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CONSENSUS STATEMENT: Guide to Bone Health and Disease in Cystic Fibrosis

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Cystic fibrosis (CF) is the most common genetic disease within the Caucasian population and leads to premature respiratory failure. Approximately 60,000 individuals are currently living with CF in North America and Europe, 40% of whom are adults. The life span of these patients has increased from approximately 2 to 32 yr of age over the last three decades. Bone disease has emerged as a common complication in long-term survivors of CF. Some studies have observed that 50–75% of adults have low bone density and increased rates of fractures. Prevention and treatment of CF-related bone disease must address the myriad risk factors (decreased absorption of fat-soluble vitamins due to pancreatic insufficiency, altered sex hormone production, chronic lung infection with increased levels of bone-active cytokines, physical inactivity, and glucocorticoid therapy) for poor bone health. This review is a condensed and updated summary of the Guide to Bone Health and Disease in Cystic Fibrosis: A Consensus Conference, a statement that evolved from a meeting convened by the Cystic Fibrosis Foundation in May 2002 to address the pathogenesis, diagnosis, and treatment of bone disease in CF. The goal of this conference was to develop practice guidelines for optimizing bone health in patients with CF. (*J Clin Endocrinol Metab* 90: 1888–1896, 2005)

BONE DISEASE IN individuals with cystic fibrosis (CF) was first described in 1979. Low bone density and increased fracture rates are now recognized complications of this autosomal recessive disease that is the leading genetic cause of early respiratory failure in the United States and Europe (1). The fundamental gene defect in this disease leads to a mutation in the CF transmembrane conductance regulator (CFTR) protein, which is a chloride channel found in epithelial tissues in the lungs, pancreas, gastrointestinal tract, and skin. CFTR modulates the transport of salt and water across these epithelia, and mutations in CFTR lead to changes in the viscosity and hydration of epithelial lining fluids, leading to alterations in host defense in the respiratory tract and, ultimately, chronic, progressive infection with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and/or other pathogens. CFTR mutations may also lead to pancreatic duct obstruction and pancreatic insufficiency (prevalence, >80%; exocrine ≫ endocrine), biliary obstruction and cirrhosis (prevalence, ~5%), and distal intestinal obstruction syndrome (prevalence, ~5%).

Changes in the clinical management of these patients, including nutritional supplementation, physical therapy, and medication regimens, have increased the life expectancy of patients with CF from the single digits in the 1960s to 32 yr in 2002. Approximately one in 2500 children in the Caucasian population are born with CF each year in the United States; 40% are currently adults. The origin of the bone disease in CF appears to be multifactorial (Fig. 1). Important contributing factors include malabsorption of vitamin D, poor nutritional status, physical inactivity, glucocorticoid therapy, and delayed pubertal maturation or early hypogonadism. Additionally, chronic pulmonary inflammation increases serum cytokine levels, which, in turn, probably stimulates increased bone resorption and decreased bone formation. Decreased quantity and quality of bone mineral resulting from these factors can lead to pathological fractures and kyphosis decades earlier than expected. Severe bone disease can lead to exclusion from lung transplantation, often a life-saving operation for individuals with CF. Prevention, early recognition, and treatment are the most effective strategies for sus-

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 sec; NTx, N-telopeptides; 25OHD, 25-hydroxyvitamin D; RCT, randomized controlled trial.

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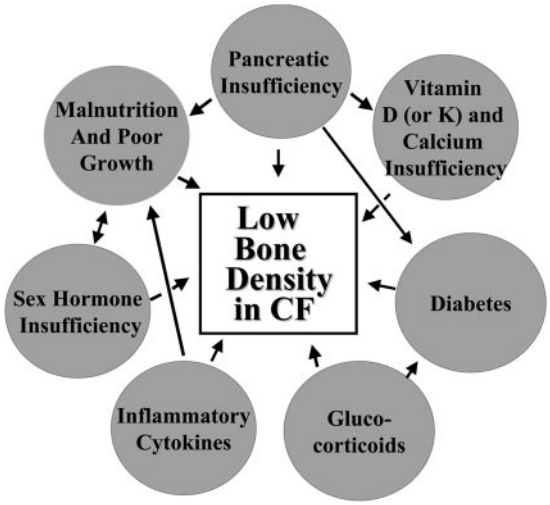

FIG. 1. Pathogenesis of bone disease in CF.

taining bone health to help maintain the quality of life of many individuals with CF.

Description and Pathophysiology of Bone Disease in CF

Clinical correlates of low bone mass

Two studies in 1979 independently reported a decrease in bone mineral content in individuals with CF compared with age-matched controls (2, 3). Since then, more than 50 reports have observed low bone mass and fractures in individuals with CF. Low bone mineral density (BMD) is commonplace in both postpubertal children and adults with CF, although adults tend to be more affected. Cross-sectional surveys of adults have found that 20–34% of adults with CF have standard z-scores (age-adjusted SD scores) below −2, whereas 10% have T-scores (SD scores compared with young adults) less than −2.5 (4–22). The prevalence of BMD below −1 SD is as high as 85% in some adult CF studies (5). BMD data must be interpreted with care, because small bone size and delayed skeletal maturation will contribute to artifactually lower BMD z-scores. Corrections can be made for bone age or bone size using bone mineral apparent density, but some additional error will be introduced by the methods used to assess bone size with dual energy x-ray absorptiometry. In some (7, 13, 19), but not all (20–24), studies, low bone mass persisted after adjusting for these factors. Some of the difference in these studies could be explained by the patients' ages, with children having better volumetric bone density than adults.

The prevalence of bone disease appears to increase with the severity of lung disease and malnutrition. Younger and healthier individuals may have normal BMD (21–25), suggesting that the bone disease is not intrinsically related to the CFTR mutation, but occurs as patients get older because of the contributing factors mentioned above. Several studies have demonstrated a positive correlation between BMD T- or z-scores and FEV_1 (forced expiratory volume in 1 sec) and body mass index (BMI) (4–7). Patients with severe pulmonary disease ($FEV_1 < 30\%$) often have severe bone disease with a high rate of kyphosis and fractures of long bones, vertebrae, and ribs (5, 9). Mean BMD z- and T-scores in these patients average −2.0 at the spine and femur, and more than 90% are more than 1 SD below the expected value (5, 9, 10). Unfortunately, concerns regarding bone fragility can be used to exclude patients from lung transplantation.

Bone histomorphometry in CF

Studies of bone histomorphometry in clinically stable adults with CF and low BMD demonstrate significantly reduced cancellous bone volume and a trend toward decreased connectivity (25). Indexes of bone formation rates were also significantly reduced. Wall width, the amount of bone formed within individual remodeling units, was decreased by 50%, as was mineralizing perimeter. The mineral apposition rate was 10% below the expected value. Analysis of resorption cavities revealed a smaller cavity area, reconstructed surface lengths, and cavity depths in the CF cohort, whereas eroded surface area was significantly higher. These results demonstrate that the main cause of low cancellous bone volume appears to be low bone formation at tissue and cellular levels. Although there was evidence of a mineralization deficit in the CF group as a whole, only one biopsy revealed osteomalacia by strict histomorphometric criteria.

A separate study of autopsy bone samples from a mixture of transplanted and nontransplanted individuals with CF demonstrated severe osteopenia in both trabecular and cortical bone (26). At the cellular level, there was decreased osteoblastic and increased osteoclastic activity. The reduction in osteoblastic activity was due to decreases in both osteoblast number and the biosynthetic potential of these cells. Osteoclast activity was increased primarily through increased osteoclast numbers. The increase in osteoclasis and the uncoupling of osteoblastic and osteoclastic activity resulted in a net increase in resorptive surfaces. Both cortical and trabecular bone mass tended to be lower after transplantation; the majority of these patients had received high doses of glucocorticoids to prevent rejection. None of the CF biopsies showed osteoid parameters characteristic of osteomalacia from vitamin D deficiency.

The pathogenesis of low BMD in individuals with CF remains uncertain despite the available data from histomorphometry, biochemical bone markers, and observations about the clinical course of bone disease. For this reason, the consensus panel chose to use the term CF bone disease rather than osteoporosis to avoid promulgating a diagnostic label that may ultimately prove to be inaccurate as the underlying pathophysiology is better defined.

Bone accrual and loss in CF

The foundation for lifetime bone health is established during infancy, childhood, and adolescence and requires adequate nutrition, body mass, physical activity, and hormone production (27). Puberty is a particularly critical period, when growth and mineral accrual are most rapid (28). These expected gains may be compromised in individuals with CF, who often suffer from delayed puberty and reduced pubertal growth. One longitudinal study of pubertal children with CF reported that inadequate bone mineral accrual resulted in lower than expected areal BMD and volumetric BMD (bone

mineral apparent density) (19). However, another small study observed normal z-scores in prepubertal CF children who had normal lung function and BMI, suggesting that normal BMD can be achieved in healthier patients with CF (29). A more recent and larger study confirmed this finding by demonstrating normal spine, femur, total body, and wrist BMD in 40 children (aged 5–10 yr) with CF, but significantly reduced total body and distal wrist (but not spine or femur) BMD in 55 adolescents (aged 11–20 yr) with CF (30). These results should be considered in light of the fact that there are limited normative BMD data during the first decade of life. To date, longitudinal data on growth and bone mineral accrual on children and adolescents with CF are limited and worthy of additional study. Taken together, these studies suggest that bone disease finds its origins in individuals with CF near or during the pubertal growth spurt.

The majority of reports of low BMD in CF have included adult patients. Each of the more than 25 published reports to date has found a high prevalence of osteopenia and osteoporosis regardless of state or country of origin. Data from the adult and pediatric studies suggest that low BMD results from inadequate bone acquisition during puberty. Subsequent bone loss has also been observed in several longitudinal studies in young adults with CF. Haworth *et al.* (31) reported mean annualized losses in BMD of 0.5, 2.1, and 1.8% at the lumbar spine, femoral neck, and total hip, respectively, in a cohort of 114 patients aged 15–49 yr (mean age, 25 yr). Aris *et al.* (32) found annualized losses of similar magnitude (1.8% at the spine and 0.7% at the hip) in a slightly older cohort (mean age, 27 yr). These rates approach those experienced by women after menopause.

Bone turnover in CF

Studies of biochemical markers of bone turnover suggest an imbalance, with bone resorption exceeding formation, even in CF patients who are clinically stable. Accelerated bone resorption was first reported by Grey *et al.* (14), who found high urinary hydroxyproline levels, and this was later confirmed by a number of different groups using urinary carboxyl-terminal propeptide of type I procollagen, N-telopeptides (NTx), and deoxypyridinoline (7, 33, 34). Serum osteocalcin levels were significantly lower in both pubertal children and young adults. Other bone formation markers have been more variable, with some studies showing lower levels and others higher ones (7, 33–36). Bone-specific alkaline phosphatase levels were associated with total alkaline phosphatase levels in one study and therefore may be a less specific formation marker in CF, because biliary obstruction may raise liver alkaline phosphatase levels, which may cross-react with bone-specific alkaline phosphatase (34). A recent isotope study of calcium kinetics directly measured rates of bone calcium deposition in a group of 22 clinically stable girls with CF (36). Average rates of bone calcium deposition were lower than those typically reported among healthy children consuming comparable calcium intakes and were inversely associated with serum osteocalcin and leptin concentrations. Thus, a reduction in the rate of bone calcium deposition may contribute to the reduced bone mass.

Pathogenesis of bone disease in CF

Pancreatic exocrine insufficiency and malabsorption. Optimal nutrient intake is required to maintain adequate body weight and bone mass. Malnutrition is common in CF, because pancreatic insufficiency results in malabsorption (even with pancreatic enzyme supplementation). Malabsorption is compounded by increased catabolism due to chronic lung infection. Low BMI is a risk factor for increased disease severity and other complications related to CF. Many studies have observed a correlation between poor nutrition (reduced BMI) and low BMD in CF (2, 4, 7, 11). Low BMD also occurs among the 10% of CF patients with pancreatic sufficiency, indicating a role for chronic infection or other factors in causing poor bone health. Regardless, maintenance of an optimal BMI is a key treatment, particularly through the pubertal growth spurt.

Despite conflicting data on the absorption and the excretion of nutrients related to bone health (37), there is a growing consensus that the absorption of vitamins D and K and calcium is inadequate to meet the needs of individuals with CF.

Unequivocal evidence from more than 20 reports indicates that vitamin D insufficiency [low or low-normal 25-hydroxyvitamin D (25OHD) levels] is common among individuals with CF regardless of season or latitude (38). Frankly low [$<$10 ng/ml (25 nmol/liter)] serum 25OHD concentrations are observed in 5–10%. The majority of adults with CF have levels in the lower half of the normal range, with a mean near 20 ng/ml. In end-stage CF, frank vitamin D deficiency is more common and may occur in 25–33% of patients (5, 39). Some reports have, and others have not, found an association between serum 25OHD levels and BMD in CF, but the failure to find an association is not unexpected, because BMD reflects bone health over the lifetime of the patient, and current vitamin D concentrations may fluctuate from season to season.

The cause of vitamin D insufficiency in CF has not been adequately studied. Lark *et al.* (40) reported that adults with CF absorbed 50% less of a test dose of oral vitamin D_2 (100,000 IU or 6.5 mmol) than did controls. Absorption varied greatly, with 20% of the individuals with CF having virtually undetectable vitamin D_2 levels (by HPLC) 0–36 h after treatment. Serum 25OHD concentrations did not rise in response to vitamin D_2 in the CF group compared with a mean doubling of the 25OHD level in the controls. Little is known about the activity of the 25-hydroxylase enzyme in CF. We speculate that both D_2 and 25OHD undergo enterohepatic recirculation and may be subject to additional malabsorption. Other possibilities for low 25OHD levels could be altered concentration or activity of the 25-hydroxylase enzyme or higher metabolic clearance rates of vitamin D or 25OHD. Although hepatocyte function is usually normal in CF patients without cirrhosis, biliary disease is common, and bile salts may inactivate the 25-hydroxylase. CF patients are also well known for having increased oxidant and P_{450} activity, which could lead to more rapid degradation of existing or newly formed 25OHD. Similarly, the kinetics of the conversion of 25OHD to 1,25-dihydroxyvitamin D in this disorder have not been defined. 1,25-Dihydroxyvitamin D levels in CF are usually similar to those in healthy individuals, raising the

possibility that elevations in PTH, reported in some, but not all, studies, enhance 1α-hydroxylation despite low levels of substrate (20, 34). Reduced absorption of vitamin D and conversion of vitamin D to its active form are likely to contribute to CF-related bone disease.

Other factors that probably contribute to vitamin D insufficiency in CF include reduced sunlight exposure and reduced fat mass. Some patients with CF have limited sunlight exposure because of illness or concern of photosensitivity from antibiotic therapy. Exposure to sunlight is helpful, but additional vitamin D supplementation or exposure to man-made ultraviolet B radiation may be needed during the winter months. Most adults have low body fat, which may diminish vitamin D reserves. In summary, vitamin D insufficiency may develop for a variety of reasons in patients with CF. Although this nutritional problem does not appear to be sufficient to explain low bone mass, it is probably one of myriad contributing factors to CF-related bone disease.

A growing body of clinical information outside of CF suggests that vitamin K may play a role in bone health. Even with routine supplementation, 40% of individuals with CF remain vitamin K deficient (41). Many individuals with CF have reduced γ-carboxylated osteocalcin, which may decrease the binding of the calcium ion of the hydroxyapatite molecule in bone (36, 42).

Pancreatic endocrine insufficiency. Diabetes mellitus has been associated with reduced trabecular and cortical bone mass in cohorts without CF (43). Diabetes develops in 10% of individuals with CF. Although CF-related diabetes may differ from classical type I or II diabetes, the abnormalities in glucose metabolism resulting from islet cell insufficiency and chronic infection, the latter leading to peripheral insulin resistance, may play a role in reduced BMD.

Physical inactivity. Individuals with CF may become inactive due to reduced lung function and prolonged treatments for respiratory infection. Most studies in CF found an association between total activity or hours of weight-bearing activity and BMD (4, 7, 11, 19, 32), similar to that in the general population.

Delayed puberty or early gonadal failure. Sex steroid deficiency from delayed puberty or early hypogonadism probably contributes to CF-related bone disease (5, 13, 19), although observational studies to date have not found a consistent association. Pubertal delay in CF has been recognized for over 20 yr and is related to disease status (44, 45). Delayed puberty may retard both bone growth and the attainment of peak bone mass. Fortunately, as the health status and survival of individuals with CF has improved over the last four decades, so has the frequency of normal pubertal development. Nonetheless, the height of adults with CF averages 2–3 inches shorter than that of their age-matched peers, and average weight falls into the lowest deciles (1, 5). Sex hormones are reduced in adolescents with CF compared with age-matched controls, although most values are normal when corrected for Tanner stage (46–49). Most young adults with CF eventually achieve normal levels of sex hormones. Estimates of intermittent menstrual dysfunction range widely, from 28–73% (46, 48). Low total testosterone levels have been found in 1.5–88% of men with CF (4, 5, 7, 12, 18). Free testosterone levels were also low in one study (4). The cause of sex steroid deficiency appears to be hypothalamic dysfunction from chronic illness, because gonadotropin concentrations are not elevated, but corticosteroid therapy may play a role as well.

Because malnutrition, corticosteroid use, physical inactivity, disease severity, and hypogonadism (particularly in males) are often present simultaneously, it is difficult to identify the independent contribution of each of these factors to low BMD in CF. Some studies have shown an association between both delayed puberty and hypogonadism and a lower BMD (4, 5, 18, 19). However, one study of teens and adults with CF detected a high prevalence of low BMD despite few abnormalities in sex hormones (12). Although delayed puberty and/or subsequent interruptions in sex hormone production probably play a role in low BMD, the degree to which these abnormalities affect each individual is variable.

Chronic infection. Bone remodeling is under the influence of systemic hormones, cytokines, and localized growth factors. Although beyond the scope of this review, there is mounting evidence for the causal role of inflammatory cytokines in bone loss in a variety of diseases other than CF (50). Many factors in the serum and respiratory tract of individuals with CF can stimulate osteoclastic bone resorption, including TNFα, PTH, vascular endothelial growth factor, and IL-1, -6, and -11. Many inflammatory cytokines are found in high concentrations in chronically infected CF lungs (sputum and bronchoalveolar lavage) and serum. The inverse association between the number of iv antibiotic courses and BMD provides indirect evidence of a link among inflammation, cytokine production, and bone health (4). During exacerbations of lung infection in CF, serum concentrations of IL-6, IL-1, TNFα, and the bone resorption markers NTx and deoxypyridinoline increase, while serum osteocalcin concentrations decrease (51). These abnormalities have been shown to resolve almost completely when lung infection is treated with antibiotics, chest physiotherapy, and nutrition supplementation. BMD tends to remain more stable for adults with CF after lung transplantation than for other patient groups despite immunosuppresssion and actually increases in CF transplant recipients who experience good outcomes. These findings suggest that the benefits for bone health of removing suppurative lungs have a counterbalancing effect on the adverse impact of immunosuppressants on bone.

Glucocorticoids. An estimated 20–50% of individuals with CF are treated with exogenous glucocorticoids intermittently to improve pulmonary function (5, 52). Inhaled glucocorticoid use is more common than chronic oral use. Many, but not all, studies have found glucocorticoid therapy to be a risk factor for low bone mass in CF (4, 5, 12, 31, 38). The association between corticosteroid use and BMD is confounded by disease severity, because sicker patients are generally selected for steroid therapy. The adverse effects of glucocorticoids on growing children with CF may be even more profound. Chronic glucocorticoid therapy in children impairs linear growth, delays puberty, and may compromise the peak bone mass attained by early adulthood. Thus, every effort should be made to minimize glucocorticoid use.

Lung transplantation and immunosuppressant therapy. Approximately one third of individuals with CF in the United States undergo lung transplantation to prolong survival and improve quality of life (1). Immunosuppression is mandatory after lung transplantation and may exacerbate the preexisting low BMD (5, 9, 53–55). For this reason, individuals with CF, very low BMD, and a history of prior fractures may be considered at high risk and excluded from transplantation on this basis. Similar to findings in kidney, heart, and liver transplant recipients (56), lung transplant recipients with various diagnoses have declines of 1–5% in spine and femur BMD during the first 6–12 months after transplant (53, 54, 57). However, these studies have included only a few CF individuals, and it is difficult to extrapolate these findings directly to CF. In CF, the declines that occur after transplant may be smaller than for other groups (55). Lung transplant recipients, in general, and those individuals with CF, in particular, appear to develop high turnover osteoporosis (58). Most importantly, patients with lung disease other than CF who have received lung transplants have alarmingly high rates of fractures, ranging from 37–42% (57, 59), presumably related to high bone turnover, reduced bone quality, or increased physical activity superimposed on preexisting low BMD.

Clinical Manifestations of Bone Disease in CF

Several cross-sectional studies have observed a higher incidence of fractures in individuals with CF (4, 5, 7, 12, 39, 60). Henderson and Specter (60) first reported that females with CF, 6–16 yr of age, had higher fracture rates than controls or male CF patients. Bachrach *et al.* (12) found 12 fractures, including one of the femur, in nine patients in a cohort of 71 children and adults. Aris *et al.* (5) reported 54 fractures from subject interviews in 70 patients with over 1410 patient-years of analysis. Fracture rates were approximately 2-fold higher in women with CF, aged 16–34 yr, and men with CF, aged 25–45 yr, compared with the general population (5). Chest x-ray review demonstrated evidence of 62 vertebral compression and 14 rib fractures, indicating vertebral and rib fracture rates that were 100- and 10-fold higher than expected. Donovan *et al.* (39) studied 30 adults with CF and found that vertebral fractures were present in 19% by radiograph review, and 41% had a confirmed history of previous fracture. Haworth *et al.* (7) reported fractures in 51 adults of a cohort of 151, for an overall incidence of 34%. Elkin *et al.* (4), who studied 107 CF adults, found that 17% had evidence of vertebral deformity by radiography, mostly in the thoracic spine, and 35% reported a history of nonvertebral fractures, of which 9% were rib fractures.

Erkkila *et al.* (61) first reported an increased prevalence of kyphosis in individuals with CF. This report was followed by several others (5, 60, 62, 63). Early reports surveying mainly children and adolescents with CF demonstrated an unexpectedly high prevalence (9–40%) of abnormal kyphosis angles, worsening kyphosis with age, and more severe kyphosis in females compared with males. Henderson and Specter (60) found kyphosis angles greater than 40° in 77% of the females and 36% of the males with CF 15 yr of age or older. Aris *et al.* (5) found that the mean kyphosis angle was markedly abnormal (44 ± 14° by the Cobb method; 62% were ≥40°) and probably contributed to a diminished stature (mean height loss of 5.9 cm). In addition to causing pain and debilitation, rib and vertebral fractures produce chest wall deformities that reduce lung function (*i.e.* lung volumes, such as total lung capacity and forced vital capacity), inhibit effective cough, hinder airway clearance, and, ultimately, accelerate the course of CF.

Screening and Treatments for Optimal Bone Health in CF

Recommendations for screening and treatment are shown in Fig. 2 and discussed below.

Vitamin D supplementation

Because bone disease in CF has only recently received attention, most therapeutic trials are either ongoing or have been published as preliminary observations. Several studies have assessed the efficacy of using vitamin D analogs to improve 25OHD levels. *Hanly et al.* (64) demonstrated that administration of 800 IU/d (20 μg/d or 0.052 mmol) vitamin D, the recommended adult supplement in the CF Clinical Practice Guidelines, was often inadequate to raise serum 25OHD concentrations. Fewer than half of the subjects with vitamin D deficiency achieved normal serum 25OHD levels after 4–10 wk of therapy, and only 30% had normal 25OHD levels after 1 yr. Kelly *et al.* (65) reported that 95% of a treated cohort of CF patients required 1800 IU (45 μg/d or 0.13 mmol) of ergocalciferol daily to achieve a 25OHD concentration above 25 ng/ml. In another preliminary report, Boyle *et al.* (66) found that even higher doses of ergocalciferol [50,000 IU (1.25 mg or 3.25 mmol), orally, weekly, or twice weekly for up to 4 months] failed to result in the targeted serum 25OHD concentration of 30 ng/ml in 58 CF adults.

In preliminary results from a case-control trial with 73 CF patients, calcifediol (0.7 μg or 1.75 nmol/kg·d) with 1 g calcium was more beneficial in improving BMD than calcium alone (67). Based upon annual dual energy x-ray absorptiometry results, 69% of calcifediol patients experienced an increase in BMD, whereas only 32% of the control patients experienced increases (mean BMD increase: calcifediol, 9.3%; calcium alone, 3.6%; $P = 0.004$). In a short-term study, Brown *et al.* (68) reported that calcitriol [0.5 μg (1.2 nmol) by mouth daily for 2 wk] significantly increased the fractional absorption of ^{45}Ca and lowered PTH ($P = 0.03$) and urinary NTx levels ($P = 0.01$) in 10 adults with CF. Thus, both calcifediol and calcitriol may provide treatment options for individuals with CF if the less polar forms of vitamin D are ineffective.

Additional research is needed to determine the optimal vitamin D analog and dose. The current recommendations from the consensus panel are to target 25OHD concentrations of 30–60 ng/ml (75–150 nmol/liter). It is likely that each of the available analogs (ergo- or cholecalciferol, calcifediol, or calcitriol), when given in appropriate doses, can improve the appropriate serum vitamin D level, measures of calcium homeostasis, and ultimately help improve BMD. Cost and safety favor ergocalciferol. Commercially available doses, 400-IU (10-μg or 0.026-mmol) tablet, 1000-IU (25-μg or 0.065-mmol) tablet (or per milliliter as a liquid), 8000 IU (200 μg or

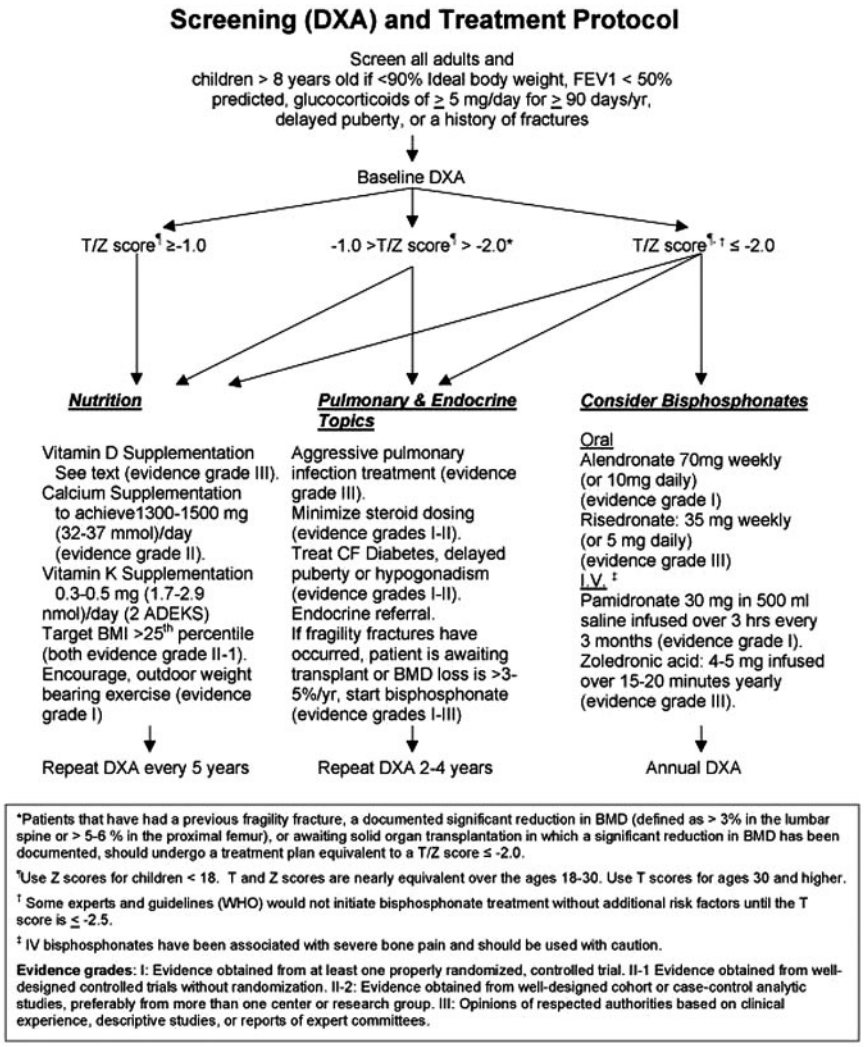

FIG. 2. Screening and treatment protocol for bone disease in CF.

0.52 mmol/ml as a liquid), or 50,000-IU (1.25-mg or 3.25 mmol) capsule can be found in both prescription and nonprescription forms and provide a variety of dosing alternatives. A minimum of 400 IU (10 μg or 0.026 mmol) and 800 IU (20 μg or 0.052 mmol) ergocalciferol should be taken daily by infants and individuals older than 1 yr of age, respectively. Doses up to 12,000 IU (300 μg or 0.78 mmol) for children less than 5 yr of age and of 50,000 IU (1.25 mg or 3.25 mmol) for patients 5 yr and older may be needed weekly or biweekly to achieve the targeted 25OHD level. If aggressive ergocalciferol supplementation is ineffective, more polar vitamin D analogs or phototherapy should be considered. A poor response to im ergocalciferol in one trial should not preclude other studies in this area, especially if oral supplementation and phototherapy are unsuccessful or impractical, but the availability of im preparations may be limited (69).

Calcium and vitamin K supplementation

To date, there have been no randomized controlled trials of these supplements in CF. In the absence of data specific to CF, calcium and vitamin K supplementation should follow the dietary reference intakes (Fig. 2). Comprehensive assessments can be performed by nutritionists affiliated with most CF centers.

Sex steroid replacement therapy

The efficacy of short-term androgen therapy for promoting growth and pubertal development has been assessed in 54 adolescent and young men with CF between the ages of 14 and 18 yr (45). In this cohort, 39% were below the fifth percentile in height, and 28% had delayed puberty. Five male adolescents were treated with testosterone supplementation [200 mg (694 mmol) testosterone enanthate, im, every 3 wk] in an uncontrolled, year-long intervention. Growth rates increased from an entry mean of 2.2 to 7.2 cm/yr. All participants had advancement in sexual maturation and trended toward achieving normal serum testosterone concentrations. Trials of estrogen replacement for females with CF and delayed puberty or premature menopause have not been conducted. Sex steroid replacement therapy may prove to benefit bone health in individuals with CF, but the complicated nature of CF bone disease and the risk/benefit ratio for hormone replacement therapy in any given patient makes individualization of therapy important.

Antiresorptive agents

Bisphosphonates have been used in several uncontrolled observational and in three randomized controlled (RCT) trials in adults with CF. Trials of these drugs in CF children have not been conducted to date. Pamidronate (30 mg, iv, every 3 months) was the first bisphosphonate used in adults with CF, because it circumvented the potential problems related to malabsorption of an oral bisphosphonate (70). In an RCT, pamidronate resulted in significant gains in lumbar spine (mean difference between arms, 5.8%; $P < 0.001$) and total hip (mean difference, 3.0%; $P < 0.05$) BMD after 6 months. Unfortunately, significant adverse events occurred with pamidronate use (71). These included moderate to severe bone pain, fever, and phlebitis in almost 75% of the patients, a number of whom required hospitalization. None of the patients taking oral corticosteroids at the time of the pamidronate infusion developed bone pain, suggesting that prednisone therapy had a protective effect. Thus, a 3- to 5-d course of prednisone may be useful before pamidronate infusions. Two RCTs are underway in CF patients with the newer iv bisphosphonate, zoledronic acid. Unpublished comments suggest that it is effective, but it, like pamidronate, is associated with bone pain. In one RCT in CF lung transplant recipients, pamidronate (30 mg every 3 months) also produced a robust response in BMD at the spine (+8.8 ± 2.5%) and the proximal femur (+8.2 ± 3.8%) after 2 yr of therapy (57). None of the patients reported fevers or bone pain, again suggesting a protective effect of immunosuppressants.

Alendronate has also shown promise for treating bone disease in CF despite early concerns that pancreatic insufficiency would limit absorption (32). A single-center, placebo-controlled, double-blinded RCT trial of alendronate (10 mg/d, orally; n = 24) compared with placebo (n = 24) was conducted for 1 yr to improve BMD. The alendronate-treated patients gained (mean ± SD) 4.9 ± 3.0% and 2.8 ± 3.2% BMD after 1 yr *vs.* controls, who lost (mean ± SD) 1.8 ± 4.0% and 0.7 ± 4.7%, in spine and femur BMD, respectively. Urinary NTx levels declined in the treatment group more than in the controls. To date, no study has been performed with risedronate.

Several potential safety issues with oral bisphosphonates may be present in individuals with CF if this therapy is used more widely. The incidence of erosive pill esophagitis may be higher because individuals with CF have a high incidence of gastroesophageal reflux. Furthermore, a minority of individuals with CF will develop cirrhosis with esophageal varices, which may complicate oral bisphosphonate therapy. Last, adherence to oral bisphosphonate may be suboptimal due to the demanding medical regimens of individuals with CF. Once weekly oral bisphosphonate dosing may improve compliance, and a study of this question is underway in CF individuals.

Anabolic agents

Anabolic agents such as PTH have not been studied in CF. Human recombinant GH has shown promise as an anabolic agent for use in children with CF. In two preliminary studies of individuals with CF (72, 73), GH therapy increased linear growth, weight, and lean tissue mass. The GH-treated group had statistically greater accretion of bone mineral content as well.

Conclusions

Despite the recent clinical research studies in CF, myriad questions remain regarding the pathogenesis and optimal management of CF-related bone disease. Low BMD, kyphosis, and fragility fractures are common complications in adults and develop in childhood in the more severely affected patients. Malnutrition, inflammation, hormone deficits, inactivity, and medications have all been implicated as risk factors for reduced bone mineral accrual or increased bone loss. However, the simultaneous presence of these factors makes it difficult to determine the contribution of each variable. Younger, healthier patients with CF achieve normal bone mass, evidence against a primary role for the CFTR defect in causing the condition. The observation of normal bone mass in well nourished patients also provides a cogent argument for aggressive nutritional support and prompt treatment of lung infection to optimize early bone mineral accrual. Additional work is needed to better define the optimal nutritional supplementation and activity programs to prevent or reverse poor bone health in this patient population. For patients with more advanced pulmonary and nutritional deficits, other therapies may be required to reduce the risk of low bone mass and disabling fragility fractures. Small RCTs support a role for bisphosphonates in adult patients with very low BMD or after lung transplantation. Broader use of bisphosphonates or treatment with newer anabolic agents cannot be endorsed without additional testing. This consensus meeting was held to examine the literature to date and to develop evidence-based practice guidelines. In the absence of adequate RCTs, the assembled panel developed recommendations based upon expert opinion and the available literature. The need for more research to refine these recommendations is clear.

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