Achieving optimal bone health in cystic fibrosis: ready for prime time?

"With the recent publication of updated European Cystic Fibrosis Bone Mineralisation Guidelines as well as an intriguing new study evaluating optimal levels of vitamin D, bone mineral density may just be coming into the limelight."

KEYWORDS: bone mineralization ■ cystic fibrosis ■ PTH ■ vitamin D

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With so many complications competing for clinicians' awareness when it comes to the care of a patient with cystic fibrosis (CF), it is easy to see how bone mineralization could be left behind. After all, in the midst of mucus and malnutrition, diabetes and depression, patients are not typically concerned about their bone density, at least, that is, until the time of their first fracture as a young adult. With the recent publication of updated European Cystic Fibrosis Bone Mineralisation Guidelines [1], as well as an intriguing new study evaluating optimal levels of vitamin D [2], bone mineral density (BMD) may just be coming into the limelight. Our goal in this article is to highlight some of the controversies surrounding the diagnosis and management of this underappreciated condition.

> *"With so many different replacement clinical regimens recommended by the various societies, it is difficult for the clinician to decide how to maintain their patient."*

It is known that CF patients have multiple risk factors for low BMD, including malnutrition with inadequate vitamin and mineral absorption, reduced exposure to sunlight, frequent glucocorticoid use, systemic inflammation and limited physical activity. Vitamin D, a fat soluble vitamin, is absorbed poorly from the GI tract of CF patients and hence oral supplements are mandatory for pancreatic insufficient patients. Annual laboratory determination of the vitamin D levels are recommended by all working groups, but the desirable level has still not been agreed upon with certainty. The European Guidelines recommend a minimum 25-hydroxy vitamin D level of 20 ng/ml, which contrasts with the most recent Cystic Fibrosis Foundation (CFF) consensus statement [3] that recommends a minimum level of 30 ng/ml based on studies in non-CF patients that show that parathyroid hormone (PTH) levels begin to increase once 25-OHD levels drop below 30 ng/ml [4,5]. The Institute of Medicine also targets a goal of 20 ng/ml [6] in non-CF individuals. The 2011 Endocrine Society Clinical Practice Guidelines label vitamin D deficiency at a 25-OHD level of less than 20 ng/ml and vitamin D insufficiency as a level between 21–29 ng/ml [7]. A recent study published in *Chest* [2], however, identified a target level of more than 35 ng/ml as this was associated with the lowest percentages of patients with PTH levels greater than 50 pg/ml. How can physicians reconcile such a wide range of target levels? While our practice is to aim for a level of greater than 30 ng/ml, one logical but unvalidated suggestion is to check individual PTH levels in patients with borderline values as a way to guide supplementation. Monitoring PTH levels is consistent with the European recommendations, which include this as part of routine annual screening, but the American guidelines do not suggest routine monitoring. Vitamin D levels paired with PTH levels on an individual basis may help to identify those patients who are at highest risk for fracture. One problem with this approach is that PTH levels should be checked after at least a 5 h fast because dietary calcium suppresses PTH levels [8].

So if the target level of vitamin D is achieved, what does the clinician do next? It makes intuitive sense to continue the patient on the supplemental dose of vitamin D that resulted in the attainment of sufficient serum levels, but European guidelines say that the dose of supplemental vitamin D should be lowered in order to maintain the desired goal level. The most recent CFF consensus statement fails to address this concept entirely. With so many different replacement clinical regimens recommended by the various societies, it is difficult

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for the clinician to decide how to maintain their patient. Ergocalciferol or cholecalciferol? Twice weekly, thrice weekly or daily dosing? In a 2010 study in the *Journal of Cystic Fibrosis* [9], Green and colleagues studied 97 children with CF who received replacement therapy with 50,000 IU of ergocalciferol daily for 4 weeks. 6 months after completion of therapy, less than 25% of these patients had maintained serum vitamin D levels greater than 30 ng/ml. This highlights the transient nature of replacement therapy. Most of the variability in response to supplementation trials in the literature is due to checking levels weeks or months after stopping a time-limited repletion effort. Therefore, we recommend checking levels during the supplementation trial for the most accurate results. Unlike most medications, vitamin D follows a multicompartment model of pharmacokinetics and the steady state of 25-OHD levels is not reached until several weeks or months after oral dosing [10].

> "*The real question is what to do once osteopenia or osteoporosis has been identified in a child with cystic fibrosis. Let's start with the basics that our mothers and pediatricians taught us: 'Go outside and play in the sunshine.'*"

Even the best formulation of vitamin D is not entirely clear. A recent study compared ergocalciferol to cholecalciferol replacement in non-CF adults and noted that cholecalciferol was 85% more potent in raising and maintaining serum 25-OHD concentrations [11]. This is in keeping with data in CF patients where cholecalciferol is more potent [12], although high-dose ergocalciferol can be very useful for correction in the appropriate circumstances [13]. Importantly, accumulation in subcutaneous fat has not been found (i.e., <20% of the administered dose was stored in fat beds); hence the purported toxicities of vitamin D are not relevant at doses of 50,000 IU weekly. While the potential for toxicity is a hot topic, toxic levels occur at greater than 150 ng/ml, which is substantially higher than proposed target levels and certainly fear of toxicity should not be a major factor in supplementation efforts. Nonetheless reviewers are quick to point out that no studies have evaluated long-term toxic effects of supratherapeutic vitamin levels. CF-specific vitamins range in vitamin D content from 400–1000 IU/tablet. However, given that greater than 90% of CF patients have vitamin D levels of less than 30 ng/ml on standard 800 IU daily dosing, it is long past the time to consider adding more vitamin D supplementation for most CF patients. Fortunately the newer vitamin formulations provide higher daily doses of cholecalciferol and corresponding higher 25-OHD levels. Even more importantly the Internet has greatly expanded our ability to obtain higher potency vitamin D products at extremely low cost (<US$5/month) from nutritional websites.

If osteoporosis is identified, the next logical step is to provide therapy to increase BMD. Unfortunately, in CF, the direction is not so clear cut. A Cochrane review in 2009 pooled five trials with a total of 145 adult patients with osteoporosis [14]. After 6 months of therapy, BMD had increased in the lumbar spine and the hip, but no fracture reduction was noted compared with patients untreated with bisphosphonates, likely related to low sample size. While fracture reduction accompanies BMD increases in the general population, this has not been proven in CF. There is a lack of a clear connection between low BMD and fracture risk in CF. Similar to glucocorticoid-induced osteoporosis or transplant-related osteoporosis, CF patients may fracture at lower T-scores compared with the general population. To prevent fractures in glucocorticoid-induced osteoporosis and transplant osteoporosis, it has been recommended that people with T-scores less than 1.5 should be treated. We continue to advocate bisphosphonate intervention for the nationally accepted standards for the general population, which include T-score of less than 2, fragility fracture (especially common in the spine, and routine lateral chest x-rays can be screened for anterior vertebral body height reductions of >20%), chronic oral steroid users, and pre- and post-transplant patients, but only time will tell which CF patients are ideal for treatment. One concern that consistently arises is administering bisphosphonates to women with child-bearing potential. Fortunately a recent review [15] of 51 pregnancies exposed to bisphosphonates *in utero* demonstrated no skeletal abnormalities in the delivered infants up to one year later. Despite this study, there are still questions regarding bisphosphonates in pregnancy, and many CF bone experts recommend stopping bisphosphonates a year prior to pregnancy if possible.

If clinicians who care for adult CF patients are in a quandary regarding appropriate treatment for optimal bone density, those who care for children struggle even more. Infants identified by newborn screening are noted to be vitamin D deficient, regardless of pancreatic function or month of birth [16]. Little attention

was paid to this crucial topic in the past, when competing concerns for lung health and nutrition took precedence over bone health. However, with the increase in life expectancy to nearly four decades, it is imperative that pediatric specialists start paying attention to bone health in CF. Once again, guidelines from the European Consensus Conference and the Cystic Fibrosis Foundation differ with respect of how children's BMD should be evaluated and treated. Limited normative data is known regarding BMD in the first decade of life. Should children be evaluated with a baseline dual-energy x-ray absorptiometry initially at 8–10 years of age [1], or should initial screening be delayed until after the onset of puberty, when much bone accrual and mineral deposition occurs? The CFF suggests children be screened starting at age 8 [3] if they are less than 90% ideal body weight, forced expiratory volume in one second is less than 50% predicted, glucocorticoids are used for more than 90 days/year at a dose of greater than 5 mg/kg, or if delayed puberty or a history of fractures is present. Hopefully this represents a minority of CF children. But what of the 14-year-old CF female whose nutrition and lung function is ideal but who has limited physical activity and sun exposure? Should screening be delayed until she becomes an adult, and is that at 18 years of age, 21 years, or simply when she transitions to an adult provider? Several studies [17,18] suggest that compared with age-, gender-, and pubertal-matched non-CF children, 50% of patients with CF have a decreased BMD, so it seems reasonable to screen children and adolescents for bone disease. A recent abstract presented at the North American Cystic Fibrosis Conference (NACFC) 2010 indicated higher fracture rates in CF children [19]. The real question is what to do once osteopenia or osteoporosis has been identified in a child with CF. Let's start with the basics that our mothers and pediatricians taught us: "Go outside and play in the sunshine." A significant correlation between 25-OHD levels and sunlight exposure has been proven [20] and as little as 15 min of sunlight exposure is adequate for vitamin D synthesis in the summer months. Patients will benefit even more if this sunlight exposure is paired with weight-bearing exercises. Bisphosphonate therapy, while more controversial in children, even in the setting of pathologic fractures [21], is now routinely safely and effectively used in disorders, such as osteogenesis imperfecta [22]. To date, only one small study has looked at bisphosphonate use in five children with CF with osteoporosis despite adequate replacement therapy with calcium and vitamin D. This study [23] showed bisphosphonates were well tolerated and significantly improved both total body and lumbar spine Z-scores. This very limited data underscores the urgent need for randomized controlled clinical trials in the pediatric CF population.

New guidelines regarding vitamin D in cystic fibrosis are forthcoming from the Cystic Fibrosis Foundation, following the recently revised European CF Bone Health guidelines. This area will continue to evolve as further studies provide new insights into CF bone disease.

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