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Review

Bone health and disease in cystic fibrosis

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SUMMARY

Low bone mineral density is common in children and adults with CF. It has a multifactorial aetiology that includes direct effects of CFTR dysfunction on bone cell activity, as well as the secondary effects of CFTR dysfunction including pancreatic insufficiency (leading to malnutrition/malabsorption of fat soluble vitamins) and pulmonary infection (leading to systemic inflammation and increased bone resorption). Strategies to improve bone health in CF include optimising general CF nutritional and pulmonary care and the judicious use of bisphosphonates in selected patients. CFTR correctors/potentiators may have positive impact on bone metabolism in people with CF.

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INTRODUCTION

Over the last three decades we have witnessed a remarkable transformation in our understanding of the pathophysiology of cystic fibrosis (CF) and this has led to improved management and survival. As a consequence of this success, new complications of the disease have been identified, one of which is low bone mineral density (BMD) [1]. Osteoporosis literally means "porous bone" and is characterized by low bone mass, a deterioration of bone tissue with disruption of bone architecture, compromised bone strength and an increased risk of fracture. While bone mass is reduced in patients with osteoporosis, there is no change in the ratio of mineralised and non-mineralised bone, in contrast to osteomalacia where there is an increase in the proportion of non-mineralised bone.

EPIDEMIOLOGY

In 2004, Buntain and colleagues published a cross-sectional prevalence study reporting BMD in Australian children, adolescents and adults with CF (n = 153) and healthy local controls (n = 149) [2]. This detailed study found that BMD was normal in well-nourished prepubertal children with CF, but deficits in BMD were apparent in adolescents and more established in adults. While BMD is usually normal in children with CF with normal nutritional and lung function parameters, low BMD has been observed in children with mild lung disease and no nutritional deficit [3]. This reflects the multifactorial nature of the disease process encompassing CF-related bone disease and also suggests the possibility of abnormal bone metabolism in patients with CF, independent of nutritional status.

With regards to adult patients with CF, prevalence data from a number of cross-sectional studies are more consistent. In a systematic review involving 1055 patients with a median age of 28 years, the pooled prevalence of osteoporosis was 23.5% (95% CI, 16.6–31.0) [4]. Of note, the study adopted the World Health Organization definition of osteoporosis (T-score ≤ -2.5), which is inappropriate in young CF patients who have not yet attained peak bone mass [5]. Cross-sectional studies performed in the UK have reported low BMD affecting between 13-34% of adults [6–8].

Longitudinal studies in CF have demonstrated suboptimal accrual of bone mass in children and adolescents [9], and premature loss in adolescents and young adults [10]. In a prospective study involving CF patients $\leq$24 years of age (n = 55) with a mean (SD) age of 19.5 (2.6) years in whom an annual increase in BMD would normally be expected, BMD increased by a mean of 2.9% (1.6 to 4.2) per year in the distal forearm, but decreased by 2.5% (−3.8 to −1.2) per year in the femoral neck and by 2.2% (−3.3 to −1.0) per year in the total hip [10]. In patients $\geq$25 years of age (n = 59) with a mean (SD) age of 30.3 (5.4) years in whom no annual change in BMD would normally be expected, BMD decreased by 1.9% (−2.9 to −0.8) per year in the femoral neck, by 1.5% (−2.4 to −0.6) per year in the total hip, and by 0.8% (−1.5 to −0.1) per year in the distal forearm (Fig. 1.) [10].

Fractures

The major consequence of low BMD is fragility fracture. A meta-analysis by Paccou and colleagues reported a pooled prevalence of vertebral and non-vertebral fractures of 14% (95%

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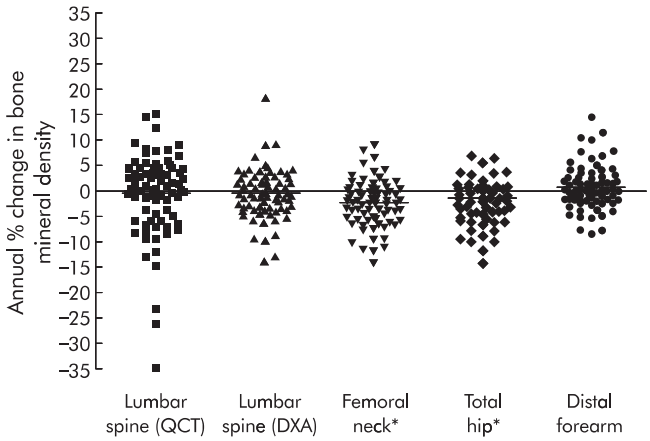

Fig. 1. Annual percentage change in bone mineral density in the lumbar spine, femoral neck, total hip, and distal forearm in 114 adult patients with cystic fibrosis (mean change indicated by horizontal line); *p<0.001 [10].

CI, 7.8–21.7) and 19.7% (95% CI, 6.0–38.8), respectively [4]. The major morbidity from rib and vertebral fractures in CF results from cough related pain, ineffective sputum clearance and pulmonary exacerbation. A further major consequence of low trauma fracture is that it is a relative contraindication to lung transplantation in some centres.

BONE HISTOMORPHOMETRY

Bone histomorphometry studies suggest that osteoporosis is the major pathology in CF related bone disease, although osteomalacia is seen [11,12]. A recent study of bone specimens obtained from 17 patients with CF at the time of lung transplantation and 21 donor controls found reduced osteoid parameters in the CF group suggesting decreased osteoblast activity, regardless of glucocorticoid and/or bisphosphonate use [13].

Aetiology of cystic fibrosis related bone disease:

The cause of CF related low BMD disease is multifactorial. Contributing factors include vitamin D and vitamin K insufficiency, calcium malabsorption, malnutrition, low physical activity, glucocorticoid use, delayed puberty and hypogonadism [1,5].

Another important factor in the aetiology of CF related bone disease is pulmonary infection and the associated systemic inflammatory response. Shead and colleagues observed an increase in the production of potential osteoclast precursors [14] and an increase in osteoclast number and resorptive activity during infective exacerbations, which subsequently reduced with intravenous antibiotics [15]. There was a positive correlation between the number of osteoclasts and the serum concentration of tumour necrosis factor alpha (TNF-α) and a negative correlation with osteoprotegerin (OPG). Collectively these data suggest that pulmonary infection and systemic inflammation stimulate bone resorption in CF (Fig. 2.).

An increasing body of evidence suggests that cystic fibrosis transmembrane regulator (CFTR) dysfunction affects bone metabolism. For example, a recent study showed evidence of CFTR-dependent chloride conductance in primary normal osteoblasts, which was reduced in F508del osteoblasts [16]. Defective maturation of F508del osteoblasts was found in bone explants from four adolescents with CF at the time of lung transplantation. Furthermore, there was a significant increase in receptor activator of Nf-κB ligand (RANKL):OPG expression ratio in F508 del osteoblasts and the basal production of OPG and prostaglandin E_2 (PGE_2) by

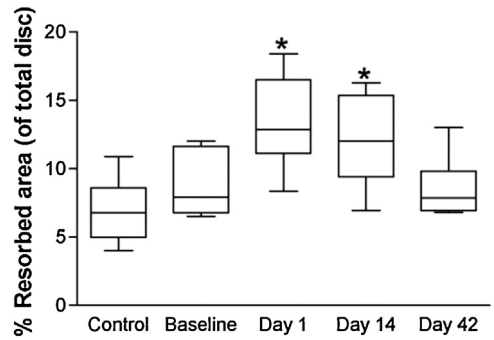

Fig. 2. Variations in osteoclast activity during intravenous antibiotic treatment for pulmonary exacerbations in people with cystic fibrosis. *p<0.05 [15].

F508del osteoblasts was reduced. These results suggest that poor bone accrual in young patients with the F508del mutation may be caused by a reduction in osteoblastic bone formation due to diminished OPG and COX-2/PGE2 expression and production. Such findings raise the possibility that small molecules directed at correcting CFTR dysfunction may have positive impact on bone metabolism.

BONE MINERAL DENSITY ASSESSMENT

The gold standard for assessment of BMD in patients with CF is dual energy X-ray absorptiometry (DXA) [1,5]. DXA scans are widely available, the data are reproducible and the scans involve a very low radiation dose. According to international guidance, BMD should be measured at the total body and the lumbar spine for patients younger than 20 years of age, and at the lumbar spine and proximal hip in patients of 20 years of age or older [5]. BMD values should be expressed as Z-scores in premenopausal women and men under 50 years of age, and as T-scores in postmenopausal women and in men 50 years of age or older [5]. With DXA, BMD deficits may be overestimated in patients with short stature, because they display a more severe decrease in bone area than in bone mineral content [5]. In children, routine bone density scans should be first performed around the age of eight to ten years. Thereafter in children and adults < 50 years of age, DXA should be repeated every five years if the BMD Z-score is > −1; every two years if the Z-score is between −1 and −2; every year if the Z-score is < −2 [5].

OPTIMIZING BONE HEALTH

Because of the multifactorial aetiology of CF related low BMD, management can be complex and requires a meticulous approach.

VITAMIN D

Vitamin D has an essential role in calcium homeostasis and bone metabolism. Vitamin D levels are often suboptimal in people with CF, primarily due to the malabsorption of fat soluble vitamins. For example, Wolfenden and colleagues reported that 76% of 185 adults with CF had a 25-hydroxy vitamin D level <30 ng/ml despite routine supplementation [17]. The optimal vitamin D level is unknown, but current European guidance suggests maintaining a minimum level of 20 ng/ml and US guidance suggests maintain a level of >30 ng/ml, noting that this is the level at which PTH secretion is suppressed [5] [1]. In pancreatic insufficient patients with CF, European guidance recommends a starting dose of 1000–2000 IU/day of vitamin D_2 or D_3 in infants, and a starting dose of 1000 to 5000 IU/day of vitamin D_2 or D_3 in children above one year of age and in adults [5]. The dose should then be adjusted aiming to

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