8. Bone disease

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1. INTRODUCTION

- CF patients are at increased risk for bone disease compared to age-matched controls.
- The prevalence of osteoporosis and osteopenia in CF is difficult to establish (mostly due to differences in the definition of osteoporosis/osteopenia in different age groups), however, it increases with age, lung disease severity, low body mass index (BMI) and malnutrition.
- Prevention, timely identification and treatment of bone disease are important aspects of CF care.

2. PATHOGENESIS OF BONE DISEASE IN CF

- The main risk factors for low bone mineral density (BMD) in CF are summarized in **Table 1.**

Table 1: Main Risk factors for low bone mineral density (BMD) in CF (adapted from[1])

Poor nutritional status, low BMI
Pancreatic insufficiency and malabsorption
Delayed puberty, hypogonadism
Severity of lung disease (lung infection, chronic inflammation, respiratory failure)
Male gender
Corticosteroids and other immunosuppressive therapies (especially in transplanted patients*)
Physical inactivity

*Severe, symptomatic osteoporosis is considered a relative contraindication for lung transplantation

3. DIAGNOSIS AND DEFINITIONS

- Dual-energy X-ray absorptiometry (DXA) represents the gold standard for BMD measurement in CF
  - The effective radiation dose is usually <1 mSv per measured site.
  - Measurements concern the following sites: lumbar spine and femoral neck.
  - **T-score** refers to the number of standard deviations (SD) above or below the mean BMD of a gender-matched young adult (25-30 years old) control population.
  - **Z-score** refers to the number of standard deviations (SD) above or below the mean BMD of an age- and gender-matched control population.

- **Definitions**
  - For postmenopausal women and men > 50 years, the T-score is recommended.
    - Osteoporosis is defined as a T-score lower than -2.5 SD
    - Osteopenia is defined as a T-score between -1 and -2.5 SD
  - For women prior to menopause and men < 50 years, the Z-score is recommended.
    - A Z-score of -2.0 SD or lower is defined as "**CF-related low BMD**".
    - A Z-score above -2.0 SD is "within the expected range for age".
    - Osteoporosis cannot be diagnosed in premenopausal women and in men under the age of 50 on the basis of BMD alone. For this population, the term osteoporosis should be reserved for those with a Z-score <-2.0 SD and a significant fracture history (low trauma fracture of a lower limb long bone, vertebral compression fracture, or two or more upper limb long bone fractures).
    - In young adult CF patients, the predictive value of BMD for the risk of fracture is not known.

4. ASSESSMENT OF BONE HEALTH IN CF

- Annual measurement of 25-hydroxyvitamin D blood levels, ideally at the end of winter when levels are at their nadir.
  - 1, 25-dihydroxyvitamin D levels should NOT be used to assess vitamin D status because they may be low, high or normal in subjects with vitamin D deficiency.
- Annual measurement of serum calcium, phosphorus, alkaline phosphatase, creatinine.
- Annual measurement of urinary calcium excretion (24h urine collection or ratio of calcium/creatinine in a fasting spot, morning urine sample).
- Regular assessment for fractures.
- Screening for bone disease in adult CF patients with DXA
  - Baseline measurements: 1) at early adulthood (after longitudinal bone growth has stopped) or, if not previously done, at transition to adult CF centre and 2) at evaluation for listing for lung transplantation.
  - Repeat DXA measurements:
    - If possible using the same machine and methodology. Assessment of DXA timing should be included in the annual review **(see also Chapter "*Annual Evaluation*")**.
    - The frequency of measurements would depend on the results of previous DXA, the presence/evolution of risk factors and the proposed interventions.
    - **For adult CF patients DXA are recommended every 2 to 5 years depending on the T or Z score.**
    - Comparison of serial DXA measurements: a change of BMD (measured in g/m^2) greater than 3% is considered to be significant.
- Bone remodeling biomarkers
  - The biomarker most commonly used in clinical practice is β-crosslaps (bone resorption biomarker). N-terminal propeptide of type-1 procollagen (P1NP) (bone formation biomarker) is used in some centers.
  - As opposed to less specific bone-related biochemical parameters such as alkaline phosphatase and fasting calcium/creatinine excretion, the more bone-specific remodeling biomarkers should NOT be routinely measured in all CF patients but rather in selected cases, before and on osteoporosis treatment.

- Indications for evaluation by a bone disease specialist
  - T-score < 2.5 SD or Z-score < 2.0 SD
  - Low trauma fracture
  - Difficult to treat vitamin D deficiency despite optimal dosing and good adherence (see **Table 3**)

5. PREVENTION AND TREATMENT OF BONE DISEASE

5.1 General recommendations for the prevention and treatment of bone disease (Table 2)

Table 2: General recommendations for the prevention and treatment of bone disease in CF (adapted from[1])

Optimal nutritional status*[a] – Sufficient BMI – Correction of vitamin D insufficiency (confirm adherence, dosing) – Calcium supplementation in case of inadequate intake
Physical activity, weight bearing exercise
Use of corticosteroids to be minimized whenever possible
In case of sex steroid deficiency*[b] hormonal replacement therapy may be indicated
Patient education on the importance of good bone status and the risks of bone disease*[c]

*[a] **See also Chapter "*Nutrition*"**

*[b] Assessed by morning total (and possibly free) testosterone in males, oestradiol in non-menstruating females and gonadotropins in both genders

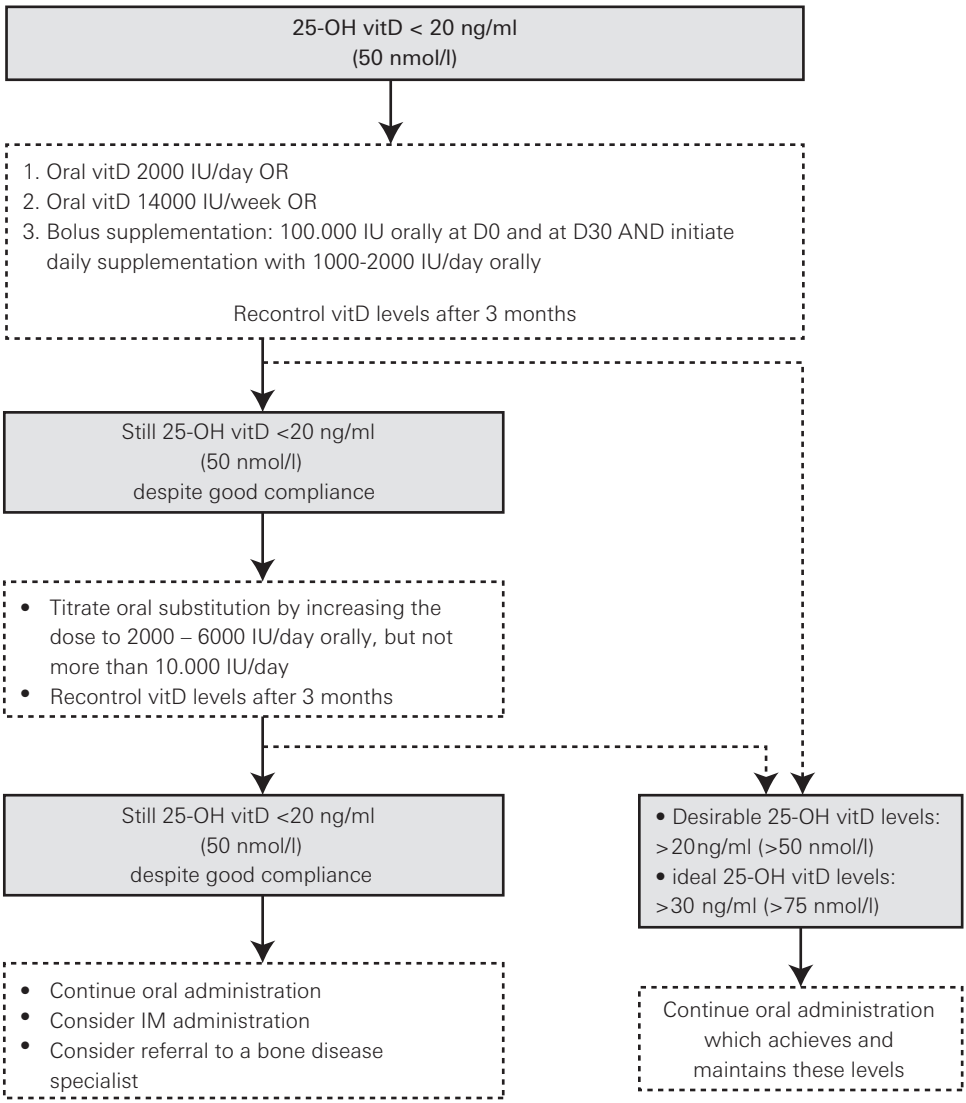
*[c] Bone disease is associated with decreased quality of life, pain impeding physiotherapy and risk of pulmonary exacerbations. Osteoporosis is a relative contraindication for lung transplantation

5.2 Vitamin D supplementation

- Supplementation with vitamin D3 (cholecalciferol) is superior to vitamin D2 (ergocalciferol).
- Target blood levels of 25-hydroxyvitamin D in CF:
  - Desirable > 20 ng/ml (50 nmol/l)
  - Ideal > 30 ng/ml (75 nmol/l) and < 45 ng/ml (112.5 nmol/l)
- Serum 25-hydroxyvitamin D levels should not exceed 100 ng/ml (250 nmol/l), due to increased risk of hypercalcemia.
- Vitamin D requirements vary enormously between individual CF patients but the routine dose in this context is approximately 2'000 IU/day.
- Different vitamin D substitution regimens have been described in the literature and practices vary among different centres. A strategy that could be applied for vitamin D supplementation of CF patients is shown in **Figure 1**.
  - Strategies to improve vitamin D absorption may also be implemented, such as vitamin D taken with fat containing food and with pancreatic enzymes.

- Weekly intake regimens of vitamin D (weekly equivalent of the daily doses) can be proposed to improve adherence to treatment.
- *Example*: if a patient takes 2000 IU/day orally → a dose of 2000 IU x 7 = 14000 IU once a week orally can be prescribed.
- *Cave*: If the serum calcium concentration is elevated, a concomitant primary hyperparathyroidism should be suspected and serum PTH checked, possibly indicating the

Figure 1: Algorithm for vitamin D (vitD) supplementation in adult CF patients[2,3]



need of evaluation by an endocrinologist. In this case, vitamin D substitution is still recommended when 25-hydroxyvitamin D level is below 50 nmol/l.

- **Tables 3 to 5** show some examples of available vitamin D supplements.
- Supplementation of vitamin D3 in its active form 1,25 dihydroxyvitamin D (calcitriol, Rocaltrol® 0.25 µg 1x/day p.o.) should be reserved for patients with severe renal insufficiency (ClCr <30 ml/min) or hypoparathyroidism. Co-administration of calcium carries a risk of hypercalcemia and for that reason close monitoring of serum calcium levels is indicated.

Table 3: Examples of liquid forms of vitamin D3 supplementation (adapted from[3])

	Vitamin D3 concentration	Administration	Comments
VitD3 Streuli® injectable solution	300.000 IU/ml	Oral, IM	IV administration is contraindicated
Zymad®	200.000 IU/ml	Oral	Available in France
Uvedose®	100.000 IU/ml	Oral	Available in France
VitD3 Streuli®	4000 IU/ml	Oral	Dosing pipette, 0.1 ml scale
VitD3 Wild®	500 IU/drop	Oral	
EveryD3®	600 IU/drop	Oral	
Vi-De 3®	100 IU/drop 4500 IU/ml	Oral	20 drops = 2000 IU

Table 4: Examples of combined Calcium and vitamin D3 supplementation

	Calcium (mg)	Vitamin D3 (IU)	Comment
Calcimagon D3®	500	400	Chewable tablets (can also be dissolved in water)
Calcimagon D3®	500	800	Chewable tablets (can also be dissolved in water)
Calcimagon D3 Forte®	1000	800	Chewable tablets (can also be dissolved in water)
Calcium D3 Sandoz 500/1000®	500	1000	Chewable tablets (can also be dissolved in water)

(continued)

Calcium D3 Sandoz 1000/880®	1000	880	Powder
Calcium D3 Mepha 1200/800®	1200	800	Effervescent tablets
Kalcipos-D3®	500	800	Tablets

Table 5: Examples of combined multivitamin preparations containing vitamin D

	Vitamin D3 (IU)	Comment
AquADEKs tablets®	600 IU/tablet	Chewable tablets. Contains vitamins A, D, E, K and hydrosoluble vitamins. Available in the USA, included in the LMIC/GGML*
AquADEKs liquid®	600 IU/mL	Contains vitamins A, D, E, K and hydrosoluble vitamins. Available in the USA
DEKAs Plus tablets®	2000 IU/tablet	Chewable tablets. Contains vitamins A, D, E, K and hydrosoluble vitamins. Available in the USA
DEKAs Plus softgel®	3000 IU/softgel	Contains vitamins A, D, E, K and hydrosoluble vitamins. Available in the USA, included in the LMIC/GGML*
DEKAs Plus liquid®	750 IU/mL	Contains vitamins A, D, E, K and hydrosoluble vitamins. Available in the USA, included in the LMIC/GGML*
DEKAs Essential capsules®	2000 IU/capsule	Contains only vitamins A, D, E, K. Available in the USA
DEKAs Essential liquid®	2000 IU/mL	Liquid. Contains only vitamins A, D, E, K. Available in the USA
Supradyn Energy®	200 IU/tablet	Tablets, effervescent tablets. Contains vitamins A, D, E, K and hydrosoluble vitamins.
Supradyn Vital 50+®	200 IU/tablet	Tablets, effervescent tablets. Contains vitamins A, D, E (no vitamin K) and hydrosoluble vitamins.

*GGML=Geburtsgebrechenmedikamentenliste, LMIC= Liste de médicaments en matière d'infirmités congénitales **(See Chapters "Nutrition" and "Administrative information")**

5.3 Calcium supplementation (see also Chapter *"Nutrition"*)

- Calcium supplementation may not be necessary for all patients. Obtain a dietary history concerning consumption of milk products and water rich in calcium.

5.4 Bisphosphonates

- The indications for bisphosphonate use in adult CF patients are presented in **Table 6**.
  - **In severely vitamin D deficient patients, vitamin D should always be given as first intervention!** Marked increases in bone mineral density may be observed after calcium and vitamin D supplementation. In these cases, specific treatment with bisphosphonates or other medications should be reevaluated as it may no longer be necessary.

Cave: when an antiresorptive treatment is initiated in a patient with a bone mineralization defect, there is an increased risk of symptomatic hypocalcemia.

- Examples of available bisphosphonates are presented in **Table 7**.
  - Oral bisphosphonates may cause erosive oesophagitis. Patient should be instructed to stay upright (not lie down) for at least 30 minutes and until after first food of the day.
  - Bisphosphonates and renal function:
    - Oral bisphosphonates may be given safely (after excluding and/or correcting vitamin D deficiency) when the creatinine clearance (ClCr) is ≥ 20-30 ml/min.
    - For iv ibandronate, dosage adaptation is necessary when creatinine clearance (Cl Creat) is between 20 and 30 ml/min (i.e. ibandronate 2 mg administered in 1 hour).
    - IV zoledronate is contraindicated when ClCr is < 35 ml/min.

Table 6: Indications for treatment with bisphosphonates in adult CF patients (adapted from[1])*

History of low trauma fracture
Lumbar spine or femoral neck or total hip Z/T score ≤ -2 SD and evidence of bone loss > 4% per year on serial DXA measurements, despite optimal clinical care
Solid organ transplantation awaited or done and Z/T score ≤ -1.5 SD
Continuous systemic corticosteroids > 3 months and T score ≤ -1.5 SD

*vitD deficiency should be corrected and calcium supplementation optimized before initiating bisphosphonates

Table 7: Examples of bisphosphonates and their dosing

	Mode of administration	Dosage
Alendronate*	Oral	70 mg / week
Risedronate	Oral	35 mg / week
Ibandronate	Oral	150 mg / month
Ibandronate	IV	3 mg /3 months
Zoledronate	IV	5 mg/year

*It also exists in an oral effervescent form (Binosto®)

- Monitoring response to treatment
  - DXA after 12 months of bisphosphonate treatment.
  - β-crosslaps (bone resorption biomarker) before, and several months after introduction of an osteoporosis treatment and once a year thereafter. For the general population a decrease of β-crosslaps by 40% suggests treatment efficacy.
- Treatment duration:
  - There are no official statements on the duration of bisphosphonates in CF patients. Nevertheless, there are rare major side effects of long-term bisphosphonate use (such as subtrochanteric or diaphyseal fractures, jaw osteonecrosis) which can also occur in patients with CF.

- According to the recommendations for postmenopausal osteoporosis of the *American Association of Clinical Endocrinologists and the American Society for Bone and Mineral Research,* bisphosphonate treatment should be evaluated after 3 years of administration and should not exceed 5 years. Benefits and potential severe side effects should be taken into consideration for continuing the treatment.

5.5 Other medications

- Indication for treatment with any of these agents needs to be discussed with a bone disease specialist.
  - Denosumab (Prolia®), a human monoclonal antibody, is an antiresorptive drug given every 6 months subcutaneously. It is approved for use in postmenopausal women with risk of osteoporosis and in male osteoporosis independent of the age. Although there is no CF-specific contraindication for its use, for adults with CF no data are available yet. Cave: severe rebound effect after Denosumab discontinuation and increased risk of vertebral fractures in 10% of patients. These side effects may probably be avoidable with potent bisphosphonates given before and after (for 1 to 2 years) denosumab.
  - Teriparatide (Forsteo®), a recombinant human parathyroid hormone, is currently the only approved anabolic medication that reduces the incidence of osteoporotic fractures. It is indicated for very severe osteoporosis, particularly for patients who have a new vertebral fracture while receiving an antiresoptive therapy and for corticosteroid-induced osteoporosis. For adults with CF no data are available yet.

6. REFERENCES

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