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## Osteoporosis in cystic fibrosis

Gerd Döring,<sup>1</sup> Steven P. Conway<sup>2</sup>

Adequate care in such a multisystem disease as cystic fibrosis (CF) involves many different disciplines.<sup>1</sup> The control of chronic lung disease by early diagnosis of bacterial infection and early administration of appropriate antibiotics as well as anti-inflammatory drugs is undoubtedly of primary importance,<sup>2</sup> since loss of lung function is the major cause of morbidity and mortality in CF. The maintenance of optimal nutrition status is also critically important,<sup>3</sup> since low body mass indexes also contribute to lung disease. Neonatal screening of CF, now established in several countries, may further increase life expectancy in CF, since early diagnosis improves growth, weight gain and lung function, and decreases hospitalization rate.<sup>2</sup> As a result of better care and therapy in the last decades, prognosis of CF has improved dramatically in many countries and most children now reach adult life. In the USA, median survival rose from 14 years in 1969 to 36.8 years in 2005. Similar improvements in survival have also occurred in Europe. Yet, differences in survival among patients persist, due to differences in treatment strategies, access to specialized CF centres and socioeconomic status.

As life expectancy increases in CF several new clinical problems that need to be identified and therapeutically addressed may become evident. One of these is CF-related bone disease.<sup>4,5</sup> What are the reasons for this complication in CF? The etiology of bone loss in CF is multifactorial, including low body mass index, vitamin D and probably vitamin K insufficiency, poor Ca<sup>2+</sup> absorption and excessive Ca<sup>2+</sup> secretion in the gastrointestinal tract, low levels of insulin-like growth factor 1, chronic bacterial lung infection with associated chronic inflammation and heightened cytokine activity, and treatment with antibiotics and glucocorticoids.<sup>4-6</sup> Studies in cystic fibrosis transmembrane conductance regulator (CFTR)-null mice and in patients with CF indicate a potential association between the gene defect in CF and osteoporosis.<sup>7,8</sup> Recent

work has identified the presence of CFTR in human osteoblasts, osteocytes, and osteoclasts.<sup>9</sup> Thus a high prevalence (40 to 70%) of decreased bone density (both osteopenia and osteoporosis) is present in the adult CF population, particularly among patients undergoing lung transplantation. When does bone disease start? Studies of bone health in small groups of well children with CF show normal bone mineral density (BMD) when the control group is matched for body size as

well as age and gender<sup>10</sup> but adolescents with CF can begin to reveal signs of bone disease.<sup>11</sup>

In the cross-sectional study by Caldeira et al. in this issue of *Jornal de Pediatria*,<sup>12</sup> the authors conclude that there is a high prevalence of low BMD among Brazilian adolescents with CF.

They investigated a group of 37 CF adolescents with a median age of 13 years, who had been diagnosed at 2 years of age. More than 50% of the patients exhibited reduced lumbar spine BMD, as determined by dual-energy X-ray absorptiometry (DEXA) and expressed as a z score, (the number of standard deviations that the BMD score is above or below the mean compared with individuals of that age).

The high prevalence of low BMD in the population studied is surprising, given that over 90% of the adolescents had adequate nutritional intake, (20-50% above the recommended dietary allowance), and over 70% had normal height for age and weight, and forced expiratory volume in one second (FEV<sub>1</sub>) > 60% predicted. Only 8% of the adolescents had FEV<sub>1</sub> < 40% predicted. This high level of reduced BMD may reflect, despite over 70% of patients showing normal height for age, that some of these adolescents have short, narrow, bones. The DEXA scan, an areal measurement, will underestimate BMD in these children. If Caldeira's results were corrected to give a bone mineral apparent density, i.e., corrected

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for body size, a lower prevalence of reduced BMD might be found. A low BMD measurement in a small-for-age child may only be due to small body size.

BMD correlated positively with body mass index ( $p = 0.04$ ). Furthermore, calcium and phosphorous levels were lower among patients with abnormal BMD, confirming previous studies. Similarly, lung disease and pancreatic insufficiency exhibited a correlation with altered BMD although multivariate analysis indicated that these variables were not statistically significant. The lack of statistical significance may just reflect the small study population and the fact that most of the adolescents had good lung function (75% with  $FEV_1 \geq 60\%$ ).

The main reason for concern about decreased BMD in patients with CF is that it may significantly increase the risk of fracture. Aris et al. report a 100-fold increase in adults when compared to age-matched healthy controls.<sup>4</sup> Other case reports document fragility fractures resulting in devastating clinical consequences. Reports of fractures in patients with CF document a particular prevalence of rib and vertebral fractures. These may be associated with a rapid decline in lung function by decreasing the effectiveness of sputum clearance or by precipitating a pneumothorax. Alterations to the chest wall structure by a vertebral fracture resulting in deformity or kyphosis may cause a reduction in forced vital capacity and a less effective breathing pattern. In some transplant centers, history of a fragility fracture or presence of low BMD are seen as relative contraindications to lung transplant. We should be careful, however, in extrapolating these data to a pediatric population. Although BMD measurements are known to predict fracture risk in non-CF adults, with a doubling of risk for each standard deviation below the mean, no such fracture threshold has been identified for children. We note with interest that Caldeira et al. demonstrate more frequent fractures among adolescent patients with abnormal BMD, suggesting that these fractures may be the first sign of osteoporosis.

Caldeira et al. report fractures in 12 of 36 patients but only 33% of these were associated with a history of trauma. There is considerable variation in reported fracture rates in the literature. In our clinic we have seen very few and these have mostly been rib fractures (presumably from vigorous coughing), or those associated with a significant trauma, for example in road traffic accidents. The relatively high incidence in Caldeira's study may reflect the high associated family history of osteoporosis (25%).

Caldeira et al. refer to the potential problems of delayed puberty in their discussion. They do not expand on this. They state that there was no delayed puberty in their population possibly because of the low median age of the sample. Nonetheless mean age was 13.2 years and therefore many of the adolescents would have been expected to have entered puberty. Some CF centers now report no delay in the onset of puberty, but this is certainly not a universal finding. Even

patients showing no delay in puberty may have reduced sex hormone levels compared to age-matched controls. We know that there is a negative correlation between peak bone mineral accrual and peak height velocity with age at menarche. Maximal bone mineral accrual velocity occurs across puberty, and pubertal delay may result in irreversible bone mineral deficiency. Thus clinicians caring for young adolescents with CF should monitor pubertal development and confer with pediatric endocrinology specialists about optimal management for those children showing pubertal delay.

None of the patients in Caldeira's study were using oral corticosteroid therapy and no effect on bone health was shown by use of inhaled corticosteroids. Previous studies are inconsistent in their conclusions about whether corticosteroid use has a negative effect on bone health or not. Nonetheless it is known that corticosteroids reduce osteoblast function and sex hormone secretion. They also interfere with intestinal calcium absorption. Although there is no conclusive evidence about the detrimental effects on corticosteroid use on BMD in patients with CF, these treatments should be used with caution and the risks and benefits of treatment should be carefully considered in each individual case.

Caldeira et al. state that treatment of osteoporosis is not very effective and is associated with potential significant side effects. Bisphosphonate therapy can cause gastroesophageal reflux and esophagitis, and has been associated with jaw osteonecrosis (although not yet in patients with CF). Nonetheless, in fact, with sensible prescribing and sensible precautions (i.e., taking bisphosphonates before breakfast with a glass of water, in an upright position, and remaining upright for the next half hour), adverse events are rare. In adult patients with CF and osteoporosis, bisphosphonates have been used successfully, preventing any further deterioration in, or increasing BMD. It is recommended that bisphosphonate use in children should be restricted to specialist CF centers. Treatment may be beneficial in children with a history of fragility fracture and those listed for, or post-lung transplantation.<sup>5</sup>

In conclusion, as CF patients in Brazil are living longer due to advances in lung disease management, the prevalence of bone disease is increasing and early diagnosis and prophylactic treatment of this complication is needed. Caldeira et al. have investigated bone health in 37 Brazilian adolescents with CF, providing very useful information for local CF care. They recommend that the concentration of efforts to prevent low BMD in people with CF should be directed at early adolescence. We suggest that prevention should start from diagnosis with optimal management of lung health and nutrition, encouragement of weight bearing exercise, and sensible exposure to sunlight. Little can be done later to increase bone mass. A multifaceted approach including optimal nutrition and intensive treatment of lung disease to reduce systemic inflammation is mandatory.<sup>5</sup> As Caldeira et al. state, longitudinal

studies in this context are needed to provide more insight into the disease process.

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# The challenge of feeding children to protect against overweight

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Pediatricians and other health professionals who work with parents of young children have the daunting responsibility of interpreting and communicating guidance about how best to feed children during their development years. Traditionally, the goals in providing such guidance have focused on assuring adequate energy and protein intake, preventing deficiencies of vitamins and minerals and preventing dental disease. However, concepts of optimal child nutrition have been expanded and the challenges of providing appropriate nutritional guidance have increased. This relates both to changes in patterns of nutrition-related disease and to recognition of the role of nutritional factors in the development of diseases throughout the life course. Goals for feeding children now also

address considerations related to prevention of chronic diseases, including cardiovascular diseases, cancers, and mental disorders – conditions for which the origins may begin very early in life even when diagnosis does not occur until adulthood.<sup>1</sup> Important concerns include not only what children eat when young but also how the eating habits they develop during childhood may affect what they eat later in life.

Within the realm of chronic diseases, concerns about obesity are particularly compelling. Epidemic levels have already been reported in many countries and are on the horizon for many others.<sup>2</sup> Food supplies are changing globally, and the availability of foods that are high in calories from fat and sugar but otherwise nutritionally-poor has increased markedly, even

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