.3}

[Grade D] Calcium requirements to reduce the risk of low bone mineral density in CF are unknown. At this time, health professionals should aim for the RDI when making calcium recommendations in CF. ¹⁵⁰

The RDI^{4*} for calcium in the general population is outlined in Table 13b. Additional information regarding the RDI for calcium can be found via the Nutrient Reference Values for Australia & New Zealand webpage - <http://www.nrv.gov.au/>.

Table 13b. RDI of Calcium for People in Australia and New Zealand*.

Age	Males (mg/day)	Females (mg/day)
1 to 3 years	360	500
4 to 8 years	520	700
9 to 11 years	800	1000
12 to 13 years	1050	1300
14 to 18 years	1050	1300
19 to 30 years	840	1000
31 to 50 years	840	1000
51 to 70 years	840	1000
> 70 years	1100	1300

*Adapted from: National Health Medical Research Council and Ministry of Health New Zealand. Nutrient Reference Values for Australia and New Zealand (2006). Available at: <http://www.nrv.gov.au/>

CONFIRMED OSTEOPAENIA OR OSTEOPOROSIS

Aim to achieve normal weight gain and growth in children and optimal weight in adults

- Nutrition support interventions may be required

Aim to supplement calcium and vitamin D

- Supplementation is recommended as first line treatment ⁴⁴²

Does supplementing calcium above the RDI improve bone mineral density in CF? ^{PICO 13.1.4}

[Grade D] There is insufficient evidence to support that routine calcium supplementation above the RDI will improve bone mineral density in CF. Consider calcium supplementation only when dietary intake is unable to meet the RDI. ¹⁵¹

In the absence of data specific to cystic fibrosis, the following consensus statements should be referred to:

- 2005 US Consensus statement: Guide to Bone Health and Disease in Cystic Fibrosis ³⁹¹
- 2011 European Cystic Fibrosis Bone Mineralisation Guidelines ¹⁴⁹

4 * RDI = the average amount of nutrient needed each day to meet the requirements of nearly all individuals.

Both recommend that calcium supplementation should follow country specific dietary reference intake (RDI) values. This is in line with a review of the evidence in the general population whereby calcium supplementation above the recommended level is unlikely to achieve additional benefit for bone health ⁶⁷¹.

The Australian and New Zealand RDIs for calcium were determined by estimating accumulation of whole body calcium and converting this to a daily rate of calcium accretion ⁴³. Excessive supplementation of calcium above this level could lead to complications including hypercalcaemia, hypercalcuria, nephrolithiasis, constipation, vascular and soft tissue calcification, interactions with zinc and iron, and prostate cancer ⁴³⁹.

MEDICAL SUPPORT

Consider pubertal status:

- regular monitoring and review is encouraged
- check gonadal hormone levels and gonadotropins in those with evidence of pubertal delay or reduced bone mineral density

Anti-bone resorptive medication (e.g. bisphosphonate treatments) are not routinely recommended for the CF population.

- Some evidence to show a potential benefit in CF whereby alendronate or zoledronate therapy can significantly improve bone mineral density in people with CF ^{442,672}
- There is no bone mineral density T-score or bone mineral density fall rate to indicate when bisphosphonate therapies should be considered. Australian prescribing criteria recommend zoledronate/alendronate or residronate therapy where:
 - Oral prednisone >7.5mg daily is used for >3 months and T scores show osteopaenia OR
 - There is a previous fracture with osteopaenic T scores (T-Score <-1.5)

Potential side effects of bisphosphonate treatments include hypocalcaemia, gastrointestinal irritation or ulceration, and musculoskeletal pain. Flu-like symptoms and injection site reactions may occur.

Hormonal therapy may be required with persistent hypogonadism or if there is pubertal delay which impacts an adolescent's interactions with their peers. Gonadal hormonal therapy remains controversial, thus endocrinologist supervision is essential ^{391,650}

- Hypogonadism can be a consequence of malnutrition, low body weight or supra-physiological doses of glucocorticoid resulting in hypothalamic – pituitary – gonadal axis suppression.
- Females who have hypothalamic suppression may require oestrogen hormonal therapy
- Gonadal steroids will not be effective if nutrition remains sub-optimal (evidence for eating disorder literature)

Due to the sensitive nature of this topic, it is important to involve both the adolescent with CF and their parents in discussions about potential use of hormonal therapy.

PHYSIOTHERAPY SUPPORT

Continue to promote exercise, including weight bearing physical activity, as this helps in maintaining bone mass and optimises lung health ^{669,670}.

Monitoring & Evaluation

Bone health status should be periodically assessed and re-assessed in individuals with CF who are over eight years old. Ongoing interdisciplinary input is essential.



Practice Points PICO 13.1.1

2006 Australasian Clinical Practice Guidelines for Nutrition in CF: Assess bone mineral density periodically in people with CF who are more than eight years of age¹. Dual energy X-ray absorptiometry scanning is the current gold standard assessment tool.

Follow up: Frequency of follow-up scanning is dependent on previous bone mineral density results, type of treatment that was initiated to improve bone mineral density and the emergency of additional risk factors of bone disease. When clinical status is stable, follow-up scanning should be conducted at least:

- every three to five years if bone mineral density was normal; Z or T scores > -1
- every two years if bone mineral density was moderately reduced; Z-score between -1 and -2; or T-score between -1 and -2.5, and
- annually if bone mineral was severely reduced; Z-score <-2 or T-score <-2.5.

More frequent DEXA scanning is suggested if significant new risk factors emerge (e.g. prolonged corticosteroid exposure)

Practice Points PICO 13.1.2

It is suggested that the general Australasian goal of ≥ 50 nmol/L serum 25(OH)D be used if measuring vitamin D at the end of winter or in early spring. If testing at other times of year, aim for a level 10-20nmol/L higher (≥ 60 -70nmol/L).

Practice Points PICO 13.1.3 and 13.1.4

Foods high in calcium include dairy foods (e.g. cow's milk, cheese & yoghurt), fortified dairy alternatives (i.e. soy milk), firm tofu & bony fish. Legumes, nuts and some green vegetables also contain small amounts of calcium. More information regarding the RDI for calcium can be found via the Nutrient Reference Values for Australia & New Zealand webpage - <http://www.nrv.gov.au/>