Journal of Cystic Fibrosis 18 (2019) S48–S55

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Cystic fibrosis bone disease: Pathophysiology, assessment and prognostic implications

Abeer Anabtawi[a,*], Trang Le[b], Melissa Putman[c], Vin Tangpricha[d,e], Maria Luisa Bianchi[f]

[a] Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism, University of Kansas Medical Center, Kansas City, KS, USA
[b] Departments of Internal Medicine and Pediatrics, Division of Endocrinology, Virginia Commonwealth University, Richmond, VA, USA
[c] Divisions of Endocrinology, Boston Children's Hospital and Massachusetts General Hospital, Boston, MA, USA
[d] Division of Endocrinology, Metabolism, & Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA
[e] The Atlanta VA Medical Center, Decatur, GA, USA
[f] Experimental Laboratory for Children's Bone Metabolism Research, Istituto Auxologico Italiano IRCCS, Milano, Italy

ARTICLE INFO

Article history:
Received 8 July 2019
Revised 19 August 2019
Accepted 19 August 2019

Keywords:
Cystic fibrosis
Cystic fibrosis bone disease
DXA
Bone turn over markers

ABSTRACT

Cystic fibrosis bone disease (CFBD) is a common long-term complication of cystic fibrosis (CF) that can lead to increased fractures and significant morbidity and mortality in this patient population. CFBD pathophysiology remains poorly understood and is likely to be multifactorial. There are limited studies evaluating diagnostic tools and tests to guide therapeutic decisions and monitoring of CFBD. This review will present and discuss the current evidence.

1. Background

Improvements in clinical care over last 40 years have led to increased survival in patients with cystic fibrosis (CF). With improving life expectancy, the prevalence of long-term complications including cystic fibrosis bone disease have increased. Studies have reported the prevalence of CFBD between 13 and 34% [1–4], with higher incidence of non-vertebral and vertebral fractures, up to 20% and 27% respectively, compared to healthy individuals [4–6]. Rib and vertebral fractures can result in significant pain and long-term deformities leading to ineffective chest physiotherapy, decrease in airway clearance, and eventually increase in pulmonary exacerbations and rapid decline in lung function (Fig. 1) [7,8]. A recent study of 42 adult patients with CF waiting for lung transplantation reported low bone mineral density (BMD) (Z-score < -2.0) in 52.4% and one or more fragility fractures in 45.2% [9]. Severe CFBD can be an exclusion criterion for lung transplantation in some centers [10].

2. Pathophysiology

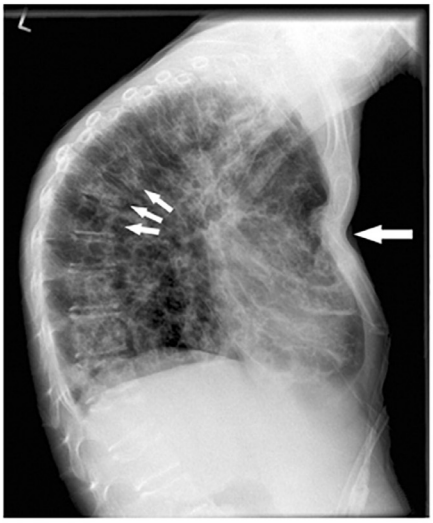
Bone is composed of an outer dense cortex (cortical bone) and an inner network of plates and rods (trabecular bone). The distal ends of long bones and the vertebral bodies are mainly made of trabecular bone, while the shafts of long bones are mainly cortical bone. In the first phases of life during childhood and adolescence, bones grow and change until the adult shape and dimensions are attained. This process is called “bone modeling”. Throughout life, the bone tissue is continuously renewed by a recurring process of osteoclast-mediated bone resorption and osteoblast-mediated bone formation, that replaces old and damaged bone with new bone. This process is called “bone remodeling”. The generic term “bone turnover” is also used to indicate the continuous renewal of bone that occurs throughout life. The balance between osteoclasts and osteoblasts activity is critical to the strength and integrity of bone. In any condition of excess bone resorption, bone minerals are more rapidly lost in the trabecular bone, while the loss of cortical bone occurs later. Such conditions weaken the bone structure and lead to a higher risk of fracture [11,12].

Peak bone mass is achieved in early adulthood and is influenced by many factors including nutrition, physical activity, gender, timing of puberty, and body composition [11]. Factors that contribute to bone strength include bone shape and size, bone mineral density, bone microarchitecture, and balance between bone formation and resorption [12,13]. Imbalance in any or a combination of these factors can lead to increased risk of fractures [14]. These and other factors contribute to the development and severity of CFBD [15] (Table 1).

Bone turnover is a very complex process involving many different factors: hormones, cytokines, and other local factors. The receptor activator of nuclear factor kappa B (NF-kB) ligand (RANKL) is an important

*Corresponding author.
E-mail address: aanabtawi@kumc.edu (A. Anabtawi).

https://doi.org/10.1016/j.jcf.2019.08.018



P Latzin et al. Thorax 2005;60:616

THORAX

Fig. 1. X-ray of vertebral fracture and kyphosis, adapt from Latzin P, Griese M, Hermanns V, et al Sternal fracture with fatal outcome in cystic fibrosis. *Thorax* 2005;60:616).

cytokine for osteoclast activation and bone resorption. It is inhibited by osteoprotegerin (OPG) which is a protein produced by osteoblasts [16]. Reactive oxygen species (ROS) which are often elevated in individuals with CF [17] are important for RANKL-induced osteoclast differentiation, activity, and potentially for increased bone resorption [18]. Oxidative stress can also induce osteoblast apoptosis and dysfunction [19].

2.1. Cystic fibrosis transmembrane regulator (CFTR) dysfunction

CF is caused by defects in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Most individuals with CF carry 2 mutations which cause severe CFTR dysfunction (such deltaF508), while others bear at least one mild CFTR mutation conferring a small amount of residual function. The level of residual CFTR function may directly or indirectly impact the development of CFBD. A prospective cross-sectional study of 88 adults with CF found significantly lower *Z*-scores at the spine and femoral neck in patients with homozygous or heterozygous F508del mutation compared to those without F508del mutation. Multiple linear regression analysis also showed F508del to be independently associated with lower bone mineral density at both spine and femoral neck [20]. Dif et al. reported significantly lower bone mineral density and altered microarchitecture demonstrated by decreased cortical width and trabecular thickness in mice with inactivation of both copies of CFTR gene compared to heterozygous and normal mice despite similar nutritional status [21]. CFTR's dysfunction can negatively affect bone formation via decreased osteoblast numbers and maturation [22]. A study by Stalvey et al. using CFTR knockout mice (cftr−/−) found significantly decreased OPG production from cftr−/− compared to cftr+/+ osteoblasts, resulting in higher RANKL/OPG ratio and increased osteoclastogenesis [23]. Studies have shown decrease in bone formation rate, lower BMD and abnormal bone microarchitecture in deltaF508 CFTR mice compared to controls independent of age and sex [24–26].

Table 1
Factors contributing to CFBD.

1. CFTR dysfunction
2. Vitamin D, Vitamin K deficiency
3. Calcium deficiency
4. Malnutrition
5. Delayed puberty and hypogonadism
6. Decreased physical activity
7. Respiratory infections and systemic inflammation
8. Exogenous glucocorticoids
9. Cystic fibrosis related diabetes

2.2. Vitamin D, vitamin K deficiency and calcium malabsorption

Severe CFTR dysfunction also causes exocrine pancreatic insufficiency which in turn causes intestinal malabsorption of fat-soluble vitamins K and D, both of which are important for bone health. Vitamin K is essential for carboxylation of osteocalcin and bone formation [15]. Vitamin D is essential for intestinal calcium absorption. Vitamin D deficiency results from insufficient skin synthesis due to reduced sunlight exposure, as well as from decreased intake of vitamin D-containing foods/supplements and intestinal malabsorption [27]. Since native vitamin D requires a 2-step activation in liver and kidney, chronic diseases of these organs such as CF related liver disease, can also cause vitamin D deficiency. Low vitamin D levels impair calcium absorption which may result in secondary hyperparathyroidism and increased bone resorption, and can contribute to low bone density in patients with CF [28].

2.3. Malnutrition, inability to achieve expected peak bone mass and delayed puberty

Malnutrition in individuals with CF can negatively affect bone mineralization, hampering the achievement of an optimal peak bone mass which can lead to a precociously reduced bone density in adult life [29]. Brookes et al. [30] evaluated bone density and strength using peripheral Quantitative CT (pQCT) in 53 prepubertal and pubertal patients with CF. At puberty, they found significantly lower bone mineral content at the tibia in both males and females, and significantly lower bone strength in females at the tibia and radius when compared to healthy controls. Bone strength parameters were not compromised before puberty in these patients. These changes were thought to be likely due to decreased bone strain load due to malnutrition and low muscle mass [30].

Sex steroids and puberty are important for accruing and maintaining bone mass. Evidence shows reduced BMD in patients with sex steroid hormone deficiency and delayed puberty [31]. Much as in healthy teens, puberty has been shown to be a strong stimulus for increase in

bone density over time in teens and young adults with CF [32]. In a study of 191 men and women with CF, Rossini et al. found below normal sex steroid levels in 23% of the women and 27% of the men studied. Estradiol levels in women correlated with femur BMD.. Later age at puberty correlated negatively with BMD at spine, hip and total body. Low testosterone levels correlated with vertebral fractures in men [33].

2.4. Decreased physical activity

Much as in those without CF, decreased physical activity in patients with CF can be associated with lower bone density. A study by Tejero Garcia S et al. examined physical activity in 50 young adult patients with CF using cardiopulmonary exercise and 6-min walk tests and found significant positive correlation between activity level and bone mineral density at the spine and femoral neck [34]. Regular weight bearing exercise can improve bone accrual in healthy children and potentially in children with CF [35].

2.5. Exogenous glucocorticoids

Patients with CF may frequently receive systemic glucocorticoids for treatment of pulmonary exacerbations as well as post lung transplant [36]. Treatment with glucocorticoids has been shown to increase bone loss [32]. Increased risk of fractures can be seen after as little as one month of treatment in high-risk populations even before decrease in bone density, indicating a negative effect on bone microarchitecture that is not detected by Dual energy X-ray Absorptiometry (DXA) [37]. Glucocorticoids decrease bone formation via accelerated apoptosis of osteoblasts and osteocytes; direct suppression of osteoblast formation as evidenced by decrease of bone formation markers (e.g. osteocalcin); as well as decreased production of local bone growth factors. Glucocorticoids also increase bone resorption by increasing production of osteoclasts via RANKL activation and OPG inhibition [38–41].

Glucocorticoids can impair intestinal calcium absorption and renal tubular calcium reabsorption, leading to hypercalciuria, secondary hyperparathyroidism and increased bone resorption [41]. Additionally, systemic glucocorticoids can decrease sex steroid hormone production as well as growth hormone secretion and action, which can further decrease bone mass [42–44]. Glucocorticoid induced hyperglycemia may also contribute to low bone mass (section 2.7 in this document).

2.6. Respiratory infections & systemic inflammation

Poor lung function in individuals with CF has been shown to correlate with low bone mass in both children and young adults with CF [32]. FEV1 can be a significant predictor of measures of bone quality and estimates of bone strength [45]. Recurrent pulmonary exacerbations have also been shown to be associated with low BMD in young adults with CF [46]. A prospective study by Shead EF et al. in 24 adults with CF during periods of infective pulmonary exacerbations demonstrated significant increase in osteoclast number, and activity and in bone resorption markers [47]. This is possibly mediated by increased inflammatory cytokines, as shown by significant positive correlation between number of osteoclasts and concentration of tumor necrosis factor alpha (TNF-α), and between osteoclast activity and serum interleukin-6 (IL-6) [47].

2.7. Cystic fibrosis related diabetes (CFRD)

Hyperglycemia associated with CFRD can lead to decrease in bone density likely via increased frequency of pulmonary exacerbations and poor nutritional status. A retrospective study by Rana M, et al. evaluated 81 patients below 18 years of age with CF, found significantly lower BMD at lumbar spine and total body in patients with CFRD (14 patients) compared to those who had normal glucose. However, no significant correlation with fractures was found [48].

2.8. Other risk factors

Organ transplantation, major depression, frequent use of proton pump inhibitors, and chronic liver disease (all of which have increased prevalence in the CF population) have been shown to increase risk of osteoporosis in postmenopausal women [49]. This would indicate that these factors could potentially increase risk of bone loss in patients with CF, but no studies have examined this to date.

3. Diagnostic workup

Evaluation of CFBD and decision to start treatment should be based on careful history regarding all risk factors contributing to the disease, and documentation of previous fracture history as well as imaging and lab studies (Tables 2, 3).

3.1. Imaging

3.1.1. Dual energy X-ray absorptiometry (DXA)

DXA is currently the gold standard for assessment of CFBD and guiding therapy for osteoporosis [1,15]. It has several advantages including easy availability, low cost and minimal radiation exposure. DXA uses the attenuation of X-ray beams of two different photon energies to differentiate bone tissues from soft tissues. Since DXA scans are 2-dimensional images, this technique measures the bone mineral content (BMC, in grams) and the bone area (in cm^2) of a selected skeletal site (e.g. lumbar vertebrae, hip, distal forearm), and can only calculate an "areal" BMD (aBMD = BMC/projection area, in g/cm^2), not a true density (g/cm^3). For mathematical reasons, the areal BMD is dependent on bone size, and this is problematic in the longitudinal evaluation of growing patients (changing bone size) and in the comparison with healthy age-matched controls (possibly different body size, and consequently bone size). This difficulty can be overcome using special "corrections" [54,55]. Additionally, DXA is unable to differentiate between trabecular and cortical bone to assess bone quality and microarchitecture.

The evaluation of DXA BMD in adults is based on the T-score (the number of standard deviations that a patient's BMD differs from that of a reference population of healthy subjects around 25–30 years of age, i.e. the age of peak bone mass and lowest fracture risk). Before the attainment of peak bone mass, i.e. in children, adolescents and young adults, the T-score cannot be used, and the *Z*-score (the number of standard deviations that the patient's BMD differs from that of a reference population of age- and sex-matched healthy subjects) must be considered [55]. The European guidelines for CF also

Table 2
Imaging tools for evaluation of low bone mass and osteoporosis.

Characteristic	DXA	QUS	HR-pQCT	MRI
Sites measured	Spine, hip, forearm, total body	Heel, radius, tibia, phalanges	Radius, Tibia QCT: spine, hip	spine, hip, proximal femur
Measures BMD (volumetric)	Yes (areal) No	No	Yes	
Fracture prediction	Yes Limited	Yes Limited	Yes (no fractures data)	Not known
Cost	low	low	High	High
Availability	Yes	Yes	Not widely	Not widely
Portability	No	Yes	No	No
Radiation	Low	None	High	None
Can assess bone microarchitecture	No	Yes	Yes	Yes
Validated for diagnosis and monitoring	Yes	No	Yes	No

Table 3
Laboratory evaluation of low bone mass and osteoporosis [1,15,49].

Laboratory studies for all patients:

1. Complete blood count
2. Chemistry (Creatinine, calcium, magnesium, phosphorus)
3. Liver enzymes and total alkaline phosphatase[a]
4. 25-OH vitamin D level
5. Parathyroid hormone (PTH)[b]
6. 24- h urine collection for calcium, creatinine[c]
7. TSH[d]
8. Sex steroid hormones (LH, FSH, estradiol (females), total testosterone(males))[e]

Other tests should be considered in selected patients:

1. Free T4 (if altered TSH)
2. Bone turnover markers (Formation markers: PINP, OC, BSAP), (Resorption markers: CTX, NTX)[f].
3. Growth hormone, IGF-1[g]
4. Prolactin[h]
5. Screening for celiac disease (anti-transglutaminase antibodies (IgA and IgG) [86].
6. Serum or urine protein electrophoresis to evaluate for multiple myeloma
7. Tests for evaluation of hypercortisolism
8. Evaluation for rheumatoid arthritis
9. Test for HIV if indicated by clinical risk factors
10. Tests for evaluation for systemic mastocytosis

Abbreviations: PINP = N-terminal propeptide of type I procollagen. CTX = C-telopeptide of type I collagen. NTX = N-telopeptide of type I collagen, LH = luteinizing hormone, FSH = follicular stimulating hormone, IGF-1 = insulin like growth factor1, HIV = Human immunodeficiency virus.

[a] screen for cystic fibrosis related liver disease.

[b] an elevated PTH might suggest inadequate calcium intake or absorption or primary hyperparathyroidism.

[c] 24-h urine calcium can help assure adequate calcium balance and rule out hypercalciuria.

[d] Check for thyroid hormone overreplacement while on therapy or if there is clinical suspicion of thyrotoxicosis.

[e] Evaluate for delayed puberty and hypogonadism.

[f] One marker of formation and one of resorption should be chosen initially, then measured at suitable intervals for follow-up.

[g] Growth hormone status can be helpful in children with compromised growth or to exclude acromegaly in adults.

[h] As indicated by sex steroid hormone testing and clinical history.

recommend using the Z-score for premenopausal women and men under the age of 50 [15].

Screening recommendations for CFBD with DXA are reviewed in article 8 in this supplement "Treatment of Cystic Fibrosis Bone Disease: Current Knowledge and Future Directions". In subjects younger than 20 years, DXA should be measured at lumbar spine (LS), typically L1 through L4, and Total Body less head (TBLH). Recent update of the International Society for Clinical Densitometry guidelines indicated possible measurement of proximal femur in children with decreased weight bearing of the lower extremities or in children with chronic diseases who are at continued risk of decreased bone mass through adulthood. In adults DXA is measured at LS and proximal femur (hip) [15]. In children, adolescents, and young adults below 20 years of age, the diagnosis of "osteoporosis" should not be made based on the BMD *Z*-score alone, but also requires evaluation of fracture history. Osteoporosis is thus defined as a Z-score below −2.0 (i.e., aBMD 2 or more standard deviations below mean for age and sex), 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). The same applies to premenopausal women and men under the age of 50. In postmenopausal women and men above 50, osteoporosis is defined as a T-score less than or equal −2.5 (i.e., aBMD 2.5 or more standard deviations below mean of healthy young adults). Low-trauma vertebral or hip fracture in adults with CF regardless of the BMD can also define osteoporosis (Fig. 2) [15,49].

3.1.2. Tools complementary to DXA

Limitations with DXA have led to the emergence of complementary tools to improve its ability to assess bone microarchitecture and predict fractures [50]. Trabecular Bone Score (TBS) (Fig. 3.) is an index derived from standard LS DXA scans. Lower TBS values are associated with increased risk for major osteoporotic fractures in postmenopausal women and older men, independently of BMD values and other clinical risk factors [51].

TBS has been shown in several studies to be a BMD independent predictor of fracture risk in other high-risk groups like patients with diabetes, and those on chronic glucocorticoid therapy [52–54]. A recent retrospective study by our group showed correlation of TBS with lung function and BMD in young adult patients with CF [55]. This tool has been studied in children; however, more studies are needed to better validate the use of TBS in this population [56,57]. TBS has not been validated to initiate or monitor therapy for osteoporosis [58].

Vertebral fracture assessment (VFA) by DXA uses a lateral projection of the thoracic and lumbar spine (T4-L4) to detect vertebral fractures. It offers an image at a lower cost and less radiation compared to conventional radiography. The use of VFA in patients at high risk for fracture, such as patients with CF can reveal previously unknown vertebral compression fractures, identifying patients at high risk for future fractures and patients most likely to benefit from therapy. No studies have evaluated use of VFA in individuals with CF to date. Hip structural analysis (HSA) can also be obtained from DXA images of the hip using hip dimensions and mineral mass distribution of the hip to compute several dimensional parameters to evaluate hip strength. Only Hip Axial Length (HAL) parameter has been shown to be associated with hip fracture in postmenopausal

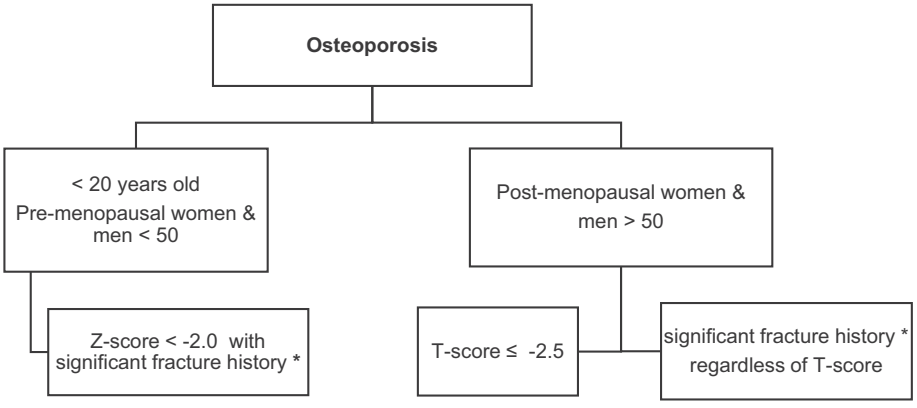


Fig. 2. Definition of osteoporosis in patients with cystic fibrosis [15].
* Low trauma fracture of a lower limb long bone, vertebral compression fracture, or two or more upper limb long bone fractures.

women [59]. There are no studies to evaluate this tool in patients with cystic fibrosis.

3.1.3. Fracture risk assessment tool (FRAX®)

FRAX® is an online calculator that can predict ten-year risk of major osteoporotic and hip fractures using several clinical risk factors, as well as femoral neck aBMD measured by DXA or Quantitative CT (QCT). Since FRAX® does not account for spine BMD, TBS can be applied to FRAX® to enhance fracture risk predictability. Unfortunately, the FRAX® calculator is only validated for use in people over 40 years of age and no studies have validated its use in patients with CF.

3.1.4. Quantitative computed tomography (QCT)

Quantitative Computed Tomography (QCT) measures volumetric bone mineral density (vBMD) in mg/cm^3 at the spine and hip, while peripheral QCT (pQCT) and High Resolution pQCT (HR-pQCT) measure vBMD at the tibia and forearm. QCT and pQCT can differentiate trabecular from cortical bone; hence they are able to assess bone microarchitecture, which cannot be done with DXA. There is some evidence that QCT could be useful for diagnosis and treatment monitoring of osteoporosis and to predict fractures in high risk groups [60].

QCT and HR-pQCT have been studied in children and adult patients with CF. Putman et al. compared 30 young adult patients with CF to 60 healthy controls using HR-pQCT at the radius and tibia and found compromised trabecular microarchitecture and lower total and trabecular vBMD and estimated bone strength at the tibia in patients with CF compared to controls after adjusting for BMI differences (Fig. 4.) [45]. In a subsequent study using Individual trabecula segmentation (ITS) analysis of HR-pQCT, patients with CF had fewer, thinner, and less connected trabecular plates and altered alignment of trabeculae after adjustment for BMI and aBMD [61]. These findings were also seen at the tibia independent of differences in limb length in patients with CF [62].

Studies evaluating QCT in children with CF showed variable changes in bone microarchitecture and strength compared to healthy controls, but consistently showed reduced bone strength and altered microarchitecture in older children when compared to healthy controls especially those with poor lung function and poor nutritional status [30,63–65].

Although QCT and HR-pQCT greatly improved our understanding of bone strength and microarchitecture, they are currently not widely available and remain mainly research tools. Additionally, they result in higher radiation exposure and are more expensive than DXA.

3.1.5. Quantitative ultrasound (QUS)

QUS can be done at peripheral sites only, i.e. calcaneus, radius, tibiae and phalanges. The advantages of QUS includes that it is inexpensive, portable and without radiation exposure. QUS essentially calculates two parameters: speed of sound (in meters per second, m/s), which is correlated with bone material properties such as elastic modulus and compressive strength, and broadband ultra-sound attenuation (decibels per megahertz, dB/MHz), which is related to BMD [66,67]. However, QUS is not validated for diagnosis or therapy monitoring of osteoporosis.

Calcaneal and radial QUS can be helpful to identify individuals with normal bone mass, however, further testing should be performed to confirm low bone mass if diagnosed by QUS [68,69]. A study on 172 adults with cystic fibrosis concluded that phalangeal QUS in contrast to calcaneal, radial QUS or DXA, can differentiate between CF patients with and without vertebral fractures [70].

3.1.6. Magnetic resonance imaging (MRI)

MRI for bone disease has not been studied in patients with CF. It can differentiate between cortical and trabecular bone and assess bone microarchitecture without exposure to ionizing radiation. However, it is not validated for diagnosis and monitoring osteoporosis therapy, and is time consuming and expensive compared to other available techniques [71].

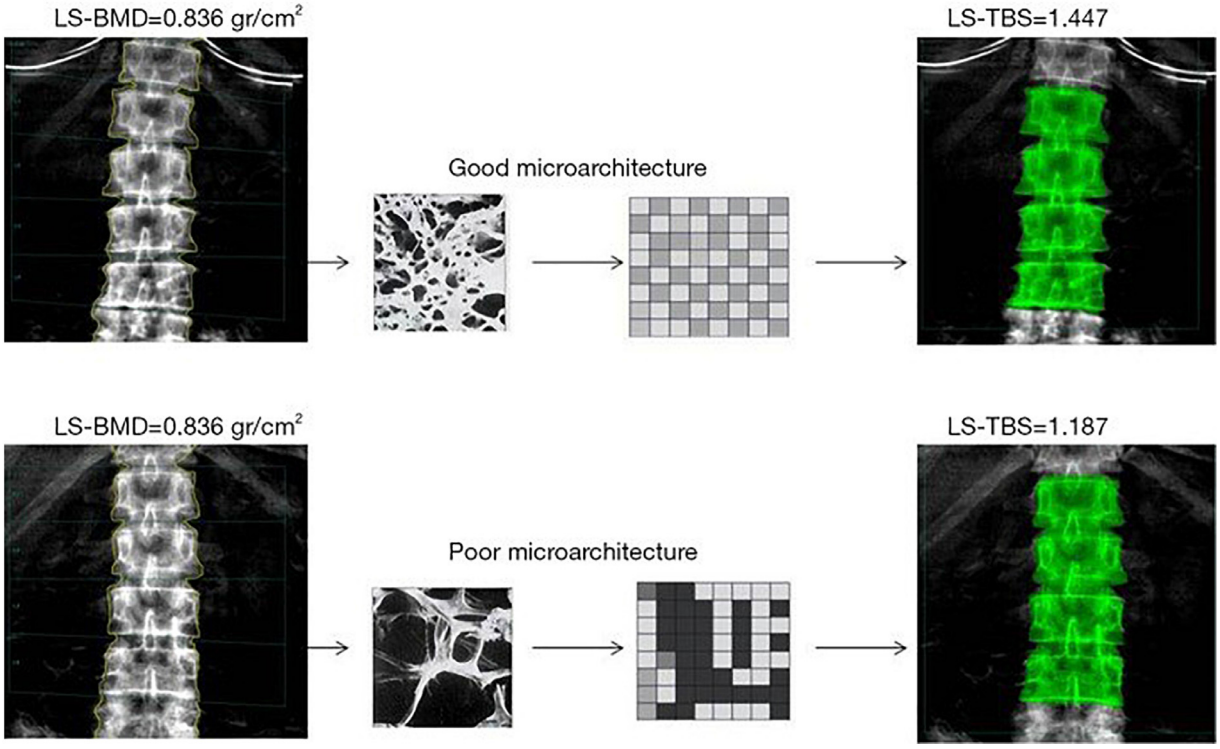


Fig. 3. DXA images of the spine, L1–L4 level of two individuals (top and bottom row); LS-BMD values are the same for both, LS-TBS in the second subject is clearly lower compared to the first subject, corresponding to deteriorated microarchitecture of the vertebral body. Adapted from L Oei. et al. *Quant Imaging Med Surg.* Dec 2016; 6(6): 680–698.

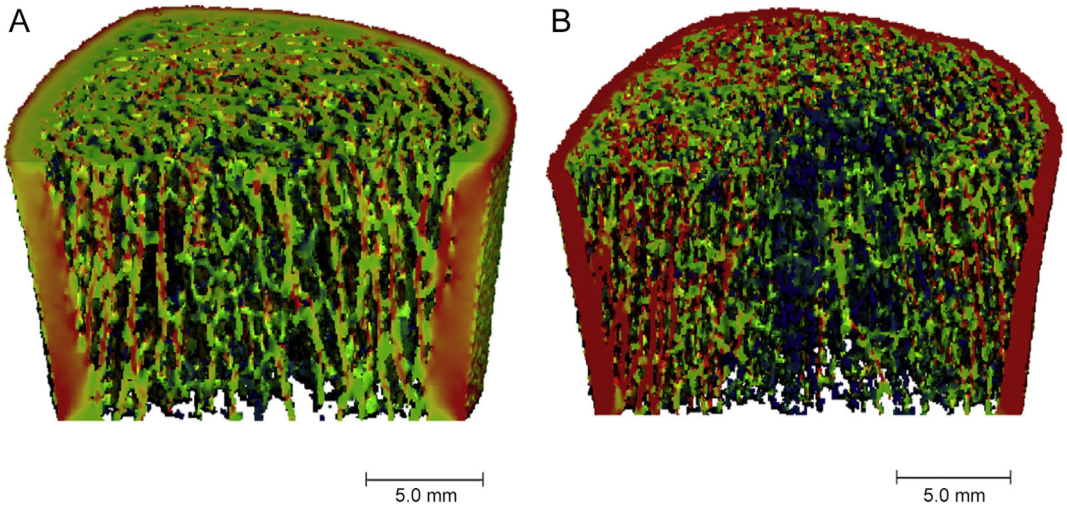


Fig. 4. Representative HR-pQCT images of the tibia of a (a) 23-year-old healthy woman and (b) 23 year old woman with CF.

3.2. Laboratory studies to evaluate secondary causes of osteoporosis

Osteoporosis guidelines recommend that laboratory exclusion of possible secondary causes of osteoporosis should be considered at initial evaluation and in cases with continued bone loss despite pharmacologic therapy [49,72]. This is also valid for CF patients.

Basic evaluation for all patients should include complete blood count, chemistry, liver enzymes and alkaline phosphatase, 25-hydroxy vitamin D level, parathyroid hormone, 24-h urine calcium and sex steroid hormones [15,49]. Additional testing can be considered in selected patients based on clinical history (Table 3).

Several "bone turnover markers" have been identified and can be measured in serum or urine. Bone resorption markers include serum C-terminal telopeptide of type 1 collagen (CTX) and urine N-terminal telopeptide of type 1 collagen (NTX). Bone formation markers include serum bone-specific alkaline phosphatase (BSAP), osteocalcin (OC), and amino-terminal pro-peptide of type I procollagen (PINP). Bone turn over markers are best measured fasting in the morning and are mainly used to evaluate the response to therapy. They are subject to variability due to several causes, including increase following fractures [73].

High bone turn over markers have been shown in some studies to predict fractures and rate of bone loss independent of BMD and estrogen levels in postmenopausal women [74,75]. Percent decrease in bone turn over markers levels of about 30–50% within 3–6 months of initiation of pharmacologic therapies, even before significant changes in BMD can be seen to indicate response to therapy. This makes bone turn over markers useful in treatment response monitoring, compliance and malabsorption assessment, and possibly prediction of fracture risk reduction while on therapy [76,77]. Bone turn over markers trend following completion of bisphosphonate therapy can potentially help decide the duration of drug holiday, although more studies are needed. Some studies showed increased levels of bone resorption markers and decreased bone formation markers in both children and adults with CF [28,78,79], especially during periods of infective exacerbations [47,80]; however, no studies to date have validated clinical use of bone turnover markers trend in management of CFBD.

4. Potential impact of CFTR modulation on bone pathophysiology

The negative effects of CFTR dysfunction on bone have led to increased awareness of potential CFTR modulator therapies for treatment and prevention of CFBD [81–83]. A study by Le Henaff et al. using miglustat, a medication partially restoring CFTR-dependent chloride transport in bone cells in deltaF508 mice, resulted in improved bone density and microarchitecture that was associated with increased bone formation and decreased bone resorption at the lumbar spine and femur [81]. Velard et al. tested the effect of CFTR modulator C18 on cultured osteoblasts from four adolescents with CF and showed 34% reduction in RANKL/OPG mRNA ratio compared to untreated deltaF508 osteoblasts [82].

CFTR modulators can potentially improve CFBD directly by targeting abnormal bone turn over and decreased bone strength induced by CFTR dysfunction and indirectly by modifying overall disease outcomes including lung function, frequency of pulmonary exacerbations, CFRD, BMI and nutritional status [84]. CFTR modulators role in therapy of CFBD is reviewed in detail in article 8 in this supplement titled "Treatment of Cystic Fibrosis Bone Disease: Current Knowledge and Future Directions".

5. Potential clinical trials and endpoints

Prediction of fractures and risk of development of CFBD with current available tools can be challenging in patients with CF. Fracture Risk Assessment Tool (FRAX®) has not been validated for use in individuals with CF. Clinical trials are needed to establish fracture risk assessment calculator specific for CF population combining clinical risk factors (including genotype), fracture history, and current imaging and lab studies. This can better help predict fractures and guide initiation of pharmacologic therapy. Clinical trials to evaluate role of bone turnover markers in monitoring response to pharmacologic therapy are also needed.

6. Future directions

Multiple imaging modalities are currently available to evaluate CFBD in clinical and research settings. DXA is the imaging modality recommended by guidelines to establish the diagnosis of CFBD, assess fracture risk and monitor response to therapy in individuals with CF. QCT can be useful to assess bone quality, strength in addition to bone density in selected patients; however, studies are needed to define best indications for QCT use in clinical practice due to concerns regarding radiation exposure and cost. Prospective studies are needed to evaluate benefit of other tools such as TBS in improving DXA predictability of fractures as seen in other high risk populations [52–54,85].

7. Clinical practice points

- Evaluation of CFBD and decision to start treatment should be based on careful history regarding all risk factors contributing to

the disease, documentation of previous fracture history as well as imaging and lab studies, and CF status (e.g. stable conditions, FEV1, planning of lung transplantation).

- DXA is currently the gold standard for assessment of CFBD and guiding therapy for osteoporosis.
- Current CF guidelines recommend screening with DXA starting at the age of 8–10 years.
- DXA measures areal BMD and not volumetric BMD and should be interpreted with care in the pediatric population as deficits in bone mass can be exaggerated in people with small body size .
- *Z*-score should be used for children, premenopausal women and men under the age of 50. T-score should not be used until after the age of 20 and only if Z-score is not available.
- The diagnosis of osteoporosis should not be made only based on BMD measurement and should consider fracture history.
- Basic evaluation for all patients should include complete blood count, chemistry (including renal function, electrolytes [calcium, magnesium, phosphorus], liver enzymes and alkaline phosphatase), 25-OH vitamin D level, PTH and 24-h urine calcium. Other labs can be considered in selected cases (Table 3).
- Bone turn over markers are not validated for diagnosis of osteoporosis and are mainly used to evaluate response to therapy.
- CFTR modulators can potentially improve CFBD via direct effect on bone and indirectly by affecting overall disease progression.

8. Summary

CFBD is a common long-term complication of CF. It is likely due to multiple risk factors including CFTR dysfunction, malabsorption of calcium, vitamin deficiencies, malnutrition, delayed puberty, prolonged treatment with glucocorticoids, recurrent pulmonary exacerbations and hyperglycemia. DXA is currently the gold standard technique recommended by CF guidelines for evaluation of CFBD [1,15]. The decision regarding initiation of pharmacologic therapy cannot be only based on DXA, but on clinical condition and fracture history. Other tools to evaluate CFBD and improve predictability and early detection of fractures including TBS and VFA have not been studied in patients with CF. QCT has improved our understanding of CFBD; however currently available as a research tool. Bone turnover markers can potentially be helpful in monitoring response to therapy in patients with CF although more studies are needed to evaluate their clinical utility in patients with CFBD.CFTR modulators may have a role in prevention and treatment of CFBD. Further studies are needed to assess whether treatment with CFTR modulators translates into clinical improvement in bone strength and decreased risk of fractures in individuals with CF.

Declaration of Conflict Interest

The authors report no conflict of interest. MSP received grant support from the National Institutes of Health (NIH K23DK102600 and R01DK119699) and a Vertex Investigator Initiated Studies Grant. VT received grant support from the National Institutes of Health (NIH 3UL1TR0002378-02s1 and R01000517815-02) and Cystic Fibrosis Foundation Center Grant CC002-AD.

Funding

This paper is part of a Supplement supported by the Cystic Fibrosis Foundation.

Acknowledgments

The authors would like to thank the Cystic Fibrosis Foundation and the faculty mentor members of the EnVision: Emerging Leaders in CF Endocrinology Program, for their ongoing support and mentorship of the program awardees. We also would like to thank Dr. Leland Graves III, MD, Endocrinology division director at the University of Kansas Medical Center for providing continued support and help.

References

[1] Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 2005;90(3):1888–96.
[2] Elkin SL, Fairney A, Burnett S, Kemp M, Kyd P, Burgess J, et al. Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study. Osteoporos Int 2001;12(5):366–72.
[3] Haworth CS, Selby PL, Webb AK, Dodd ME, Musson H, Mc LNR, et al. Low bone mineral density in adults with cystic fibrosis. Thorax. 1999;54(11):961–7.
[4] Paccou J, Zeboulon N, Combescure C, Gossec L, Cortet B. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int 2010;86(1):1–7.
[5] Stephenson A, Jamal S, Dowdell T, Pearce D, Corey M, Tullis E. Prevalence of vertebral fractures in adults with cystic fibrosis and their relationship to bone mineral density. Chest. 2006;130(2):539–44.
[6] Wolfenden LL, Judd SE, Shah R, Sanyal R, Ziegler TR, Tangpricha V. Vitamin D and bone health in adults with cystic fibrosis. Clin Endocrinol (Oxf) 2008;69(3):374–81.
[7] Aris RM, Renner JB, Winders AD, Buell HE, Riggs DB, Lester GE, et al. Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. Ann Intern Med 1998;128(3):186–93.
[8] Latzin P, Griese M, Hermanns V, Kammer B. Sternal fracture with fatal outcome in cystic fibrosis. Thorax. 2005;60(7):616.
[9] Cairoli E, Eller-Vainicher C, Morlacchi LC, Tarsia P, Rossetti V, Pappalettera M, et al. Bone involvement in young adults with cystic fibrosis awaiting lung transplantation for end-stage respiratory failure. Osteoporos Int. 2019;30:1255–63.
[10] O'Reilly R, Fitzpatrick P, Leen G, Elnazir B, Greally P. Severe bone demineralisation is associated with higher mortality in children with cystic fibrosis. Ir Med J 2009;102(2):47–9.
[11] Gordon CM, Zemel BS, Wren TA, Leonard MB, Bachrach LK, Rauch F, et al. The determinants of peak bone mass. J Pediatr 2017;180:261–9.
[12] Seeman E, Delmas PD. Bone quality–the material and structural basis of bone strength and fragility. N Engl J Med 2006;354(21):2250–61.
[13] Fonseca H, Moreira-Goncalves D, Coriolano HJ, Duarte JA. Bone quality: the determinants of bone strength and fragility. Sports Med 2014;44(1):37–53.
[14] Stalvey MS, Clines GA. Cystic fibrosis-related bone disease: insights into a growing problem. Curr Opin Endocrinol Diabetes Obes 2013;20(6):547–52.
[15] Sermet-Gaudelus I, Bianchi ML, Garabedian M, Aris RM, Morton A, Hardin DS, et al. European cystic fibrosis bone mineralisation guidelines. J Cyst Fibros 2011;10(Suppl. 2):S16–23.
[16] Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nat Med 2013;19(2):179–92.
[17] Bezzerri V, Piacenza F, Caporelli N, Malavolta M, Provinciali M, Cipolli M. Is cellular senescence involved in cystic fibrosis? Respir Res 2019;20(1):32.
[18] Callaway DA, Jiang JX. Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases. J Bone Miner Metab 2015;33(4):359–70.
[19] Tian X, Cong F, Guo H, Fan J, Chao G, Song T. Downregulation of Bach1 protects osteoblasts against hydrogen peroxide-induced oxidative damage in vitro by enhancing the activation of Nrf2/ARE signaling. Chem Biol Interact 2019;309:108706.
[20] King SJ, Topliss DJ, Kotsimbos T, Nyulasi IB, Bailey M, Ebeling PR, et al. Reduced bone density in cystic fibrosis: DeltaF508 mutation is an independent risk factor. Eur Respir J 2005;25(1):54–61.
[21] Dif F, Marty C, Baudoin C, de Vernejoul MC, Levi G. Severe osteopenia in CFTR-null mice. Bone. 2004;35(3):595–603.
[22] Velard F, Delion M, Le Henaff C, Guillaume C, Gangloff S, Jacquot J, et al. Cystic fibrosis and bone disease: defective osteoblast maturation with the F508del mutation in cystic fibrosis transmembrane conductance regulator. Am J Respir Crit Care Med 2014;189(6):746–8.
[23] Stalvey MS, Clines KL, Havasi V, McKibbin CR, Dunn LK, Chung WJ, et al. Osteoblast CFTR inactivation reduces differentiation and osteoprotegerin expression in a mouse model of cystic fibrosis-related bone disease. PLoS One 2013;8(11):e80098.
[24] Le Henaff C, Gimenez A, Hay E, Marty C, Marie P, Jacquot J. The F508del mutation in cystic fibrosis transmembrane conductance regulator gene impacts bone formation. Am J Pathol 2012;180(5):2068–75.
[25] Haston CK, Li W, Li A, Lafleur M, Henderson JE. Persistent osteopenia in adult cystic fibrosis transmembrane conductance regulator-deficient mice. Am J Respir Crit Care Med 2008;177(3):309–15.
[26] Paradis J, Wilke M, Haston CK. Osteopenia in Cftr-deltaF508 mice. J Cyst Fibros 2010;9(4):239–45.
[27] Tangpricha V, Kelly A, Stephenson A, Maguiness K, Enders J, Robinson KA, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. J Clin Endocrinol Metab 2012;97(4):1082–93.
[28] Aris RM, Ontjes DA, Buell HE, Blackwood AD, Lark RK, Caminiti M, et al. Abnormal bone turnover in cystic fibrosis adults. Osteoporos Int 2002;13(2):151–7.
[29] Sharma S, Jaksic M, Fenwick S, Byrnes C, Cundy T. Accrual of bone mass in children and adolescents with cystic fibrosis. J Clin Endocrinol Metab 2017;102(5):1734–9.
[30] Brookes DS, Briody JN, Munns CF, Davies PS, Hill RJ. Cystic fibrosis-related bone disease in children: examination of peripheral quantitative computed tomography (pQCT) data. J Cyst Fibros 2015;14(5):668–77.

[31] Seeman E. Estrogen, androgen, and the pathogenesis of bone fragility in women and men. Curr Osteoporos Rep 2004;2(3):90–6.
[32] Bianchi ML, Romano G, Saraifoger S, Costantini D, Limonta C, Colombo C. BMD and body composition in children and young patients affected by cystic fibrosis. J Bone Miner Res 2006;21(3):388–96.
[33] Rossini M, Del Marco A, Dal Santo F, Gatti D, Braggion C, James G, et al. Prevalence and correlates of vertebral fractures in adults with cystic fibrosis. Bone 2004;35 (3):771–6.
[34] Tejero Garcia S, Giraldez Sanchez MA, Cejudo P, Quintana Gallego E, Dapena J, Garcia Jimenez R, et al. Bone health, daily physical activity, and exercise tolerance in patients with cystic fibrosis. Chest 2011;140(2):475–81.
[35] Hind K, Truscott JG, Conway SP. Exercise during childhood and adolescence: a prophylaxis against cystic fibrosis-related low bone mineral density? Exercise for bone health in children with cystic fibrosis. J Cyst Fibros 2008;7(4):270–6.
[36] Cheng K, Ashby D, Smyth RL. Oral steroids for long-term use in cystic fibrosis. Cochrane Database Syst Rev 2015;12.
[37] Adami G, Saag KG. Glucocorticoid-induced osteoporosis: 2019 concise clinical review. Osteoporos Int. 2019;30:1145–56.
[38] Prummel MF, Wiersinga WM, Lips P, Sanders GT, Sauerwein HP. The course of biochemical parameters of bone turnover during treatment with corticosteroids. J Clin Endocrinol Metab 1991;72(2):382–6.
[39] Brennan-Speranza TC, Henneicke H, Gasparini SJ, Blankenstein KI, Heinevetter U, Cogger VC, et al. Osteoblasts mediate the adverse effects of glucocorticoids on fuel metabolism. J Clin Invest 2012;122(11):4172–89.
[40] Hofbauer LC, Gori F, Riggs BL, Lacey DL, Dunstan CR, Spelsberg TC, et al. Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. Endocrinology 1999;140(10):4382–9.
[41] Bianchi ML. Glucorticoids and bone: some general remarks and some special observations in pediatric patients. Calcif Tissue Int 2002;70(5):384–90.
[42] Mazziotti G, Giustina A. Glucocorticoids and the regulation of growth hormone secretion. Nat Rev Endocrinol 2013;9(5):265–76.
[43] MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med 1986;104(5):648–51.
[44] Hsueh AJ, Erickson GF. Glucocorticoid inhibition of FSH-induced estrogen production in cultured rat granulosa cells. Steroids 1978;32(5):639–48.
[45] Putman MS, Milliren CE, Derrico N, Uluer A, Sicilian L, Lapey A, et al. Compromised bone microarchitecture and estimated bone strength in young adults with cystic fibrosis. J Clin Endocrinol Metab 2014;99(9):3399–407.
[46] Alicandro G, Bisogno A, Battezzati A, Bianchi ML, Corti F, Colombo C. Recurrent pulmonary exacerbations are associated with low fat free mass and low bone mineral density in young adults with cystic fibrosis. J Cyst Fibros 2014;13 (3):328–34.
[47] Shead EF, Haworth CS, Barker H, Bilton D, Compston JE. Osteoclast function, bone turnover and inflammatory cytokines during infective exacerbations of cystic fibrosis. J Cyst Fibros 2010;9(2):93–8.
[48] Rana M, Munns CF, Selvadurai H, Briody J, Craig ME. The impact of dysglycaemia on bone mineral accrual in young people with cystic fibrosis. Clin Endocrinol (Oxf) 2013;78(1):36–42.
[49] Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al. American association of clinical endocrinologists and american college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2016. Endocr Pract 2016;22(Suppl. 4):1–42.
[50] Shepherd JA, Schousboe JT, Broy SB, Engelke K, Leslie WD. Executive summary of the 2015 ISCD position development conference on advanced measures from DXA and QCT: fracture prediction beyond BMD. J Clin Densitom 2015;18(3):274–86.
[51] Martineau P, Leslie WD. Trabecular bone score (TBS): method and applications. Bone 2017;104:66–72.
[52] Dhaliwal R, Cibula D, Ghosh C, Weinstock RS, Moses AM. Bone quality assessment in type 2 diabetes mellitus. Osteoporos Int 2014;25(7):1969–73.
[53] Leib ES, Winzenrieth R. Bone status in glucocorticoid-treated men and women. Osteoporos Int 2016;27(1):39–48.
[54] Neumann T, Lodes S, Kastner B, Lehmann T, Hans D, Lamy O, et al. Trabecular bone score in type 1 diabetes–a cross-sectional study. Osteoporos Int 2016;27(1): 127–33.
[55] Anabtawi A, Holyoak M, Cristiano E, Lalani N, Grdinovac K, Graves L. Evaluation of trabecular bone score in cystic fibrosis patients. Pediatr Pulmonol 2018;53(S2): S148–456.
[56] Shawwa K, Arabi A, Nabulsi M, Maalouf J, Salamoun M, Choucair M, et al. Predictors of trabecular bone score in school children. Osteoporos Int 2016;27(2): 703–10.
[57] Donaldson AA, O'Donnell JM, Gordon CM, Feldman HA, Gopalakrishnan G. Spinal bone texture assessed by trabecular bone score in adolescent girls with anorexia nervosa. J Clin Endocrinol Metabol 2015;100(9):3436–42.
[58] Silva BC, Broy SB, Boutroy S, Schousboe JT, Shepherd JA, Leslie WD. Fracture risk prediction by non-BMD DXA measures: the 2015 ISCD official positions part 2: trabecular bone score. J Clin Densitom 2015;18(3):309–30.
[59] Broy SB, Cauley JA, Lewiecki ME, Schousboe JT, Shepherd JA, Leslie WD. Fracture risk prediction by non-BMD DXA measures: the 2015 ISCD official positions part 1: hip geometry. J Clin Densitom 2015;18(3):287–308.
[60] Engelke K, Lang T, Khosla S, Qin L, Zysset P, Leslie WD, et al. Clinical use of quantitative computed tomography (QCT) of the hip in the management of osteoporosis in adults: the 2015 ISCD official positions-part I. J Clin Densitom 2015;18(3):338–58.
[61] Putman MS, Greenblatt LB, Sicilian L, Uluer A, Lapey A, Sawicki G, et al. Young adults with cystic fibrosis have altered trabecular microstructure by ITS-based morphological analysis. Osteoporos Int 2016;27(8):2497–505.
[62] Nishiyama KK, Agarwal S, Kepley A, Rosete F, Hu Y, Guo XE, et al. Adults with cystic fibrosis have deficits in bone structure and strength at the distal tibia despite similar size and measuring standard and relative sites. Bone 2018;107:181–7.
[63] Kelly A, Schall J, Stallings VA, Zemel BS. Trabecular and cortical bone deficits are present in children and adolescents with cystic fibrosis. Bone 2016;90:7–14.
[64] Braun C, Bacchetta J, Braillon P, Chapurlat R, Drai J, Reix P. Children and adolescents with cystic fibrosis display moderate bone microarchitecture abnormalities: data from high-resolution peripheral quantitative computed tomography. Osteoporos Int 2017;28(11):3179–88.
[65] Bai W, Binkley TL, Wallace JW, Carver Jr. TW, Specker BL. Peripheral quantitative computed tomography (pQCT) bone measurements in children with cystic fibrosis. Pediatr Pulmonol 2016;51(1):28–33.
[66] Gong B, Mandair GS, Wehrli FW, Morris MD. Novel assessment tools for osteoporosis diagnosis and treatment. Curr Osteoporos Rep 2014;12(3):357–65.
[67] Hans D, Baim S. Quantitative ultrasound (QUS) in the management of osteoporosis and assessment of fracture risk. J Clin Densitom 2017;20(3):322–33.
[68] De Schepper J, Roggen I, Van Biervliet S, Robberecht E, Gies I, De Waele K, et al. Comparative bone status assessment by dual energy X-ray absorptiometry, peripheral quantitative computed tomography and quantitative ultrasound in adolescents and young adults with cystic fibrosis. J Cyst Fibros 2012;11(2):119–24.
[69] Flohr F, Lutz A, App EM, Matthys H, Reincke M. Bone mineral density and quantitative ultrasound in adults with cystic fibrosis. Eur J Endocrinol 2002;146 (4):531–6.
[70] Rossini M, Viapiana O, Del Marco A, de Terlizzi F, Gatti D, Adami S. Quantitative ultrasound in adults with cystic fibrosis: correlation with bone mineral density and risk of vertebral fractures. Calcif Tissue Int 2007;80(1):44–9.
[71] Chang G, Boone S, Martel D, Rajapakse CS, Hallyburton RS, Valko M, et al. MRI assessment of bone structure and microarchitecture. J Magn Reson Imaging 2017;46(2):323–37.
[72] Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25 (10):2359–81.
[73] Vasikaran S, Eastell R, Bruyere O, Foldes AJ, Garnero P, Griesmacher A, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int 2011;22(2):391–420.
[74] Garnero P. Markers of bone turnover for the prediction of fracture risk. Osteoporos Int 2000;11(Suppl. 6):S55–65.
[75] Ross PD, Knowlton W. Rapid bone loss is associated with increased levels of biochemical markers. J Bone Miner Res 1998;13(2):297–302.
[76] Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res 2003;18(6):1051–6.
[77] Eastell R, Vrijens B, Cahall DL, Ringe JD, Garnero P, Watts NB. Bone turnover markers and bone mineral density response with risedronate therapy: relationship with fracture risk and patient adherence. J Bone Miner Res 2011;26 (7):1662–9.
[78] Ambroszkiewicz J, Sands D, Gajewska J, Chelchowska M, Laskowska-Klita T. Bone turnover markers, osteoprotegerin and RANKL cytokines in children with cystic fibrosis. Adv Med Sci 2013;58(2):338–43.
[79] Ambroszkiewicz J, Gajewska J, Sands D, Chelchowska M, Oltarzewski M, Laskowska-Klita T. Assessment of selected bone metabolism marker concentrations in children with cystic fibrosis. Med Wieku Rozwoj 2012;16(2):117–23.
[80] Aris RM, Stephens AR, Ontjes DA, Denene Blackwood A, Lark RK, Hensler MB, 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(5):1674–8.
[81] Le Henaff C, Hay E, Velard F, Marty C, Tabary O, Marie PJ, et al. Enhanced F508del-CFTR channel activity ameliorates bone pathology in murine cystic fibrosis. Am J Pathol 2014;184(4):1132–41.
[82] Velard F, Delion M, Lemaire F, Tabary O, Guillaume C, Le Pimpec Barthes F, et al. Cystic fibrosis bone disease: is the CFTR corrector C18 an option for therapy? Eur Respir J 2015;45(3):845–8.
[83] Jacquot J, Delion M, Gangloff S, Braux J, Velard F. Bone disease in cystic fibrosis: new pathogenic insights opening novel therapies. Osteoporos Int 2016;27 (4):1401–12.
[84] Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. J Cyst Fibros 2019 Jun 10. https://dx.doi.org/10.1016/j.jcf.2019.05.015. Epub ahead of print.
[85] Leib E, Winzenrieth R, Lamy O, Hans D. Comparing bone microarchitecture by trabecular bone score (TBS) in Caucasian American women with and without osteoporotic fractures. Calcif Tissue Int 2014;95(3):201–8.
[86] Putman MS, Haagensen A, Neuringer I, Sicilian L. Celiac disease in patients with cystic fibrosis-related bone disease. Case Rep Endocrinol 2017;2017:2652403.