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## Research Article

# Inflammation and CFTR-Related Bone Remodeling in Patients in Cystic Fibrosis

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**Abstract**

The hallmark pathological features of bone disease in patients with cystic fibrosis (CF) include bone micro architectural changes and chronic inflammation which are associated with an irreversible loss in bone strength and density that tracks from childhood to adulthood. Given the equal importance of inflammation and CFTR-related remodeling in bone pathogenesis, there is a significant disparity in studies undertaken to investigate the contribution of each. Up to now, the majority focus on the role of systemic and lung inflammation, and although novel therapeutics such as improved pulmonary function and inflammation have arisen, it is apparent that targeting inflammation alone has not allowed amelioration of cystic fibrosis-related bone disease (CFBD). Therefore, unless bone remodeling is addressed for future therapeutic strategies, it is unlikely that we will progress towards a cure for bone disease. Having acknowledged these limitations, the focus of this review is to highlight the gaps in our current knowledge about the mechanisms underlying CFTR-related bone remodeling, the relationships between inflammation, bone remodeling and clinical phenotypes, and the importance of utilizing innovative pre-clinical models to uncover effective, disease-modifying therapeutic strategies.

**INTRODUCTION**

The hallmark pathological features of CFBD include bone micro architectural changes (bone remodeling) characterized by reduced trabecular and cortical volumetric bone mineral density (vBMD), increased fracture rates, in particularly of ribs and vertebrae and chronic lung inflammation which are associated with an irreversible loss in bone density that tracks from childhood to adulthood [1,2]. Reduced vBMD associated with CF disease are becoming more important as the life expectancy of patients continues to improve. Vertebral compressions and rib fractures lead to excessive kyphosis in CF which compromises the thoracic skeletal architecture, with the consequence of an accelerated decline in lung function, ineffective cough and airway clearance, limitations in chest physiotherapy, and potentially contribute to the development of pulmonary exacerbations [3-5]. CFBD is a common and serious complication, and has been correlated with severity of lung disease [6,7]. Whether CFBD is more likely to occur in patients with worse pulmonary disease and exacerbations remains uncertain, as does whether or not CFBD contributes to worsening of respiratory function.

Less than 5% of children with CF have CFBD, but this proportion increases to 20% in adolescence, with 55-65% of patients

older than 45 years affected [8]. The bone density changes are apparent in CF even in mild disease; however, the degree of bone deficit often worsens with increasing lung disease severity [9]. In addition, the onset of the bone pathological changes can occur early in the course of CF [10,11].

Given the importance of both inflammation and remodeling in bone pathogenesis, there is a significant disparity in the number of studies that have investigated the contribution of each. Most studies, both clinical and mechanistic, focus on lung and systemic inflammatory parameters alone. Several factors contribute to this bias and assessments of bone remodeling cannot be made noninvasively at present since the gold standard remains tissue analysis which requires bone biopsy. Although imaging with HR-pQCT scans can be used, the data is variable and currently CT scans are not a reliable surrogate for tissue assessments. Even when pre-clinical studies are considered, few models investigate molecular mechanisms of bone remodeling, perhaps because remodeling assessments require long-term models in CFBD [12-15].

Having acknowledged these limitations, the main focus of this review will be to highlight the gaps in our current knowledge relating to CFTR-related bone remodeling in CF, and to identify

future approaches that will allow better understanding of the relationships between remodeling and function, potential relationships with clinical phenotypes, and the importance of utilizing innovative pre-clinical models to discover novel therapies targeted to bone micro architectural changes. Overall, therapies to date that have targeted inflammation alone have not resulted in CF bone modification. A useful strategy may therefore be to give bone formation and remodeling processes equal importance for future therapeutics in order to progress towards disease-modifying therapies in CFBD.

## RECOGNISING BONE REMODELING PHENOTYPES IN ADDITION TO CLINICAL AND INFLAMMATORY PHENOTYPES IN CFBD

The CFBD is likely directly related to the CFTR defect itself [15-18], but is worsened by secondary factors such as pulmonary inflammation/infection, pancreatic insufficiency, diabetes mellitus, use of exogenous glucocorticoids and physical inactivity [3-5,16,17,19-22]. The extent to which the shorter stature observed in individuals with CF is a direct manifestation of altered CFTR function rather than a manifestation of nutritional deficiencies and inflammation, is still unknown [23]. Interestingly, a recent clinical study has shown that children with CF had thicker and denser cortical bone compared to age- and sex-matched controls with greater differences in older children, but this not compensate for the smaller bone size which compromised the bone strength in children with CF [24]. In a relatively large group of children, adolescents and young adults with mild to moderate lung disease, multiple measures of tibial cortical geometry, density, and strength were reduced compared to a healthy cohort [10]. In addition, in CF males, worsening pulmonary function was associated with greater deficits that was not explained by increasing age or compromised nutritional status. These data suggested that bone remodeling was also related to lung function. Other clinical data have also shown a strong association between increased bone resorption and systemic inflammation induced by chronic lung infection and acute bronchial exacerbations, suggesting that aggressive treatment of lung infection may prevent the progression of CFBD [7,9,25].

It is certain that future therapeutic strategies for CFBD will incorporate phenotype-specific approaches as we head towards a personalized approach to treating bone disease, but to allow this to be successful, it is essential that we include both CFTR-related bone remodeling and inflammatory markers in analyses. The identification of alterations in bone geometry and strength in CF are important given that bone size is predominantly established during childhood and is a key determinant of bone mass and ultimately fracture risk. A recent study showed a 9-fold higher fracture rate in young German CF adults compared to the age-matched reference population [26]. Bone quality and fragility, the subject of growing interest and research efforts, comprises a number of parameters such as the micro-architecture of trabecular bone, bone geometry, prevalence of micro cracks, and importantly, bone matrix material properties including elastic modulus and fracture toughness [27].

We need to accept that CFBD incorporates a clinical phenotype, inflammatory phenotype and bone remodeling phenotype, and

the interactions and contributions from each facet will determine the most effective therapy in the individual patient (Figure 1).

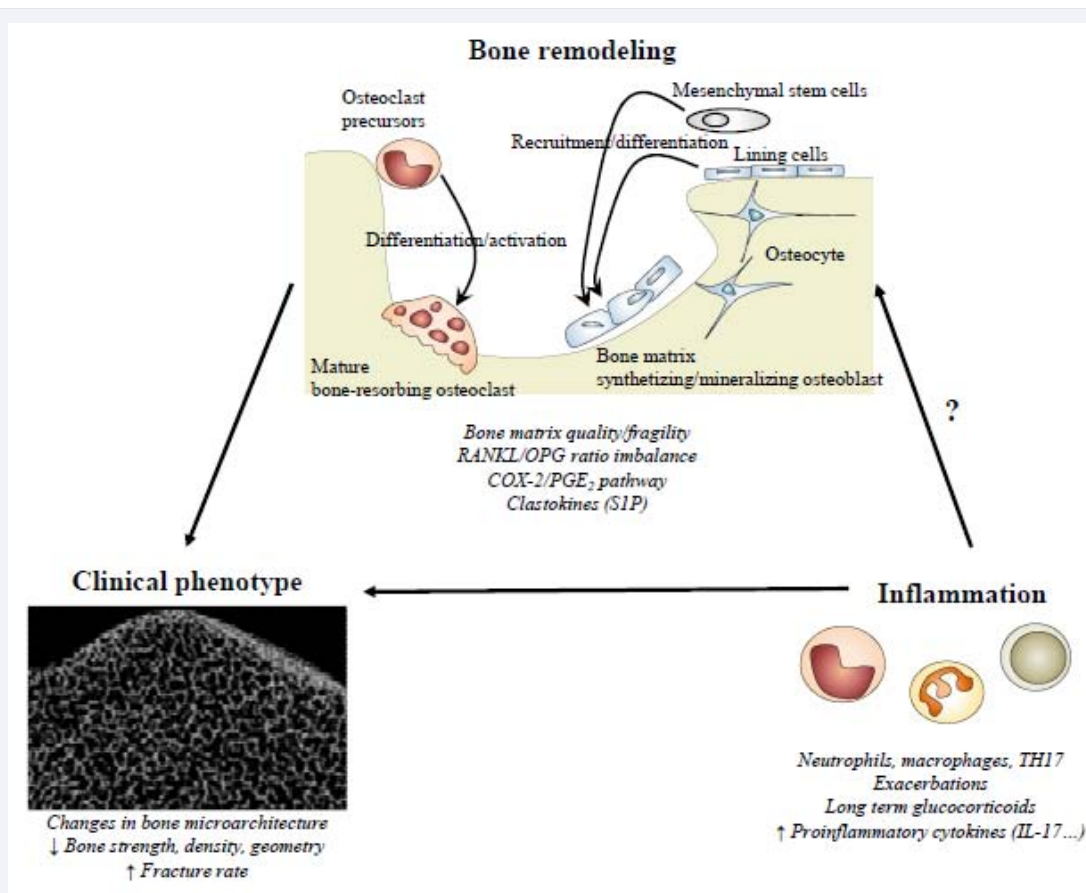
An example of the use of bone micro architectural changes to identify phenotypes was undertaken using HR-pQCT scans in both children and adults with CF. This allowed distinction of patients into phenotypes according to their bone geometry and strength and revealed one specific phenotype had evidence of bone changes with lower bone strength that might be compatible with fracture trabecular-rich bones, such as ribs and vertebrae [10,28]. An interesting avenue for future investigation would be to define the degree of each bone microstructural change in a patient to see whether there is concordance; so does a deficit in trabecular bone strength associate or not with an inflammatory phenotype in the same patient?

During the past 15-20 years, improvements in the control of lung infections, therapies towards a better inflammatory control and an early identification of non-pulmonary complications have contributed to ameliorate the clinical care of young patients with CF [29-31]. However, despite significant improvements in clinical care and life expectancy, recent data from Putman et al. demonstrated that average BMD in spine and distal radius in young adults with CF is always reduced and has not changed over a 15-years period when compared to that previously evaluated in an age-, race-, and gender-matched cohort of young adults with CF in the 1995-1999 period [32]. Therefore, despite improved respiratory function and lower prevalence of vitamin D deficiency in these CF patients, other factors such as inflammation, hyperglycemia, reduced physical activity and the CFTR dysfunction itself, may be playing an important role in the pathogenesis of CFBD.

## RELATIONSHIPS BETWEEN INFLAMMATION AND BONE REMODELING: DO ANY EXIST?

Dysregulated inflammation leads to increased bone resorption and suppressed bone formation. Crosstalk among inflammatory cells and cells related to bone healing is essential to the formation, repair and remodeling of bone [33]. Until recently, it was thought that in CF patients with bone disease, chronic inflammation may drive bone remodeling, but increasingly this proposition has been disputed. Studies in infants and from animal models have been the strongest to refute the notion that inflammation causes structural bone changes. In children with CF as early as 6 years of age lower bone mineral density gains were observed with mild disease and normal nutritional status, suggesting that CFBD may in part, be due to a primary defect in bone metabolism [11]. Ten years ago, CFTR protein was discovered in human normal bone cells [34] and was reported to be expressed early during development [35], so in utero alterations are plausible. Indeed, studies in pigs, rats and mice with CF shortly after birth reveal abnormalities in bone development [13,15,36] and tracheal cartilage with early airflow obstruction [37-40], suggesting a critical role of CFTR dysfunction independent of deficient ion transport/airway surface liquid depletion.

A limitation of human studies, especially paediatric studies, is the relative difficulty in obtaining invasive biopsies to assess longitudinal changes in pathology over time. Access to bone tissue in newborns is extremely limited, and the invasive *in vivo*



**Figure 1** Interaction between bone remodelling, clinical and inflammatory phenotypes characterizes cystic fibrosis bone disease. Remodeling and inflammation may directly influence clinical manifestation of bone disease. Interactions and contributions from each facet will determine the most effective therapy in the individual patient. Receptor activator of nuclear factor  $\kappa$  B ligand=RANKL. Osteoprotegerin=OPG. Cyclooxygenase-2=COX-2. Prostaglandin E<sub>2</sub>=PGE<sub>2</sub>. Sphingosine-1-phosphate 1=S1P. Interleukin-17=IL-17.

and *ex vivo* experimental interventions required elucidating the pathogenesis most often cannot be performed in humans. However, evidence that pathophysiological abnormalities of bone cells had become apparent from rib explants harvested in adolescents and young adults with CF during lung transplantation [17]. In this study, we confirmed the genetic contribution by which F508del mutation in *Cftr* resulted in severely compromised maturation of osteoblasts (cells that form bone) associated with an elevated RANKL-to-OPG mRNA ratio, reduced COX-2 mRNA expression and a drastic reduction in prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production, the latter being identified as a key regulator of skeletal growth and efficient bone fracture healing [41,42].

### TARGETING BONE REMODELING TO ACHIEVE CFBD MODIFICATION: POTENTIAL CELLS AND MEDIATORS OF INTEREST

Bone-mass regulation depends on the dynamic balance between bone formation and bone resorption, which are driven by both the activity of osteoblasts and osteoclasts (cells that resorb bone). Major pathogenic mechanisms mediating the development of CFBD may result from a combination of episodes of low bone turnover and formation rate during periods of disease stability, and an increased bone turnover and resorption during inflammation and infective exacerbations. Studies have

reported that CF newborns are shorter and have a lower body weight than non-CF newborns [43]. Others have suggested that reduced levels of serum insulin-like growth factor I (IGF-1) might be responsible, at least in part, for the growth defect reported in patients with CF [44] which was also observed in both *Cftr*<sup>-/-</sup> mouse and newborn *Cftr*<sup>-/F508</sup> pig models [36]. Reinforcing these findings, we also reported lower levels of serum IGF-1 in young and adult F508del mice which might contribute to the reduced bone formation [13].

A low bone turnover with reduced bone formation and no evidence for increased bone resorption has been reported in young adults with CF [45-47] which might be related to sex steroid imbalance [5]. Regarding sex hormones, 17 $\beta$ -estradiol deficiency is known to affect bone metabolism in both humans and mouse models [48]. Interestingly, both the CF mouse models with the 489X and F508del mutation in *Cftr* gene display higher follicular stimulating hormone levels, suggesting a possible decrease in 17 $\beta$ -estradiol production [49]. Low serum 17 $\beta$ -estradiol levels were found in patients with CF with prevalent vertebral fractures in both genders [50].

### Osteoblasts

Bone formation is a complex process [51] which starts with the recruitment of mesenchymal skeletal (stromal) cells

(MSCs) located within the bone marrow stroma, or of pericytes in sinusoids in the bone marrow. The commitment and differentiation of these cells to osteoblasts is dependent on the expression of the osteoblast transcriptional factors Runx2 and Osterix, followed by the expression of alkaline phosphatase, type 1 collagen and non-collagenous proteins, leading to matrix deposition and mineralization [52,53]. At the end of the bone formation period, some osteoblasts die by apoptosis or become flattened lining cells, whereas others are embedded in the bone matrix as osteocytes which control bone remodeling [54]. The activity of bone formation at the tissue level is dependent on both the number and function of differentiated osteoblasts. Both the number of functional osteoblasts and the activity of each osteoblast are controlled by transcriptional and epigenetic mechanisms and are regulated by hormonal and local regulatory proteins [55], mechanical strain, cell-cell and cell-matrix interactions [56]. Thus, any cellular and molecular abnormalities in the recruitment, function or life-span of osteoblasts induced by genetic diseases may impact bone formation at the tissue level.

Patients with CF often display low bone mass with a significant clinical increase in bone fragility [2,5,8]. The underlying mechanisms remain unknown but may involve alterations in bone metabolism. CFTR was reported to be expressed in human osteoclasts and osteoblasts, but its role in bone cells is elusive [34,57]. In a CF mouse model, global *Cftr* knock-down causes bone loss and altered bone microarchitecture associated with decreased bone formation and increased bone resorption [58], but cell mechanisms that cause these effects are unknown. More relevant to the human disease, we have showed that prevalent F508del mutation in *Cftr* was found to cause decreased bone formation in mice, as a consequence of reduced osteoblast activity, independently of other etiological factors such as inflammation and nutritional defects [59]. Furthermore, we found that oral administration of a CFTR corrector led to improved bone formation rate, bone mass and microarchitecture in F508del mice, suggesting a potential therapy strategy to reduce bone loss in CF patients [13]. More recently, we reported an over-expression of receptor activator of NF- $\kappa$ B ligand (RANKL) and high membranous RANKL localization related to defective CFTR channel chloride activity in human osteoblasts bearing the F508del mutation in *Cftr*, and therefore may worsen bone resorption leading to bone loss in patients with CF [16].

## Osteoclasts

Coupling between bone formation and bone resorption refers to the process within basic multicellular units in which resorption by osteoclasts is met by the generation of osteoblasts from precursors, and their bone-forming activity, which needs to be sufficient to replace the bone lost [55]. Osteoclasts, bone-resorbing multinucleated cells, are differentiated from the monocyte-macrophage lineage under the tight regulation of osteoblasts. Osteoblasts express two cytokines essential for osteoclast differentiation: RANKL and macrophage colony-stimulating factor (M-CSF). M-CSF is constitutively expressed by osteoblasts, whereas the expression of RANKL is up-regulated by osteogenic factors [60,61].

The separate origins of the osteoblast from mesenchymal and osteoclast from hemopoietic precursors was not accepted

until the late 1970s, which was also the first time that bone cells could be cultured and studied *in vitro*. When it was suggested that the osteoblast lineage might control osteoclast formation and activation, this was greeted with skepticism. This theory was, and still is, often misinterpreted as suggesting that osteoclastogenesis is stimulated by the same cells that produce the bone matrix, but this was not the case [62]. It nevertheless led to the discovery of the physiological control of osteoclast formation and activity by osteoblast lineage-derived RANKL, its signaling through its receptor, RANK, on hemopoietic cells, and inhibition of this by the decoy receptor, osteoprotegerin (OPG), derived from osteoblasts [60]. The importance of this control mechanism in bone remodeling is well established. During the chronic inflammatory process observed in some patients with CF, the balance between formation and bone resorption could be skewed toward osteoclast-mediated bone resorption [7,9]. An alternative theory speculates that disruption of osteoblastic activity, in the face of normal osteoclastic activity leads to a failure to lay down enough bone. There is evidence in F508del mice that osteoblasts are dysfunctional [12,59]. Further support of this theory is the normal level of markers of bone resorption in patients with CF [63]. However, the clinical use of biochemical bone markers remains controversial because values in individual patients are variable and difficult to interpret, and because bone turnover markers have not been found effective in following skeletal manifestations of CF [8,64]. Indeed, serum resorption markers are not consistently elevated, serum osteoclast precursors seem to be increased only in the context of infective exacerbations [7] and potent inhibitors of bone resorption, as oral bisphosphonates have modest effects in amelioration of bone mass in CF [65].

Of all the pathological parameters that might affect the natural history of CFBD development from childhood to adulthood, current data suggests the function of bone cells, including osteoblasts and osteoclasts, may be the most important. However, nothing is known about bone cell function in infants or adolescents with CF. Studies involving children at early age might reveal the origins of CFBD and thereby change the clinical practice. Additional reasons to elucidate the origins of the CFBD are the implantation of universal screening to detect CF in newborns and potential novel therapeutic avenues that target directly CFTR [66,67].

In box 1, we have outlined novel ideas and hypotheses for strategies optimizing bone health in CF patients.

### Box 1 Strategies for optimizing bone health in cystic fibrosis

- Not all patients with cystic fibrosis have similar changes in each parameter of bone remodeling. Remodeling phenotypes should therefore be delineated, i.e. the contribution of each bone micro architectural change (trabecular and cortical volumetric bone mineral density (vBMD) in vertebrae and distal tibia, bone geometry and strength evaluated by cross section areas and section modulus, and individual trabecular segmentation (ITS)-based morphological analysis) using high-resolution peripheral quantitative computed tomography (HR-pQCT) scans in an individual patient needs to be assessed. Subsequently, together with the clinical phenotype and inflammatory phenotype, the most appropriate

personalized therapy can be identified for the individual.

- Getting bone microarchitecture data in youngest population using radiological tools will be challenging but highly relevant.
- The bone remodeling phenotype of no inflamed children, adolescents and young adults needs to be investigated early to allow discovery of effective molecular therapies.
- Clinical trials should incorporate HR-pQCT scans of radius, tibial and vertebral bone as outcome measures in both children and adults.

## THE NEED OF CLINICALLY RELEVANT MODELS TO IDENTIFY THERAPEUTIC TARGETS FOR BONE REMODELING

Studies in pigs, rats and mice with CF shortly after birth reveal abnormalities in bone development [13,15,36] and tracheal cartilage with early airflow obstruction [37-40]. In order to identify novel therapeutics to target bone remodeling, several factors need to be considered. First, pre-clinical models that are translatable and truly reflect patient phenotypes must be used. An example is the recent development of a mouse model in which features of bone disease with osteoblast dysfunctions in F508del-Cftr mice [13,59]. Not only can this be used to study factors underlying bone disease remission, but also to understand disease persistence. Genetic studies have showed that the deletion of intermediate filament protein keratin 8 (Krt8(-/-)) in F508del-Cftr mice increased the levels of circulating markers of bone formation, corrected the expression of osteoblast phenotypic genes, promoted trabecular bone formation and improved bone mass and microarchitecture [12]. Mechanistically, Krt8 deletion in F508del-Cftr mice corrected overactive NF-kappaB signaling and decreased Wnt-beta-catenin signaling induced by the F508del-Cftr mutation in osteoblasts. *In vivo*, short-term treatment with compound 407, a CFTR corrector, ameliorated the altered Wnt-beta-catenin signaling and bone formation in F508del-Cftr mice. Collectively, these results showed that genetic or pharmacologic targeting of Krt8 leads to correction of osteoblast dysfunctions, altered bone formation and osteopenia in F508del-Cftr mice, providing a therapeutic strategy targeting the Krt8-F508del-CFTR interaction to correct the abnormal bone formation and bone loss in CF.

There are many sources of activities that contribute to coupling at remodeling sites, including growth factors released from the matrix, soluble and membrane products of osteoclasts and their precursors, signals from osteocytes and from immune cells and signaling taking place within the osteoblast lineage. As bone remodeling occurs at many sites asynchronously throughout the skeleton, locally generated activities comprise very important control mechanisms [55,56]. It has become increasingly clear that CFTR plays a role in immune cells, and that the dysfunction of the CFTR affects immune cell responses [68,69]. T-helper 17 lymphocytes (Th17) has been implicated in various immune-mediated diseases [70]. In patients with CF, there is some evidence that Th17, neutrophils and natural killer T cells, all producing the pro-inflammatory cytokine IL-17A perpetuate the excessive inflammatory process in lung tissue [71,72]. Moreover, IL-17 has been implicated in the pathogenesis

of bone diseases such as rheumatoid arthritis, osteoarthritis [73,74] and post-menopausal osteoporosis through an alteration in the RANKL-to-OPG system in osteoblasts [75]. However, in patients with CF, data supporting a bone deficit by elevated IL-17 levels is currently lacking.

Increasing evidence highlights the local actions of lipids in bone physiology [76]. CFTR dysfunction causes abnormalities in sphingolipid metabolism [77,78], and a decreased level of sphingosine-1-phosphate (S1P) was observed in CF lung disease [79,80], a ubiquitous signalling mediator that directs a diverse array of biological processes in vertebral development, physiology and pathology [81-83]. S1P is a well-known bioactive lipid mediator, playing important roles in many tissue repair processes, including bone regeneration and osseous tissue growth *in vivo* [84]. CFTR has been shown to be involved in the cellular uptake of S1P in a mouse model of heart failure [85,86], and new data highlight S1P as a potentially important player in the activity of osteoblasts by increasing the RUNX-2 expression and PGE2 production, reducing the RANKL/OPG ratio expression, and ameliorating bone formation [87-89]. The egress of osteoclast precursors from the vasculature is stimulated by chemotactic factors including S1P [90] via a process that is stimulated by 1,25-dihydroxyvitamin-D3 [91]. There are nevertheless paradoxical actions of 1,25-dihydroxyvitamin-D3 on bone that continue to pose questions, [92] and local events related to remodeling are providing clues. S1P is a lysophospholipid mediator in blood that facilitates the migration of osteoclast precursors from bone to blood through actions on one of its receptors, S1PR1 [90]. A second receptor, S1PR2, mediates the reverse effect of chemo repulsion, resulting in a change in direction of osteoclast precursors from blood to bone. Active vitamin D has been shown to inhibit production of the chemo repulsive S1PR2, thereby inhibiting osteoclast generation and bone resorption [91]. These actions related to S1P are all the more intriguing because it is one of the several osteoclast-derived factors currently postulated as contributing to the coupling of bone formation to resorption.

Although the role of S1P in the process of bone remodeling is suggestive, it needs to be explored in CFBD development further and put into the context of other actions of S1P, which has been invoked as a signaling mechanism in the actions of a number of cytokines, growth factors and hormones [93]. Among these an interaction with vitamin D has been reported, in that 1,25-dihydroxyvitamin-D3 inhibition of apoptosis in HL60 cells [94] and keratinocytes [95] has been found to be mediated by S1P; perhaps a similar antiapoptotic role for S1P exists in osteoblasts. It is thus tempting to speculate that CFTR might be also involved in the S1P signalling in bone cells, which would explained some of the aberrant activities observed in CFTR-deficient osteoblasts. Future studies also need to analyze the S1P role in CFBD development and more particularly its involvement in the regulation of osteoblasts-osteoclast coupling factors modulating bone formation.

## EMERGING NOVEL THERAPIES FOR CFBD

Early recognition and treatment are the most effective strategies for sustaining bone health to help maintain quality of life in young patients with CF. Strategies for optimizing

bone health and providing preventive care are necessary from childhood to adolescence to minimize CFBD in adult patients. Clinical trial data are especially limited in the CF pediatric age group. Clinical trials are underway with the goal of finding new potential treatments that might prevent the development of CFBD including anti-resorptive agents such as oral bisphosphonates [96] and anabolic agents such as human recombinant growth hormones (hrGH) and parathyroid hormone (PTH) in CF adults [65]. One report provides convincing evidence that the oral bisphosphonate alendronate is effective, well tolerated and safe for young patients with CF [96]. However, the use of bisphosphonates in children with CF is controversial because of potential long-term safety and tolerability concerns including over suppression of bone formation. Intravenous administration of bisphosphonates in CF adults has been also associated with bone pain and flu-like symptoms, which could adversely impact the pulmonary status of patients with CF [5]. Denosumab, an available antiresorptive medication that targets RANKL in postmenopausal women and osteolytic diseases such as rheumatoid arthritis [97,98] might be particularly effective in CF patients to counteract elevated membranous RANKL observed in F508del-Cftr osteoblasts. Hence, targeting upstream factors responsible for the membranous localization of RANKL also could lead to a specific therapeutic approach in CFBD.

New treatments that target the CFTR mutations through the use of potentiators and correctors of chloride channels are being developed in the care of cystic fibrosis-related lung pathology [99]. The CFTR corrector Ivacaftor (VX-770) improves respiratory function and nutritional status in patients with CF carrying the p.Gly551Asp mutation [100]. Recently, we showed that the rescue of mutated CFTR protein by invocator also improves bone remodeling in patients and support the link between CFTR and bone cell physiology [101]. A combined therapy with a CFTR corrector and potentiator (VX-809 and VX-770) named Orkambi has been tried in patients with CF carrying the F508del mutation, on pulmonary end-points (FEV1), with promising data based on hypothesized synergic effects of two combined molecules [67]. We reported that the corrector C18, a dual F508del-Cftr potentiator and corrector, significantly decreased the RANKL production by F508del-Cftr osteoblasts, even under inflammatory condition, suggesting a strong potential for therapeutic trials with CFTR correctors and potentiators in CFBD [16,18].

## CONCLUSION

Inflammation and CFTR-related bone remodeling are critical components of the pathophysiology of CFBD. Although both contribute significantly to disease pathogenesis, to date mechanistic studies and drug discovery have focused on inflammatory targets. Although novel therapeutics such as improved pulmonary function and inflammation has arisen, it is apparent that targeting inflammation alone has not allowed amelioration of bone disease. Therefore, we suggest that to make a step-change in CFBD therapy, the focus of research now needs to be on investigating mechanisms underlying the coupling of the activities of bone formation and resorption, and the approaches used will have to reflect disease heterogeneity, and include complex experimental approaches with *in vitro*, *in vivo*, animal and human studies. CFBD is a common and serious complication

in the aging CF population, and can significantly affect the health, well-being, and longevity of these patients. Getting bone microarchitecture data in youngest population using radiological tools will be challenging but highly relevant. The longer life expectancy and better diagnostic methods have made CFBD one the prevalent co-morbidity of CF, beside typical lung pathology and diabetes.

## AUTHOR CONTRIBUTIONS

All authors contributed to the drafting and revising of this review. All authors read and approved the final submitted manuscript.

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