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CALCIUM AND BONE MINERAL METABOLISM IN CHILDREN WITH CHRONIC ILLNESSES

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■ **Abstract** Increased longevity and improved medical management of children with chronic illnesses has led to a focus on the short- and long-term consequences of these conditions on bone health. Bone loss is influenced by diet, malabsorption, and disease-related imbalances in bone turnover. It may be exacerbated by common medications, especially corticosteroids. Assessment of bone mass and quality, calcium absorption, kinetically derived rates of bone turnover, and biochemical markers of bone turnover have increased our knowledge of the pathophysiology of bone loss in these children as well as provided insights into possible therapeutic interventions. Increased intake of calcium and vitamin D, while useful, is unlikely to prevent or resolve bone loss in many chronically ill children. Emphasis on combination of nutritional interventions with exercise and newer bone-sparing therapies may be necessary.

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INTRODUCTION

Increasing numbers of children in the United States and throughout the world are receiving long-term medical care for chronic health disorders. This is due, in part, to medical advances that have greatly increased the life expectancy of children with conditions such as cystic fibrosis, leukemia, and cerebral palsy. This increased longevity has focused attention on issues of bone health and long-term fracture risk that were, until recently, not generally considered in the management of these children. The etiology of bone mineral deficiency in children with chronic diseases is often multifactorial and therefore simple solutions such as increasing dietary mineral intake are often unsuccessful. Unique bone health considerations are evident in pediatric populations because this age group is still building skeletal mass, and deficits in bone accretion at this key age can have a significant impact on attainment of peak bone mass and subsequent risk of fracture and osteoporosis.

ASSESSMENT OF BONE MINERAL STATUS

Bone Mass Measurements

Elaborate homeostatic mechanisms exist to tightly regulate serum calcium (Ca) concentrations, yet no such mechanisms exist to maintain an "adequate" bone mass in the face of mineral deficiency. If Ca intake and absorption from the diet are insufficient to offset daily urinary, dermal, and endogenous fecal Ca losses, bone mineral is resorbed to provide the needed calcium. Even in growing children, bone Ca reserves can be depleted, if necessary to the point of bone fragility and fracture. In children with chronic illnesses, evaluation of bone health is often warranted to identify deficits and to initiate appropriate interventions prior to the attainment of peak bone mass. Techniques available to obtain information on bone mass and quality include X-rays, single or dual X-ray absorptiometry, quantitative computed tomography, and quantitative ultrasound (27). These techniques vary by radiation exposure, accuracy, accessibility, cost, and type of information provided on bone mass, quality, or density(Table 1).

TABLE 1 Existing techniques to assess bone density and quality

Technique	Precision (%CV)	Advantages	Disadvantages
X-rays and radiographic absorptiometry	1%–2%	Inexpensive Equipment widely available Can provide a measure of bone age and additional diagnostic information	Limited ability to predict fractures Poor sensitivity for detecting bone loss or response to treatment
Dual X-ray absorptiometry	1%–2%	Measures both axial and appendicular bone density Low radiation exposure Can provide additional information on body composition	Not a true volumetric "density" (g/cm^2) Limited age-based normative data in pediatric populations
Quantitative computed tomography	1%–3%	Provides a three-dimensional measure of bone density (mg/cm^3) Can be performed on any clinical computed tomography scanner Distinguishes cortical from trabecular bone	Requires higher radiation exposure (50 μSv) Limited normative data
Quantitative ultrasound	0.1%–5%	No exposure to radiation Portable equipment Ease of use and low cost	Limited normative data in children Limited to axial skeleton Lack of standardization between instruments

Information on bone density can be obtained using X-rays but this technique is not particularly sensitive and approximately 30%–40% of bone must be lost before osteopenia can be visualized. Radiographic absorptiometry of the hand can provide a measure of bone density using a small aluminum wedge in the image field. Standardized hand radiographs also provide dimensions of the cortical thickness, cortical area, and percentage of cortical area, which can be diagnostic in assessing causes of bone resorption based on the pattern of bone loss (71). Some pediatric populations routinely get standard X-rays as part of their clinical management. For example, periodic chest X-rays are recommended for children with cystic fibrosis to evaluate lung function. In addition to a recommendation for lung function assessment, the recent Cystic Fibrosis Foundation Bone Health Consensus guidelines now encourage physicians to capture supplementary information on bone health by regularly evaluating these scans for osteopenia and previous rib fractures.

Single photon absorptiometry (SPA) or X-ray absorptiometry (SXA) measures the degree of attenuation of photons or low-dose X-rays as they are passed through the appendicular skeleton. Dual photon absorptiometry (DPA) or dual X-ray absorptiometry (DXA) has largely replaced SPA/SXA, and can assess bone mineral content and density at both the appendicular and axial skeleton. This technique is also capable of providing additional information on body composition. Total body exposures associated with DXA is less than or comparable to one day of exposure to natural background (27).

In chronically ill children several issues make interpretation of standard DXA measures difficult. First, typical measures of bone mineral density (BMD) provide a t-score, or standard deviation, from the mean expected at peak bone mass. This measure is not appropriate to utilize in children who have not yet achieved peak bone mass. Age-adjusted measures of BMD (z-scores) are primarily available in commercial DXA instruments for the lumbar spine. This site is not necessarily the most important in considering bone mineral status in children. Second, many chronically ill children experience delayed growth and are shorter and weigh less than their healthy peers. This makes it difficult to interpret the degree to which observed reductions in bone density are related to the smaller body weight and decreased height of the chronically ill child. Third, both SPA/SXA and DPA/DXA methods do not provide a true volumetric density. Equations have been applied to attempt to overcome this limitation by presenting data as areal BMD (45). An advantage to DXA is that this approach can be utilized to provide a measure of total body bone mineral content. Because 32.3% of bone mineral content is calcium (24), longitudinal total body DXA studies provide information on average daily Ca accretion or loss over a given interval. In pediatric populations this information can be assessed to address the relative gain in bone mass as children progress through puberty, but at present this is predominantly a research tool. Recently, several pediatric databases were made available via the Internet to assist clinicians and researchers in assessment of DXA data in relation to age, gender, ethnicity, and height.

Quantitative computed tomography (QCT) is an alternate method that provides a true volumetric density of trabecular or cortical bone (mg/cm^3) at axial or peripheral

sites (pQCT) (27). The ability to obtain additional information on bone structure may improve fracture risk predictions.

Quantitative ultrasound can assess the physical properties of bone by providing a measure of speed of sound and broadband ultrasound attenuation as sonogram pulses are transmitted through bone (usually the calcaneus or tibia). This method has advantages in that it requires no radiation exposure and can readily be brought to the bedside of critically ill infants and children. From these measures a calculated quantitative ultrasound index is obtained. The ability of this technique to predict risk of fracture in pediatric patients has not been well studied and at present there are no consistent guidelines for which to compare these measures to the World Health Organization's definitions of low bone mass.

For all of the measures mentioned, insufficient normative databases are currently available for children. In addition, while the techniques mentioned above provide an indication of bone density or quality, it remains difficult to relate these values to risk of fracture in this age group. Continuing development of new techniques and expansion of pediatric databases will further the noninvasive assessment of bone in pediatrics.

Calcium Balance

In a mass balance study, the net absorption of a nutrient is calculated by measuring the difference between mineral input from the diet and total fecal mineral output (52). The fecal output of mineral includes both unabsorbed dietary mineral and mineral which has been secreted into the intestine and not reabsorbed (usually referred to as endogenous fecal excretion). These two sources of mineral, which appear in the feces, cannot be distinguished by a mass balance study. Calcium absorption has also been estimated from the calciuric response to an oral Ca load. In this case, after a large oral Ca dose, one measures the rate at which Ca appears in the urine or changes in serum levels of ionized and total Ca or other bone mineral markers. This test may be useful for comparing some Ca sources, but cannot provide an accurate measure of dietary Ca absorption and is less preferable than tracer or mass balance methods (2).

Isotope Studies

Multiple techniques exist for using tracers to measure mineral absorption. In the single-isotope technique, a mineral isotope is given orally and then a complete fecal collection is carried out until virtually all the unabsorbed oral tracer is recovered. The absorbed fraction of administered tracer is calculated from the difference between the amount dosed orally and the amount recovered in the feces. A disadvantage of the use of this oral tracer approach is that extended fecal collections are required and the accuracy of the results depends on the completeness of the fecal collection.

We prefer to utilize a dual-tracer technique to measure Ca absorption. In this technique, one Ca isotope is given orally (typically with a meal) and a different

isotope is given intravenously. The orally administered isotopic tracer is absorbed into a central body pool, which for Ca is believed to represent serum, extracellular fluid, and some metabolically active bone (2). After administration of the tracers, a complete 24-hour urine collection is obtained. The relative fraction of the oral versus the IV tracer dose in this pool is determined and represents the fraction of the dietary calcium that was absorbed.

CAUSES OF ABNORMALITIES OF BONE MINERAL METABOLISM

Dietary Intake and Absorption

Low dietary intake of Ca and low levels of vitamin D intake have been implicated as a contributing factor to the development of low bone mass in both healthy children and those with chronic illnesses. Although the classic example of this is the development of vitamin D–dependent rickets from inadequate vitamin D intake or sunshine exposure, Ca-deficient rickets has been well documented in healthy children, especially those in Africa, and has recently been described in infants from the United States (22).

Dietary intakes of nutrients essential for bone can be particular problems for children with chronic illnesses. The intake of Ca is closely correlated to total energy intake (12), which suggests that disorders in which anorexia occurs may also lead to low Ca intake. This may be psychological, as in anorexia nervosa, or related to conditions that decrease appetite or diminish oral feeding ability. For example, infants with bronchopulmonary dysplasia (BPD) have decreased intake of food related to both reflux and to the high energy utilization associated with eating. It has been suggested that parents may decrease the amount of food they give these infants because of these issues. Singer et al. (73) reported that postdischarge, infants with BPD spent less time sucking and took in less formula per feeding than infants without BPD, whereas this difference was not observed in comparing other very-low-birth-weight infants with full-term infants. Of particular interest was their observation that symptoms of maternal depression or anxiety may have led to less prompting by some mothers of their infant to feed.

This problem may also occur in children with severe neurological problems, including those with severe cerebral palsy and congenital malformations or chromosomal disorders. Two recent studies have demonstrated both low energy and micronutrient intake in children with cerebral palsy, which may be related to the low bone mass that is frequently evident in these children (37, 77). In the study by Henderson et al. (37), increased feeding problems were significantly associated with both low femur and lumbar spine BMD. Calcium intake itself could not be correlated to low BMD, although only a small percentage of the children had very low Ca intakes. Interestingly, low 25-hydroxyvitamin-D values were not significantly related to low BMD values in this population, in spite of the finding of

low 25-hydroxyvitamin-D values in many of the children studied (37). Of course, other problems, including decreased mobility, also contribute to low bone mass in some of these conditions, but the role of adequate intake and potential feeding limitations in this group should not be disregarded.

The possibility of decreased absorption of Ca or vitamin D has been considered extensively in circumstances where there might be malabsorption, especially fat malabsorption. This can be related to genetic conditions such as cystic fibrosis or loss of part of the intestine from surgery or congenital malformations. Medications, such as prednisone, or conditions, such as anorexia nervosa, affect corticosteroid status and may lead to decreased Ca absorption (61). In general, a decreased rate of Ca absorption does not appear to be the principal factor leading to bone loss in most chronic illnesses in vitamin D–sufficient children.

Increased Excretion

Metabolic acidosis, as may occur in numerous chronic conditions, has been shown to stimulate bone resorption and increase urinary Ca excretion. This may play a role in bone loss in some chronic conditions in children. Idiopathic hypercalciuria is associated with bone demineralization in both adults and children. It can be difficult to accurately assess the level of acidosis in many chronic illnesses in children and its direct effect on bone mass. It is possible that intermittent acidosis will lead to bone loss in children with diabetes. Although this link has not been proven, some studies have found both low bone mass and increased urinary Ca in diabetic children (31).

Steroids

Steroids are widely used in pediatrics to care for children with a range of acute and chronic conditions. The effects of steroids on decreasing Ca absorption, increasing urinary Ca excretion, and decreasing bone formation have been described in detail elsewhere (46). One of the major areas of concern in recent years has been the widespread use of inhaled steroids in asthmatic children, and there is a growing concern of the long-term impact of inhaled steroids on other diseases such as cystic fibrosis. A review of this topic in adults indicated that bone turnover markers may be affected by high-dose inhaled steroids, but that the evidence for a significant effect on bone density and fractures are minimal (21). It is possible that a small negative effect on bone is counterbalanced by the overall improvement in exercise tolerance of those who use these agents (85).

In children, studies similarly have not demonstrated a significant inhibitory effect on bone mineralization for commonly prescribed inhaled corticosteroids. A recent study comparing two classes of these steroids found comparable rates of mineralization with two years of fluticasone propionate compared to nedocromil sodium (64). Although this study did not include a placebo control, the rates of mineralization achieved were very comparable to those found in healthy, nonsteroid-treated children. This finding is consistent with a recent cross-sectional study

showing no effect on BMD of budesonide in comparison to children with asthma who were not steroid treated (10).

Medications Other Than Steroids

Methotrexate has been extensively evaluated for its effects on bone metabolism. High doses have generally been shown to inhibit bone mineralization by inhibiting the actions of osteoblasts, but lower doses, such as typically used in children with juvenile arthritis (see below), have not generally been shown to have a substantial effect (15).

The effects of childhood malignancies and their therapy on bone mass have only recently been evaluated. A recent study of bone mass in survivors of childhood Hodgkin's disease showed significantly lower bone mass 11 years later (56). This effect was relatively small, was related to irradiation therapy, was more common in males, and was associated with reduced height. A recent review of studies primarily evaluating the long-term effect of acute lymphocytic leukemia on long-term bone mass found greater associations between bone mass and cranial irradiation for high-doses of steroids than with the disease itself or other medical therapy (6). At this time, the collection of more longitudinal data, especially on children who do not receive cranial irradiation, will assist in further defining these risks.

Anti-Retroviral and Protease Inhibitors

There are few data on the effects of HIV infection on bone mineralization in children but improvements in survival of children with this disease have increased research and attention on bone health in this group. Decreases in predicted total body bone mineral content and alterations in calcitropic hormones have been reported in children with perinatally acquired HIV-infection in comparison to normative values expected in age-, height-, and race-matched children (58). Recently, low osteocalcin levels were found in a group of vertically infected prepubertal children, although low bone mineralization was found only in those children with evidence of significant immune dysfunction (86). This is consistent with recent data in adults supporting a loss of bone mass associated with bone HIV infection and possibly with multidrug therapy for HIV (80).

Protease inhibitors may be protective against the loss of bone in HIV-infected adults (9). Significant alterations in markers of bone formation and resorption have also been reported in HIV-infected children receiving highly active antiretroviral therapy combined with a protease inhibitor (79). Given the variety of multidrug therapies available, further study is needed to identify the impact of variable drug combinations on bone acquisition in children with HIV infection.

Immobility

Bone responds to mechanical forces and the amount of weight that it must support, a response that has been termed the mechanostat theory (29). If the amount of

physical loading on bone becomes inadequate, bone resorption will exceed formation, and bone will be lost until a new steady state, sufficient to accommodate the amount of loading, is reached. The magnitude of this response can be significant; individuals who become immobilized because of a spinal cord injury lose approximately 40% of total body bone mass within the first year following the injury (49). Under extreme conditions of skeletal unloading, such as those experienced during the weightlessness of space flight, an average of 1.5% of bone mass is lost per month (74).

Less data are available on the relative impact of immobility on bone health in chronically ill children and it is often difficult to differentiate the relative impact of immobility on bone versus the other comorbid problems that may be associated with the cause or treatment of the immobility. However, one recent study unexpectedly found no significant differences in bone density (when corrected for bone volume) in 10 immobile or less-mobile children with cerebral palsy or myelomeningocele compared to 20 healthy ambulatory children (81). Further data are needed, however, relating chronic decreased mobility and peak bone mass.

Nutrition, Body Weight, and Bone Health

Body weight is a significant determinant of bone mass in both healthy children and in those with chronic diseases (23). To insure optimal bone health, growth and body weight should be closely monitored. Nutritional support and supplementary feeds should be utilized as necessary in children with delayed growth and insufficient weight gains. Failure to maintain body mass may also delay the onset of puberty and further increase the risk of deficits in the attainment of peak bone mass. Many children with chronic diseases experience delayed puberty (72), placing them at greater risk for inadequate attainment of peak bone mass. Optimal nutritional intakes assist in attainment of an adequate body weight and have the added benefit of improving the intake of additional nutrients (other than Ca and vitamin D) required for the mineralization and maintenance of bone, including phosphorus, vitamin K, protein, and trace elements such as copper and zinc.

Growth Factors, Cytokines, and Bone Mass

Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1, IL-6, and IL-11 can stimulate osteoclastic bone resorption and may inhibit osteoblast function (30, 48). Cytokine- and growth factor–mediated alterations at the systemic and local bone microenvironment may impact the balance of bone turnover and further compromise bone health. Increased inflammation and production of inflammatory cytokines have been associated with many pediatric illnesses, including cystic fibrosis (20), Crohn's disease (78), juvenile rheumatoid arthritis (69), and HIV infection (86). Increased cytokines, IL-6, IL-1, and TNF-α have been related to increased indirect markers of bone resorption in adults with cystic fibrosis (8, 40) and in HIV-infected adults (9).

Alterations in growth factors such as insulin-like growth factor-1 and vascular endothelial growth factor may also impact bone health in pediatric populations. Vascular endothelial growth factor can stimulate osteoclastic bone resorption (55). This growth factor has been found to be increased in cystic fibrosis patients with lung infections (53), in children with Crohn's disease (16), in patients with juvenile rheumatoid arthritis (47), and in pediatric heart transplant recipients (3).

SPECIFIC CONDITIONS

Juvenile Rheumatic Disorders

There are few if any conditions in which bone metabolism in childhood illnesses have been more studied than in juvenile rheumatic arthritis (JRA) and related conditions including dermatomyositis. It is generally accepted that osteoporosis is frequently found in children with these conditions and that both childhood fractures and low peak bone mass, which causes increased risk of eventual osteoporosis, are major issues in managing children with JRA and related conditions.

A large number of factors have been associated with this problem. The most important include the long-term use of systemic steroids and the persistence of high levels of inflammation. Clinically, it has been shown that disease activity and duration as well as Ca intake and weight-bearing physical activity all relate to low bone mass in children with JRA. These factors are interrelated and it can be difficult to sort out the relative contributions of each (43).

It was recently shown that a substantially larger proportion than expected of adults (mean age 35) diagnosed with JRA before the age of 26 years had osteopenia at the lumbar spine and/or femoral neck. Severity of childhood arthritis, smoking, and low Ca intake in adolescence were significantly correlated with low BMD in this population of adults (28).

As in other populations, there is new evidence that genetic factors may also be involved in bone loss in children with JRA. Polymorphisms of the vitamin D receptor as well as the calcitonin receptor have been linked to lower bone mass in children with arthritis (51).

The physiological changes leading to decreased bone mineralization in children with JRA have been evaluated in several studies. We were not able to identify abnormalities in Ca absorption except in children treated with steroids (61). In children with dermatomyositis, we found a marked effect of steroid treatment on decreasing bone formation and resorption (60). Using bone turnover markers, lowered rates of bone formation and bone resorption have been found in children with JRA. This finding of low rates of bone formation is relatively consistent in studies of children with JRA (62).

Cystic Fibrosis

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator and affects approximately 1 in 3200 white and 1 in 15,000

black live births in the United States (36). Compromised bone health in children with this disease may be related to malabsorption of fat-soluble vitamins and nutrients, alterations in gut permeability, inflammation, insufficient physical activity, hypogonadism, and glucocorticoid therapy.

Vitamin D insufficiency is frequently evident in children with cystic fibrosis despite the fact that most children receive daily supplementation with fat-soluble vitamins (59). Deficiency of vitamin K may adversely impact bone health by limiting vitamin K–dependent carboxylation of glutamyl residues on bone proteins, including osteocalcin. Vitamin K deficiency is common in unsupplemented children with cystic fibrosis (63), and higher than expected percentages of uncarboxylated osteocalcin have been reported in girls with this disease (68).

Several unique aspects of this disease may limit Ca retention and compromise bone mineralization. Children with cystic fibrosis are encouraged to ingest liberal sodium intakes to prevent heat injury or illness due to fluid imbalances (83). This may increase urinary Ca losses because dietary sodium is one of the strongest predictors of urinary Ca excretion in children (57). Although it is known that cystic fibrosis increases dermal sodium losses, the potential for dermal Ca losses to also be increased as a result of this disease has not been examined to date.

It has been believed that calcium absorption is compromised in children with cystic fibrosis based on indirect evidence (34). In adults, absorption of oral ^{45}Ca from a high Ca load did not significantly differ between adults with cystic fibrosis (studied in the presence of pancreatic enzymes) and age-matched controls, but was significantly lower when studied in cystic fibrosis patients in the absence of pancreatic enzymes (7). Recently, we carried out a Ca kinetic study to characterize Ca absorption, endogenous fecal Ca secretion and rates of bone Ca deposition, and resorption in clinically stable girls with cystic fibrosis (ages 7–18 years), who were taking pancreatic enzyme replacement if pancreatic insufficient (67, 68). We found that Ca absorption was comparable to normative data in girls using similar techniques. It was, however, significantly positively associated with percent fecal fat, which suggests that increased intestinal pathology may improve Ca absorption, perhaps through altered gut integrity. Although absorption appeared to be sufficient, 35% of this cohort had previously experienced a fracture and 47% had lumbar spine z-scores below –1 (68). Low bone mass in spite of adequate Ca absorption may be related to alterations in endogenous fecal Ca losses or an imbalance in the rates of bone Ca turnover.

Potential cystic fibrosis–related alterations in intestinal permeability, paracellular or transcellular flux, or elevated Ca loss in pancreatic or biliary secretions may limit net Ca availability. Intestinal permeability is known to be increased in patients with cystic fibrosis (35). We also observed increased endogenous fecal calcium (EFC) secretion in pancreatic-insufficient girls with cystic fibrosis (67). No significant relationship was found between EFC and fecal fat, which suggests that coprecipitation of EFC with luminal fats was not the primary cause of these increased losses. These losses were elevated in girls with increased use of

pancreatic enzymes and acid inhibitors, which suggests that increased disease severity and impaired absorptive pathways were related to increased EFC secretion (67).

Inflammatory Bowel Disease

Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis have been related to low bone mass in children with these diseases (41). These illnesses may compromise Ca and vitamin D retention. Intestinal inflammation, resections, and use of steroids for the treatment of flares may further compromise bone mineralization. Intestinal permeability is increased in individuals with Crohn's disease (38), and similar to cystic fibrosis, endogenous fecal Ca losses have been reported to be elevated in adults with Crohn's disease (54). To overcome the impact of altered gut integrity on dietary vitamin D absorption, triweekly use of tanning beds has been used as an effective means of improving vitamin D status in an adult with severe Crohn's disease (44).

Cholestasis

Recently, in adults, the use of ursodeoxycholic acid was shown to increase Ca absorption in adults with primary biliary cirrhosis. However, the increase left the subjects with an absorption fraction far below that of healthy controls (82). Of interest is that in a small study (five patients), abnormalities of Ca absorption were not shown in children with chronic cholestatic liver disease (17).

It is likely that the etiology of bone disease in children with chronic cholestasis is multifactorial. Treatment with vitamin D has not always been effective, and of interest is that adults with cholestasis have decreased bone formation. A small study using bone turnover markers in children demonstrated decreased bone formation as evidenced by decreased osteocalcin and normal resorption as evidenced by type I collagen telopeptide (42). These preliminary results suggest a problem associated with toxic effects limiting bone formation. It is likely that vitamin D deficiency remains a factor in cholestatic liver disease in children, but it may not be the only factor, and osteodystrophy may not readily respond to vitamin D supplementation.

Celiac Disease/Gluten Enteropathy

Celiac disease has a prevalence of up to 1% in Western populations and is caused by an immune response to antigens in wheat gluten (18). This disease causes chronic malabsorption and is associated with poor appetite, short stature, and pubertal delays (18). Many studies have documented compromised bone mass in children with this disease (14). Similar to pediatric diseases that impact gut integrity, reductions in bone mass are believed to be due to intestinal malabsorption of Ca and vitamin D and to the impact of other cytokine and disease-related changes on bone turnover (14). At present the standard therapy for this disease is elimination

of gluten-containing products from the diet. Studies in children have found that elimination of gluten from the diet leads to substantial improvements in bone mass (14). Dietary therapy does not appear to have as large an impact on bone mass in adults (14), which stresses the importance of diagnosis and implementation of dietary changes in children with this disease.

Chronic Renal Failure

Renal osteodystrophy is a well-known complication of chronic renal failure in both children and adults. Secondary hyperparathyroidism due to various factors including hyperphosphatemia and hypocalcemia are important causes. Because the kidney is responsible for the hydroxylation step needed to synthesize the active form of vitamin D (calcitriol), renal failure leads to compensatory hyperparathyroidism triggered by low levels of calcitriol. Renal osteodystrophy is often associated with osteomalacia and decreased rates of bone formation and turnover (65). Aluminum toxicity may contribute to bone disease, but this has been reduced by removing aluminum-binding compounds from the care of renal failure patients. A high-turnover bone lesion, called osteitis fibrosa, also occurs in renal failure patients, as can evidence of a mixed high- and low-turnover state. Low-turnover bone disease may be, in part, a result of therapy for osteitis fibrosa with calcitriol and calcium (39).

Therapy for renal osteodystrophy includes the use of both a low-phosphate diet and phosphate-binding agents. Calcium supplementation has been used for this purpose. In addition, either oral or intravenous calcitriol is helpful in reducing hyperparathyroidism.

Organ Transplantation

Since 1988, nearly 10,000 organ transplants have been performed in children under the age of 17 years in the United States, and 3% of the U.S. organ waiting list is comprised of children less than 17 years of age (5). Poor nutrition, insufficient physical activity, sex steroid deficiency, use of preoperative chemotherapy, and very-long-term exposure to glucocorticoids and immunosuppressive agents may compromise bone acquisition in these children. Growth is frequently compromised posttransplantation, with younger children (0–5 years) exhibiting the most rapid catch-up growth (26). Growth velocity appears to be improved posttransplant if maintenance deflazacort is used in place of methylprednisone (26). Deflazacort may have additional benefits: Significant reductions in bone loss have been reported in prepubertal, postkidney transplant children after one year of treatment with deflazacort compared to methylprednisone (25). Reductions in bone mass have also been reported in 7.3% of pediatric liver transplant patients ($n = 109$) when studied an average of 6.2 years posttransplantation. Previous history of rejection and higher cumulative prednisone exposures were associated with an increased risk of reduced bone mass in this group (32).

THERAPEUTIC INTERVENTIONS

Calcium and Vitamin D

As described previously, Ca and vitamin D insufficiency have been related in part to bone mineral insufficiency in both healthy children and those with chronic diseases. It is therefore reasonable to consider the role of supplementation in therapeutic interventions for these disorders. The impact of Ca and vitamin D supplementation in healthy adults and children has been extensively discussed and debated in the medical literature in recent years. In children and adolescents, numerous well-controlled trials have found a benefit to Ca supplementation on attainment of maximal peak bone mass, although the magnitude and duration of that benefit remain uncertain. This benefit is the basis for Ca dietary recommendations from the National Academy of Sciences and the American Academy of Pediatrics (75a, 11).

In general, except in cases of overt deficiency, there is little evidence that Ca and vitamin D supplementation at high levels are useful in most chronic illnesses. If vitamin D insufficiency is caused by malabsorption or abnormalities in the formation of calcitriol (1,25-dihydroxyvitamin D), then medical intervention with direct supplementation of calcitriol may be warranted. A routine recommendation for supplementation with this potentially toxic vitamin D compound is not advised pending further research demonstrating the criteria for its initiation, dosing, and withdrawal in any chronic illness.

Families may often ask about the role of Ca supplementation in children. Although it is likely that Ca intake from food is often less than recommended, at present there is no evidence that routine Ca supplementation above currently recommended intakes is of value in chronically ill children. It is reasonable to assess Ca intake and recommend a dietary or supplement-based approach to ensure intakes that reach the recommended value in all children, including those with most chronic illnesses.

Physical Activity and Bone Health

Exercise is a key factor in bone health. Exercise intervention studies in healthy children have found positive benefits on bone mass with Ca intake and genotype interacting to affect the impact of exercise on bone acquisition (49, 75). Adequate strain and mechanical force on bone may be particularly important in children during the growth period where activity may affect both bone strength and geometry (33).

Few data have addressed the impact of exercise training on bone mass in chronically ill children and additional constraints may be evident in children that have limited mobility due to joint pain, lung function, or disease severity. Previous pediatric exercise intervention studies have produced ground reaction forces of 8 times body weight. These forces are not likely to be appropriate for children with compromised bone mass, previous fractures, or constraints in physical

mobility. However, even moderate increases in physical therapy sessions were found to improve measures of bone mass in physically challenged children with cerebral palsy (19). Improvements in physical activity may also improve muscle function and muscle strength, which impacts bone health and fall prevention and may have other benefits on lung function in diseases like cystic fibrosis.

Medications

GROWTH HORMONE Growth hormone has been advocated in the treatment of many conditions, including the bone demineralization associated with chronic illnesses in children. A study of children with juvenile arthritis, including those being treated with steroids, showed an increase in bone mineralization with growth hormone therapy, although evidence for long-term benefit is not available (25).

The effect of growth hormone in girls with Turner's syndrome was assessed in a multicenter trial. Seven years of therapy led to significant increases in BMD standard deviation scores. At baseline BMD was essentially normal in the girls (66).

BISPHOSPHONATES Although, relative to adults, there is little information on the use of bisphosphonate therapy in children, an increasing number of reports and patient series have been reported over the last several years. Bisphosphonates are synthetic analogs of pyrophosphate in which the substitution of a carbon for oxygen in the phosphoanhydride bond allows the addition of side chains to the carbon. They have been used in pediatrics to treat osteogenesis imperfecta and various other congenital conditions leading to bone loss.

More recently they have been tried in children with juvenile rheumatoid arthritis, corticosteroid-induced bone loss, cerebral palsy, and other related conditions (70). A recent noncontrolled study demonstrated increased BMD of a variety of conditions—including Duchenne's muscular dystrophy, cystic fibrosis, and osteogenesis imperfecta—to once-every-three-month palmidronate infusions. Response was significantly greater in children not receiving systemic steroids than in those who received steroids (76). It has been recommended that these medications only be used under the guidance of specialists and that widespread use should be limited pending further clinical efficacy and safety studies (50, 84). However, it is clear that, to date, these medications have been used in a significant number of children with relatively few complications noted (13).

TNF-α BLOCKADE Several studies in patients with rheumatic disease have utilized drugs such as infliximab to block the action of anti-TNF-α. These agents are efficacious not only in improving the inflammation associated with these diseases but may have additional benefits on bone that have yet to be fully explored. Studies in adults with spondyloarthropathy have found significant increases in bone density following six months of treatment with anti-TNF-α (4).

SUMMARY

The importance of maintaining adequate calcium and bone mineral status is increasingly recognized in the long-term management of chronic pediatric diseases. Because the majority of bone mass is genetically determined, additional efforts should link disease-related genotypes with variation in bone mass. During this key period of growth it is also essential to minimize the use of medications that are known to limit attainment of peak bone mass. Because optimal nutrition plays a significant role in attainment of bone mass and is related to disease severity, pubertal progression, and clinical outcomes, nutritional support and attainment of optimal body weight should be emphasized. Exercise and weight-bearing activities should be advocated as tolerated in relation to existing bone mass and physical abilities. Continued advances in the medical management and nutritional support of children with chronic illnesses, and use of improved therapeutic options that limit bone loss, will assist in both acute and long-term bone health in this vulnerable age group.

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