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Treatment of cystic fibrosis related bone disease

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ABSTRACT

The advent of highly effective CFTR modulator therapies has slowed the progression of pulmonary complications in people with cystic fibrosis. There is increased interest in cystic fibrosis bone disease (CFBD) due to the increasing longevity of people with cystic fibrosis. CFBD is a complex and multifactorial disease. CFBD is a result of hypomineralized bone leading to poor strength, structure and quality leading to susceptibility to fractures. The development of CFBD spans different age groups. The management must be tailored to each group with nuance and based on available guidelines while balancing therapeutic benefits to risks of long-term use of bone-active medication. For now, the mainstay of treatment includes bisphosphonates. However, the long-term effects of bisphosphonate treatment in people with CF are not fully understood. We describe newer agents available for osteoporosis treatment. Still, the lack of data behooves trials of monoclonal antibodies treatments such as Denosumab and Romozosumab and anabolic bone therapy such as teriparatide and Abaloparatide. In this review, we also summarize screening and non-pharmacologic treatment of CFBD and describe the various options available for the pharmacotherapy of CFBD. We address the prospect of CFTR modulators on bone health while awaiting long-term trials to describe the effects of these medications on bone health.

Introduction

Highly effective CFTR modulator therapy is linked with improved quality of life and longer life expectancy in people with cystic fibrosis [1,2]. It is expected that the pulmonary disease burden will lessen but other chronic complications such as cystic fibrosis bone disease (CFBD) may add to a higher morbidity associated with CF in the form of fractures, pain and disability. The pathophysiology of CFBD is multifactorial and poorly understood [3]. The treatments vary through different stages of life and must contend with balancing therapeutic benefit over long term adverse effects. In this review, we summarize the non-pharmacologic and pharmacologic therapies for CFBD across various stages of life for people with CF (PCF).

Bone health screening

Bone mineral content accrual is highest during childhood and adolescence and impaired bone modeling during this time can have a significant impact on bone health in adulthood. Dual-energy x-ray absorptiometry (DXA) is the gold standard imaging tool for clinical assessment for bone health in children and adults, measuring both bone mineral content (BMC) and area bone mineral density (aBMD). Low BMD, defined by DXA-derived height and age adjusted Z-scores of less than or equal to -2.0 standard deviations (SD), has been reported between 9 and 32% in children and adolescents with CF [4–6] and is associated with low BMI, low vitamin D levels, and higher disease severity scores [6]. Osteoporosis in this age group can be diagnosed by

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low BMD with long bone fractures (up to 2 fractures by age 10 or 3 fractures by age 19) or by the presence of a vertebral fragility fracture, independent of Z-score BMD [7]. Small cross-sectional studies report an increased risk of vertebral and rib fracture compared to healthy children and teens [8]. Fracture risk assessment remains limited in this age group, however, current guidelines are available to assist in directing the initiation and monitoring of non-pharmacologic and pharmacologic therapies [9]. Screening, risk stratification and treatment guidelines are offered by the Cystic Fibrosis Foundation (CFF), European, French, and Australian groups for children and adults with CF and are summarized in Table 1 [6,10,11].

In adults with CF, screening for CFBD starts at age 18 based on CFF guidelines. The French, European and CFF guidelines recommend DXA screening of children >8 years with significant risk factors for bone disease [11]. The CFF, European and French guidelines for screening [6,10] recommend screening based on T-score and Z-scores > -1 SD: every 5 years; ≤-1 SD and > -2.5 SD, every 2 years and ≤ -2SD every year with the European guidelines recommending screening every year if scores are ≤ 2.5 SD or the presence of low trauma fractures. High risk groups are identified as PCF with low trauma fractures, Z-scores of less than -2 SD at the spine with a rapid bone loss of > 4% per year, candidates awaiting lung transplantation or with use of high dose steroids. There are no CF-specific guidelines for postmenopausal osteoporosis and men over 50 years. The National Osteoporosis Foundation guidelines are

not CF specific but offer recommendations for this age group [12].

Nonpharmacological therapy

Role of minimizing respiratory exacerbations in improving bone health

Non-pharmacologic treatments may be effective for preventing CF bone disease and often align with other health priorities. For example, minimizing pulmonary exacerbations is advantageous for CF lung disease as well as likely protective against CF bone disease. CF pulmonary exacerbations are temporally associated with elevated inflammatory markers IL-6, IL-11, and TNF-alpha, elevated N-telopeptide and deoxy-pyridinoline, and reduced osteocalcin, suggesting that the acute inflammatory response to pulmonary exacerbations increases bone resorption and diminishes bone formation [13]. Additionally, a longitudinal study demonstrated that the frequency of IV antibiotics was inversely associated to bone mineral density as measured by DXA [14]. These data suggest that preventing pulmonary exacerbations and the associated inflammatory response protects bone health.

Nutrition

Maintaining adequate nutrition is another non-pharmacologic strategy to promote bone health. Numerous studies demonstrate an

Table 1
Comparison of available guideline for bone health screening and non-pharmacologic treatment with calcium and vitamin D and biochemical measurements.

	Cystic Fibrosis Foundation [11]	European (ESPEN-ESPGHAN-ECFS) Guidelines [92]	French Guidelines [93]	Australian Guidelines [94]
Baseline Screening Bone Density	8 year of specific risk factors* (*<90% ideal body weight, FEV1 < 50% Predicted, Glucocorticoid >=5 mg for > 3 months/year, delayed puberty, or history of fractures) OR at 18 years of age	8 to 10 years of age every 1–5 years	8 years	8 years
Adults	1300–1500 mg per day (ages 9 and above) * *This recommendation is not a guideline based but available in CFF publications	0–6 months 200 mg 7–11 months 280 mg 1–3 years 450 mg 4–10 years 800 mg 11–17 years 1150 mg 18–25 years 1000 mg >25 years 950 mg		0–6 months 210 mg 7–12 months 270 mg 1–3 years 500 mg 4–8 years 700 mg 9–11 years 1000 mg 12–13 years 1300 mg 14–18 years 1300 mg
Vitamin D levels	30–60 ng/ml (75–150 nmol/L)	above 20 ng/mL (50 nmol/L)		Adult 19–70 1000 Adults > 70 and Women > 50 1300 ≥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 10–20 nmol/L higher (i.e. ≥ 60–70 nmol/L)
DXA Monitoring	Z-scores	Z-scores	Z-scores	Every 3–5 years if bone mineral density is normal; Z or T-scores > -1
Children	>-1: every 5 years	>-1: every 5 years	>-1: every 2 years	Every two years if bone mineral density was moderately reduced; Z-score between -1 and -2; or T-score
Adults	≤-1 and > -2: every 2–4 years <-2: every year	≤-1 and > -2: every 2 years ≤-2, and or low trauma fracture: screen every year T-scores >-1: every 5 years ≤-1 and > -2.5 : every 2 years ≤-2.5 and or low trauma fracture: every year	≤-1: every year T-scores >-1: every 5 years ≤-1 and > -2: every 2 years ≤-2 : every year	between -1 and -2.5 Annually if bone mineral density was severely reduced; z-score < -2 or T-score < -2.5
Biochemical Measurements		Serum calcium, phosphate, 25(OH) D, PTH Urinary calcium excretion, prothrombin time	Serum: Albumin corrected calcium, fasting phosphate, 25(OH)D, PTH, prothrombin time Urine: Sodium and calcium on second morning urination Serum osteocalcin and resorption markers	Serum calcium Vitamin D, PTH Urinary sodium : creatinine ratio – aiming for 17–52 mmol/mmol

association between poor nutrition and low aBMD in CF [13–17]. Mechanisms linking malnutrition to low bone mineral density include low calcium, vitamin D, or vitamin K, protein deficiency, and hypogonadism [18,19]. Pancreatic enzyme replacement therapy (PERT) is key to achieving nutritional goals for pancreatic insufficient patients with CF. Nutritional guidelines recommend 110–200% calories per day with 35–40% calories from fat to maintain BMI > 50 percentile for youth and > 22 or 23 kg/m² for adult females and males respectively [20]. While these guidelines were designed to optimize pulmonary function, achieving recommended BMI targets is expected to optimize bone health as well.

Glucocorticoids

Glucocorticoids are a common treatment for CF pulmonary exacerbations with negative impact on bone health. Glucocorticoids stimulate bone resorption and inhibit bone growth through multiple mechanisms, including reduced IGF-1 synthesis and suppressed sex steroids [17]. Glucocorticoid treatment is associated with reduced BMD in multiple studies, though this effect is confounded by disease severity [14,16]. Avoidance of glucocorticoid therapy and use of the lowest therapeutic dose when necessary is likely to preserve BMD among PCF.

Cystic fibrosis related diabetes

PCF with hyperglycemia have lower muscle mass and insulin treatment is associated with gain of lost muscle suggesting insulin has an anabolic effect on the musculoskeletal system by inhibition of proteolysis [21]. PCF with early onset diabetes tend to have lower fat percentage, lower weight, and lower leptin levels [22]. Leptin has a direct anabolic effect on osteoblasts and other indirect effects that positively impact bone health [23]. All forms of diabetes impact bone health due to insulinopenia, inflammation, and elevated advanced glycation end products [24,25]. PCF with CFRD are particularly vulnerable to reduced bone turnover with reported negative associations with fasting glucose [26].

Physical activity

Engaging in physical exercise is another non-pharmacologic strategy to promote bone health among people with CF. The functional bone-muscle unit is affected in pediatric chronic illness. Muscle mass and strength increase during growth and puberty, leading to increased mechanical load on the bone, resulting in a positive change in the dimension and strength of bone. In chronic illness, decrease in lean muscle mass due to reduced mobility, pubertal delay, and glucocorticoid exposure impact bone accrual [27,28]. Earlier models of CF-related physiotherapy focused on inhalation therapy and airway clearance. With an increasing awareness of CFBD, physiotherapy has expanded to include physical education and exercise [29] with efforts directed at increasing mechanical loading to skeletal regions, above what is performed at baseline. Increase in weight bearing activity stimulates bone accrual during periods of growth as well as in adulthood [30]. While future randomized control trials (RCTs) are needed to assess a true causal relationship between increased exercise and improved bone health, multiple studies in children and adolescence point to a positive association [14,31,32]. In prepubertal and early puberty, prescribed weight-bearing exercise resulted in a gain in BMD at the femoral and lumbar spine (LS) regions of 6.6% and 5.5%, respectively. A smaller effect was noted in pubertal children, where the influence of sex and growth hormones had a stronger effect on bone mineral accrual [30]. At present, recommendations include engaging in higher impact weight bearing exercise at least 3 days per week [8,33] with an attention to adjusted nutritional targets to compensate for increased energy expenditures.

Exercise is associated with higher bone mineral density among the general population and moderate reduction in fracture risk [34]. A study

of CF adults found that exercise frequency positively correlated with BMD [14]. Other studies demonstrate correlation between results of the 6-minute walk test and exercise capacity with BMD among adults with CF [16,17]. Although data regarding the impact of exercise on fracture risk in CF is lacking, physical activity has multiple other health benefits and is generally advisable. Exercise for adults promotes muscle preservation in addition to improving glucose tolerance, and reducing inflammatory cytokines [35]. Individualized, unsupervised home exercise training has shown improved fitness, and improved lung function [36]. While there are no RCTs that have directly shown benefits in CFBD, data can be extrapolated from other studies [37].

Calcium

Adequate calcium intake is critical during childhood and adolescence as most of the total body calcium content resides in the skeleton [38]. In CF, there are multiple factors leading to calcium deficiency, including malabsorption, increased intestinal permeability [8], increased urinary calcium excretion as a result of a high salt diet, vitamin D deficiency, and alterations in dietary intake. While most people with CF usually meet goals for calcium intake due to a high caloric diet, ongoing yearly monitoring of calcium and urinary calcium [33] and as needed supplementation should be considered. Daily recommended calcium intake for all youth to achieve a maximum net calcium balance is 250 mg/d in infants, 500 mg/d in children 1–3 years, 800 mg/d at 4–8 years, 1200–1500 mg/day at 8–10 years, and 1200–1300 mg/day for preteens and teens [38,39]. Calcium rich foods and fortified drinks are preferred over oral supplementation due to increased bioavailability and absorption [40].

Concomitant vitamin D and calcium supplementation in adults reduced the rate of bone turnover and bone loss in PCF. This choice is particularly important for women desiring pregnancy who would like to avoid the potential risks of bisphosphonates on the fetus [41]. Most studies indicate the need for a calcium intake of 1000–1200 mg of elemental calcium by means of supplementation and diet in adults [42]. The need for calcium in pregnancy and lactation is about 10–20% higher. In general, increasing calcium intake might be beneficial in reducing intestinal hyperabsorption of dietary oxalate which is known to increase the risk of urinary oxalate stones in PCF [43].

Vitamin D

Vitamin D deficiency is common among pancreatic insufficient individuals with CF, with 15–26% of CF patients demonstrating vitamin D deficiency (25-OH vitamin D < 20 ng/mL) and 26–90% demonstrating vitamin D insufficiency (25OH vitamin D 20–30 ng/mL) [10–13]. Typical doses of vitamin D are generally insufficient for people with CF due to persistent fat malabsorption [18]. A randomized study of UV light exposure in adults with CF to bypass intestinal absorption issues and promote natural vitamin D synthesis, failed to demonstrate significant improvement in vitamin D levels, possibly due to poor adherence [44]. Vitamin D and/or calcium deficiency can cause secondary hyperparathyroidism, which increases bone resorption with adverse consequences on bone density and strength. On the other hand, over-treatment of vitamin D deficiency has the potential to suppress PTH and reduce healthy bone turnover [6]. The US CFF guidelines recommend annual vitamin D assessment and re-assessment after vitamin dose changes [11,45]. European guidelines also recommend periodic assessment of calcium, phosphorus, PTH, and urine calcium levels [6]. Urine sodium excretion is proportional to urinary calcium loss. French guidelines further recommend urine sodium and albumin assessment [10,18]. These are summarized in Table 1.

Vitamin K

Vitamin K is a necessary cofactor for clotting factor production as well as for the carboxylation of osteocalcin into its active form. In CF, deficiency of vitamin K results from losses (fat malabsorption, liver disease) and insufficient production (long term antibiotic use) [8,40].

There is limited evidence that supports vitamin K supplementation can improve bone mineralization [46,47] and as a result, there remains a lack of consensus on optimal daily vitamin K dose. Daily supplementation is still recommended, ranging from 0.3 to 1 mg per day, with preference for daily instead of weekly dosing due to rapid turnover [6,11]. Future RCTs in children and adults measuring DXA outcomes and coagulation effects are needed.

Secondary causes of low bone density

Evaluation of secondary causes of bone loss should be considered in cases of decreased bone mineralization. Celiac disease is an autoimmune disease affecting the small intestinal mucosa due to sensitivity to dietary gluten. This condition is known to cause metabolic bone disease [48]. Consideration should be given to serologic testing for celiac antibodies if there is severe bone disease, failure of vitamin D repletion with high vitamin D doses, or failure of antiresorptive therapy [49]. There is some recent literature linking CFTR dysfunction and celiac disease suggesting the concomitant incidence of CF and celiac disease up to 1.4% [50,51]. Hyperparathyroidism [52] and thyroid dysfunction [53] should also be ruled out in cases of failure of antiresorptive therapy.

Growth hormone (GH) and IGF-1 work at the growth plates of long bones to enhance linear growth, with the highest rates of growth occurring in infancy and puberty. Malnutrition and chronic inflammation lead to the suppression of the GH-IGF-1 axis with resulting reports of low IGF-1 levels in children and adults [54]. Glucocorticoid use, both oral and inhaled, have been implicated in further growth suppression by means of decreased GH secretion, decreased IGF-1, and direct action on chondrocytes at the growth plate [54]. Treatment with recombinant human growth hormone (rhGH) in children with CF is considered safe based on limited available data, with small trials reporting an improvement in height and trend towards increased BMC [55]. Anorexia, hypothalamic amenorrhea and eating disorders are not uncommon in adolescents and adults with CF and should be addressed if present [56].

Hypogonadism: Sex steroids are important for generation and maintenance of bone health. Delayed puberty is defined as absence of secondary sexual characteristics by age 13 for females and 14 for males [57]. Pubertal delay is estimated to occur in 20–60% of CF patients in older studies, while more recent studies demonstrate no difference in puberty timing between CF patients and controls [58,59]. Among the general population, pubertal delay is associated with delay to achieve peak bone mass and lower BMD at age 25 years [60,61]. Although CF-specific evidence is limited, it is reasonable to expect that pubertal induction in adolescents with CF who have delayed puberty, may positively impact bone health.

Hypogonadism impacts approximately 25% of adult males with cystic fibrosis and testosterone treatment is indicated to treat hypogonadism [62]. Testosterone improves BMD in hypogonadal men in the general population, but CF-specific data is lacking [63]. The prevalence of hypogonadism in females with CF is uncertain. A small study of 20 females with CF found similar follicle stimulating hormone and estradiol levels compared to controls; however, females with CF demonstrated low Anti-Müllerian Hormone (AMH) and reduced antral follicle counts [64]. Interestingly, treatment with exogenous estrogen does seem to improve BMD for women with CF. A study of 145 women with CF demonstrated higher BMD in women treated with exogenous estrogen up to age 21, but no benefit with treatment after age 21 [65]. Progesterone-only contraceptives are known to reduce bone formation in adolescents in the general population and should generally be avoided in women with CF unless necessary [66].

Fracture management in CFBD

Rib and vertebral fractures are the most common form of fractures seen in PCF [67]. The treatment is generally a combination of pain management, vertebroplasty or kyphoplasty in select patients [68–69]. Long bone fractures are treated by standard procedures.

Pharmacologic therapy

CFBD is a multifactorial disease. Pharmacotherapy for CFBD should be considered in conjunction with non-pharmacologic therapy. Some treatments have been well studied and are supported by evidence, however, other treatment such as calcitonin etc. that lack evidence for treatment. Consideration should be given to referring to or consulting with multidisciplinary CF centers with expertise in the treatment of CFBD. Fig. 1 summarizes various identification or mitigation efforts that need to be considered in conjunction with non-pharmacologic therapy. Table 2 summarizes pharmacotherapy for CFBD.

Antiresorptive therapy

Bisphosphonates

Bisphosphonate in children. Bisphosphonates are used in the treatment of osteoporosis and low-trauma fractures. Multiple intravenous and oral formulations are available and all work to reduce bone resorption by inhibiting osteoclast function [70]. As a result, there is a net increase in BMC and BMD, with greater effect in children due to ongoing bone modeling. Bisphosphonate therapy should be considered in children who have failed conservative therapy and meet diagnosis for osteoporosis. It may also be considered in those who may be at further risk of bone mineral deficits from lung transplantation or prolonged glucocorticoid use. In pediatric patients with chronic illness and osteoporosis, IV bisphosphonate therapy over 12 months resulted in a significant increase in LS BMD Z-score with a mild side effect panel [71]. A 2013 randomized control trial looking at oral bisphosphonate therapy in children, adolescents, and young adults with CF (age 2–30 years) showed increase in bone mineral apparent density at the LS and hip over a 2 year period [72]. The most significant increase occurred in younger children compared to young adults. Low fracture incidence and small study sample size in these trials limit evaluation of fracture risk assessment in those who have been treated.

Bisphosphonate in adults. There is extensive data supporting the use of bisphosphonates in adult CFBD. Both oral and intravenous preparations have been shown to increase BMD [70]. Bisphosphonates were particularly effective in improving BMD at the LS and hip region.

In adults, the recommendations for treatment include supra-physiologic systemic steroids with a T or Z-score of ≤ 1.5 , low trauma fracture while on steroids, fracture in the central sites or bone loss of $>4\%$ per year, awaiting transplantation or >3 month course of steroid with a Z/T score of -1.5 or less [6].

Denosumab

Denosumab is a monoclonal antibody directed against the receptor activator of nuclear factor kappa b ligand (RANKL). RANKL stimulates osteoclast action that break down bone. Denosumab is administered as a subcutaneous injection every 6 months. There is theoretical evidence that denosumab might be beneficial in CFBD [73] because murine models show that CFTR knockout mice osteoblasts have a higher RANKL: osteoprotegerin (OPG) ratio favoring bone loss. Use of denosumab might alter this ratio leading to benefit in CFBD. There are ongoing trials examining the effects of denosumab on CFBD. Denosumab should not be administered if there is preexisting hypocalcemia, and close post treatment monitoring of calcium is necessary for people with eGFR <30 ml/min. The other risks associated with denosumab include osteonecrosis of the jaw, atypical femoral fractures, and serious infections. Cessation of treatment with denosumab needs to be followed by alternative therapy to avoid rebound vertebral fractures [74].

Selective estrogen receptor modulators (SERM)

Raloxifene and Bazedoxifene are both selective estrogen receptor

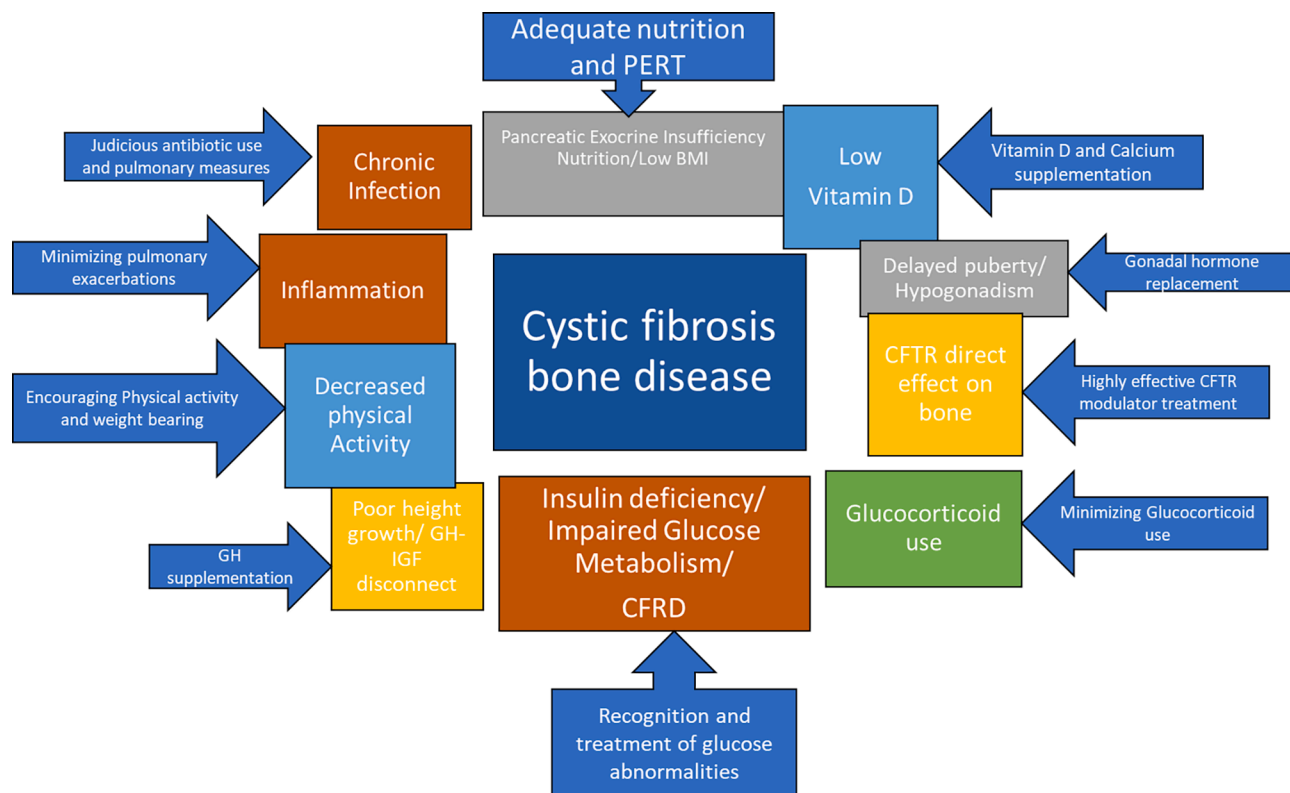


Fig. 1. Cystic Fibrosis bone disease (CFBD) is a multifactorial problem that necessitates a multipronged approach to treatment and mitigation. The figure below highlights the major factors that contribute to the pathogenesis of CFBD (shown in boxes) and the appropriate mitigation strategy (shown with arrows) that should be considered along with pharmaceutical therapy if indicated. (Abbreviations: PERT, pancreatic enzyme replacement therapy; CFTR, Cystic Fibrosis Transmembrane Conductance Regulator; GH, Growth Hormone; IGF-1, insulin-like growth factor-1; CFRD, cystic fibrosis related diabetes).

modulators (SERMs) that are approved for prevention of post-menopausal osteoporosis [75]. Raloxifene can also be used for treatment. Bazedoxifene is combined with conjugated estrogen and is approved for vasomotor symptoms of menopause. Their use in CFBD is limited to a small subset of women who are post-menopausal with intact uteri. Their use in CFBD is not widespread. The major adverse effects are an increase in venous thromboembolic events and stroke. The minor side effects include hot flashes, leg cramps and edema.

Calcitonin

Calcitonin is a nasal spray indicated for the treatment of post-menopausal osteoporosis in women >5 years post menopause when alternative treatments are not suitable. Fracture reduction efficacy has not been demonstrated. Adverse effects include hypersensitivity reactions, nasal side effects such as rhinitis or epistaxis. Metanalysis data suggest an association with cancer in long term use [76].

Anabolic therapy

Anabolic bone agents are a group of medications that promote new bone formation [77]. There are 3 agents that are currently FDA approved for treatment of osteoporosis. There are two parathyroid hormone (PTH) analogs, Teriparatide and Abaloparatide, and one sclerostin antibody, Romozosumab.

Teriparatide is a recombinant 1–34 N-terminal active fragment of PTH. It is used in people with a high risk of fractures in postmenopausal women with osteoporosis, hypogonadal osteoporosis in men, and in sustained systemic glucocorticoid therapy. Teriparatide can be used in CFBD as a daily injection. Teriparatide activates osteoblasts and promotes new bone formation. Murine data suggest that canonical Wnt-signaling, a pathway essential for osteoblast differentiation, is not activated in CFTR [73]. Thus, teriparatide may have a blunted effect on

CFBD. However, there are case reports that support the use of teriparatide but no controlled trials [78]. Abaloparatide is a synthetic analog of parathyroid hormone related peptide (PTHrp) and has a 42% homology to the PTH molecule [79]. In rodent studies, glucocorticoid use blunted the benefits of Abaloparatide with the frequency of glucocorticoid use in CF, the question of the efficacy of Abaloparatide in CFBD will require further clinical trials [79,80].

Romozosumab is a monoclonal antibody that binds sclerostin and promotes a dual action of increasing bone formation and decreasing bone resorption [81]. It is currently approved as a monthly injection at a dose of 210 mg for severe osteoporosis for 12 months. The major risk of this medication is the lack of cardiovascular safety with data indicating a risk of myocardial infarction, stroke and cardiovascular death. However, most PCF are not high risk for cardiovascular disease and may be potential candidates for therapy [82].

Management of CFBD in lung transplantation and chronic use of steroid

About 80 % of people awaiting lung transplantation have abnormal bone density with 61% having osteopenia or osteoporosis [83]. Furthermore, people with CF have lower BMD than other lung transplant candidates likely due to lack of bone-active treatments, inadequate calcium supplementation, and a high degree of vitamin D deficiency [83]. PCF undergoing transplantation show improvement in trabecular bone score and LS BMD if treatment is initiated compared to transplantation for other pulmonary causes [84]. Initiation of pharmacologic therapy should be considered prior to transplantation due to significant bone loss after transplantation due to steroid administered for immunosuppression induction or prolonged immobilization.

Table 2

Available pharmacotherapy for Cystic Fibrosis Related bone disease, route of administration, dosing, adverse effects, CF specific data and duration of therapy.

	Cystic Fibrosis Related Studies	Route of administration and dose	Salient Adverse effects	Maximum Duration of therapy
Bisphosphonates				
Alendronate	R.M. Aris et al. [95] Papaioannou et al. [42] M.L. Bianchi et al. [72]	Orally administered Children Adults ≤25 kg, 35 mg weekly 70 mg weekly >25 kg, 70 mg weekly	Oral bisphosphonates are associated with reflux, esophagitis Intravenous bisphosphonates are associated with flu like symptoms, arthralgia, and muscle aches.	10 years and reassess
Risedronate	C.S. Haworth et al. [96]	Orally administered Children Adults Not indicated 35 mg once weekly 150 mg once monthly	This is prominent in CF patients and some may require transient treatment with steroids. Rare side effects include osteonecrosis of the jaw and atypical femoral fractures	10 years and reassess
Ibandronate		Children Not indicated Adults Orally or intravenous administration 150 mg P.O. once monthly I.V. 3 mg every 3 months		10 years and reassess
Pamidronate	R.M. Aris et al. [97] C.S. Haworth et al. [98]	Children 1st lifetime dose, 0.5 mg/kg (max 30 mg) Subsequent doses, 1 mg/kg (max 60 mg) q6-12wks Adults 30-60 mg every 3 months		Unknown but can be used for longer periods due to short duration of action
Zoledronic acid	Karahasanovic A, et al. [97] Chapman, H. et al. [99]	Children I.V. 1st lifetime dose, 0.0125 mg/kg Subsequent doses, 0.025-0.05 mg/kg q6 months Post-pubertal, 5 mg every 12 months Adult I.V. 5 mg every 12 months		5 years and reassess
SERMs				
Raloxifene	Indicated for post-menopausal women None available	Oral: 60 mg once daily.	Venous thromboembolism,	
Bazedoxifene	None available	Oral: Conjugated estrogens 0.45 mg and bazedoxifene acetate 20 mg	Weight gain, edema	
Denosumab	None available	Children Subcutaneous 1 mg/kg every 6 months Adults Subcutaneous 60 mg every 6 months		Lifelong, plan for alternative treatment needs to be formulated for denosumab cessation
Anabolic Bone agents	Subcutaneous dosing in adults. Not indicated in pediatric age group			
Teriparatide	O. Siwamogsatham et al. [78]	20mcg subcutaneously daily	Short term risks include hypercalcemia, hypercalciuria, hypotension	2-year lifetime use
Abaloparatide	None available	80 mcg subcutaneously daily	Long term therapy has a theoretical risk of osteosarcoma	2-year lifetime use
Romozosumab	None available	210 mg subcutaneously once monthly	Cardiovascular effects including myocardial infarction and stroke	12 months

Potential impact of CFTR modulator

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators are a revolutionary class of medications targeting the underlying genetic defect causing CF. Ivacaftor is a small molecule potentiator, promoting the “open” position for the CFTR chloride channel. Lumacaftor, Tezacaftor, and Elexacaftor are correctors, aiding misfolded proteins to fold properly and traffic to the cell surface. Approximately 90% of people with CF can now be treated with a highly effective CFTR modulator, either with Ivacaftor or a combination of Elexacaftor/Tezacaftor/Ivacaftor (E/T/I) [85].

CFTR modulator therapies may improve bone density by targeting dysfunctional CFTR in the bone or by ameliorating other risk factors for CF bone disease [86]. CFTR is expressed in human osteoblasts and CFTR-deficient cells demonstrate increased RANK-L:OPG ratio and reduced prostaglandin E-2 (PGE-2) levels, suggesting tissue-level alteration in bone modeling pathways [87]. Importantly, application of the C18 corrector to cultured osteoblasts increased RANK-L and PGE-2, suggesting that CFTR modulator therapy may directly treat low BMD in

people with CF [88]. CFTR modulator therapy may also indirectly improve bone health by improving nutrient absorption, hypogonadism, and pulmonary disease [86]. Clinical studies of Ivacaftor in adults with CF with at least one copy of the G511D mutation suggest some impact on BMD. Sermet-Gaudelus et al. demonstrated improvement in lumbar BMD on DXA (mean -1.1 to -0.4) in seven adults treated with Ivacaftor for 1-3 years [89]. A larger study by Putman et al. evaluated 28 youth and adults with DXA and quantitative CT and found no difference in BMD measured by DXA after Ivacaftor. The adult cohort did demonstrate increased cortical volume, area, and porosity of the radius and tibia on quantitative CT, but not the youth cohort [90]. Observational studies of patients taking E/T/I are ongoing and may shed further light on the impact of highly effective modulator therapies on bone health [91].

Future directions

CFBD is becoming an area of increasing focus in clinical care and research. Highly effective modulators bring a new ray of hope but their

effects on mitigating CFBD are yet to be fully explored. Anabolic bone agents and Denosumab are agents that need to be better studied in CFBD. Preventative measures instituted early during childhood and adolescence will allow PCF to achieve a normal peak bone mass thus allowing a more normal trajectory for bone accrual and maintenance.

Declaration of Competing Interest

Conflict of Interest or Competing Interest: My coauthors and I do not have any conflict of interest other than the fact that 3 of us were funded by the Cystic Fibrosis Foundation.

A Declaration of Interest: there is no financial/personal interest or belief that could affect our objectivity, and there is no potential competing interests.

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