

Osteoporosis in Pediatrics

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Objectives After completing this article, readers should be able to:

1. Identify determinants of bone mass.
2. Delineate pediatric populations at risk for osteoporosis.
3. Describe test procedures to measure parameters such as bone mineral density, bone formation, and bone resorption.
4. Describe methods to interpret pediatric DEXA scan results.
5. Identify measures to maximize peak bone mass in children and adolescents.
6. Identify osteoporosis treatments available for children and adolescents.

Definition

Bone consists of a collagen matrix into which calcium, in the form of hydroxyapatite, is deposited. The accumulation and maintenance of the substance of bone is the result of a continuous process of formation, predominately mediated by osteoblasts, and resorption, facilitated by osteoclasts. During childhood and adolescence, the process of formation predominates, leading to a net increase in bone mass and size. Infancy and adolescence are periods of particularly rapid formation. Peak bone mass is achieved shortly after completion of puberty and normally remains stable until the third decade of life, when age-related (involutional) bone loss begins.

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures. It is the most common metabolic bone disorder in adults. Approximately 13.8 billion dollars were spent in 1995 in the United States for treatment of osteoporotic fractures. Osteoporosis incidence increases with age; an estimated 30% to 40% of adults older than age 60 years have osteoporosis. Genetics, age, and menopause are important, relatively unchangeable determinants of osteoporosis risk in adulthood. However, other factors, such as chronic illness, nutrition, medications, and lifestyle, clearly modify the rapidity and severity of bone loss in aging adults.

Epidemiology

Osteoporosis generally has been considered an adult disease, but there is increasing evidence that its roots lie in childhood. The loss in bone mass begins in the third decade of life and involves a steady decline (about 1% annually) from the peak bone mass attained in early adulthood. Therefore, failure to achieve optimal peak bone mass represents a significant and preventable risk factor for osteoporosis in later years. Furthermore, osteoporosis that is symptomatic during childhood is emerging as a newly recognized problem among specific at-risk populations. Thus, it is becoming increasingly clear that childhood factors, such as diet, lifestyle, chronic illness, and medications, can have both an important short-term impact on bone health and a sustained effect on the achievement of peak bone mass, with the potential for long-term morbidity in adulthood.

Both intrinsic and extrinsic factors (Table 1) play roles in determining peak bone mass in an individual. Unmodifiable intrinsic factors, including genetic background, race, and gender, have a dominant role (75% to 80%). However, potentially modifiable extrinsic factors comprise a significant component of the variability in ultimate bone mass.

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Dr Zeitler has received a supply of drugs from Novartis Pharmaceuticals for a research protocol.

Table 1. Determinants of Bone Mass

Intrinsic Factors	Extrinsic Factors
<ul style="list-style-type: none"> • Gender • Family background • Ethnicity 	<ul style="list-style-type: none"> • Diet • Hormonal milieu • Illness

Intrinsic Factors

GENDER AND RACE. Important gender and racial differences exist in bone mineral density accretion. For example, males have higher bone mass at nearly all ages and at the time of peak bone mass achievement. The higher peak bone mass, in combination with larger bone size and slower decline in sex steroid levels, results in a lower incidence of osteoporotic fractures among aging men than women. Risk of osteoporosis and fracture also is lower among African-Americans, both male and female, because of higher peak bone mass relative to peers in other ethnic groups. Less is known about bone mineral density in other ethnic groups, but these data are emerging rapidly.

FAMILY HISTORY. There is also a familial component to bone mineral density in adults. For example, elderly women and men have an increased risk for osteoporosis when there is a history of other family members affected by osteoporosis. Similarly, premenopausal daughters of postmenopausal women who have osteoporosis have lower bone mineral densities than do daughters of postmenopausal women who do not have osteoporosis. However, attempts at identifying a specific genetic marker responsible for the familial determinant of peak bone mass have been unsuccessful. Suspect genetic candidates that have been evaluated include vitamin D receptor alleles, estrogen receptor alleles, insulin-like growth factor (IGF)-1 receptor alleles, and alleles involved in collagen synthesis.

Extrinsic Factors

CALCIUM AND VITAMIN D. Calcium and vitamin D play important roles in bone formation. Optimal calcium intake is necessary to maximize and maintain peak bone mass and to minimize bone loss during aging. Calcium requirements increase during periods of rapid growth, such as in infancy and adolescence. Furthermore, supplemental calcium intake has been shown to improve bone mineral density in both children and adults. In retrospective studies, adequate calcium intake during childhood

and adolescence was associated with a lower incidence of osteoporosis in postmenopausal women. Similarly, in a 3-year, prospective, pediatric study of twins, twins given 1,000 mg of calcium daily had significantly greater bone mineral density in the spine and radius compared with control twins.

Vitamin D is critical for normal calcium absorption from the diet. Although vitamin D in its inactive form can be synthesized endogenously from cholesterol metabolites in the presence of sunlight, dietary vitamin D serves as an important precursor for activation in most nontropical latitudes. A diet poor in vitamin D, the use of anticonvulsants that accelerate vitamin D catabolism, and low sunlight exposure all can lead to low levels of vitamin D and subsequent impairment of calcium absorption. The recommended daily allowance (RDA) for vitamin D is 400 IU/d. Treatment with larger amounts may be necessary in deficiency states.

The importance of adequate intake of calcium and vitamin D in maintaining bone health cannot be overemphasized. Numerous epidemiologic studies have indicated that the average dietary calcium intake is about 50% of the RDA in most adolescents (particularly in girls). Dietary sources should be the primary means for obtaining daily calcium, but calcium supplements or a combination of diet and supplements may be required to achieve adequate daily intake. Table 2 outlines the most recent guidelines from an American Academy of Pediatrics (AAP) policy statement about calcium intake, which are based on guidelines from the National Academy of Science. The major source of dietary calcium in most diets is milk or other dairy products. It should be emphasized that skim and reduced-fat milk or dairy products contain the same amount of calcium as milk and dairy products that have higher fat contents. Table 3 lists the calcium content in a few common foods.

BODY WEIGHT AND WEIGHT BEARING. A positive correlation between body weight, as reflected by body mass

Table 2. National Academy of Science Adequate Calcium Intake Guidelines

Age Group	Adequate Daily Calcium Intake
Birth to 6 mo	210 mg
6 to 12 mo	270 mg
1 to 3 y	500 mg
4 to 8 y	800 mg
9 to 18 y	1,300 mg

Table 3. Calcium Content in Some Commonly Eaten Foods

Food	Serving Portion	Calcium Content
Milk	1 c	300 mg
Cheddar cheese	1.5 oz	300 mg
Low-fat yogurt	8 oz	300 to 415 mg
Calcium-fortified orange juice	1 c	300 mg
Cooked broccoli	1/2 c	35 mg

index (BMI), and bone mineral density has been noted in adults and adolescents. For example, low body weight in menopausal women is an independent risk factor for fracture. Impact exercises that place weight-bearing forces on the skeleton, such as soccer or tennis, also have positive effects on bone size and mineralization. For example, in a study of twins, longer duration of weight-bearing activity was related to increases in femoral neck bone mineral density, indicating that moderate increases in physical activity are associated with moderate increases in skeletal mass.

OTHER RISK FACTORS. Smoking, in addition to its other attendant risks, has been associated with decreased bone mineral density in a prospectively studied adolescent population. Alcohol abuse, a factor not yet studied in adolescent populations, also has been cited as an osteoporosis risk factor in the elderly.

All the major hormones of the body, including growth hormone, thyroid hormone, parathyroid hormone, and sex steroids, have various effects on bone. Excesses or deficiencies in any of these hormones can lead to decreased bone mineral density.

Lastly, the overall health of an individual represents the most important modifiable osteoporosis risk factor. A number of chronic pediatric illnesses can result in impaired bone formation or increased bone resorption, leading to symptomatic osteoporosis. The negative effects of chronic illness on the bones may be magnified further by the impact of poor nutrition, decreased physical activity, and medications.

Pathogenesis

Osteoporosis in an otherwise healthy child or adolescent is extremely rare, although cases of idiopathic juvenile osteoporosis have been reported. Rather, pediatric osteoporosis is much more likely to be seen in the setting of chronic illness. This impact of illness and treatment is

being recognized increasingly as a significant contributor to the morbidity associated with survival of severe pediatric disease. Tables 4 and 5 and the next sections review some of the illnesses and treatments that place children and adolescents at risk for osteoporosis.

Osteogenesis Imperfecta

Osteogenesis imperfecta is an inherited disorder of collagen formation that leads to abnormal bone formation and rapid turnover. There are four different types, with severity ranging from lethal to relatively mild. The age at which low bone density and fractures appear varies, depending on the type. The “classic” physical finding of blue sclera is not seen consistently; therefore, a relatively high index of suspicion is needed to diagnose this condition in children sustaining frequent fractures with minimal trauma. Currently, the disorder usually is diagnosed by collagen analysis from a skin biopsy, although more exact genetic diagnosis is available.

Gastrointestinal (GI) Disease

GI diseases associated with low bone mineral density include inflammatory bowel disease, celiac disease, and cholestatic liver disease. The causes of osteoporosis in these diseases are probably multifactorial and include poor nutrition, calcium malabsorption, vitamin D deficiency, delayed puberty, glucocorticoid usage, and possibly direct inflammatory effects. Glucocorticoid usage is a particularly strong predictor of reduced bone mineral density in patients who have inflammatory bowel disease. In celiac disease and inflammatory bowel disease, osteoporosis appears to be related primarily to calcium and vitamin D malabsorption. Optimal management of these disorders improves bone mineral density, and adequate provision of nutrients is extremely important. In celiac disease, treatment with a strict gluten-free diet has resulted in normalization of bone mineral density. Malabsorption of calcium and vitamin D as well as impairment of vitamin D hydroxylation are factors related to the risk for osteoporosis in cholestatic liver disease.

Endocrine Disorders

Growth hormone plays an important role in the development and maintenance of bone mineral density through the action of locally produced IGF-1 on osteoblast function. Therefore, it is not surprising that growth hormone deficiency can affect bone metabolism negatively, and decreased bone mineral density is a feature of growth hormone deficiency in both children and adults. A recent study in growth hormone-deficient adults showed an 8% decrease in femoral neck bone mineral

Table 4. Illnesses Associated With Increased Osteoporosis Risk

Illnesses	Comments
• Celiac disease	• Malabsorption of calcium and vitamin D
• Inflammatory bowel disease	• Glucocorticoids in IBD
• Cholestatic liver disease	
• Solid organ and bone marrow transplants	• Glucocorticoid use • Immunosuppressive use
• Collagen–Vascular disease	• Glucocorticoid use
• Hypogonadism/Amenorrhea	• Secondary amenorrhea in elite female athletes
• Chronic renal disease	• Secondary hyperparathyroidism • Impaired vitamin D hydroxylation
• Growth hormone deficiency	
• Cushing syndrome	
• Spina bifida	• Lack of weight bearing
• Neuromuscular disorders	• Hypotonia
• Severe cerebral palsy	• Effect of anticonvulsants on vitamin D
• Cystic fibrosis	• Malabsorption of calcium and vitamin D • Glucocorticoid use
• “Steroid-dependent” asthma	• Chronic oral glucocorticoids • High doses of inhaled glucocorticoids
• Anorexia nervosa	• Malnutrition • Secondary amenorrhea
• Osteogenesis imperfecta	
• Hyperthyroidism	
• Hyperparathyroidism	

density relative to healthy matched controls. Similarly, bone mineral density at the spine and hip were significantly reduced in young adults who experienced childhood-onset growth hormone deficiency an average

of 7 years after discontinuation of previous growth hormone therapy compared with healthy controls, further demonstrating the positive effects of growth hormone on bone mass.

Long-standing hyperthyroidism, either from Grave disease or supraphysiologic dosages of thyroid hormone, can lead to osteoporosis by stimulating increased bone turnover. Hyperparathyroidism leads to increased osteoclast-mediated bone resorption. Although primary hyperparathyroidism is rare in children, secondary hyperparathyroidism is a well-recognized complication of renal disease and severe vitamin D deficiency. The osteoporosis associated with glucocorticoid excess is the result of increased bone resorption and impaired bone formation. Glucocorticoid excess due to therapy for an underlying disease is encountered much more commonly than Cushing syndrome or disease.

Estrogen has been shown to be important in increasing and maintaining bone mass in both women and men. Menarche and regular menses in females are strong predictors of increasing bone mass. In a 2-year study of late adolescent girls that quantified multiple factors into an estrogen exposure score, girls whose exposure scores were lower had significantly lower spinal bone mineral densities relative to their peers in the study. Estrogen deficiency leading to bone loss or lower bone mass is seen more commonly in females, but male hypogonadism should not be overlooked. Lower testosterone levels in men are associated with lower bone mineral density and an increased incidence of hip and spine fractures. Treatment of hypogonadal men has been shown to normalize bone mineral density rapidly and to maintain long-term normal bone mineral density.

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Table 5. Treatments Predisposing to Osteoporosis

Treatments	Comments
Irradiation	<ul style="list-style-type: none"> • Direct effects on bone • Pituitary hormone deficiencies from cranial irradiation
Chronic glucocorticoid use	<ul style="list-style-type: none"> • Definitely with oral use and possibly with high-dose inhaled steroids
Chemotherapy	<ul style="list-style-type: none"> • Methotrexate • Cyclosporin A • FK-506
Long-term anticonvulsant therapy	<ul style="list-style-type: none"> • Vitamin D deficiency

Respiratory Illnesses

Children who have cystic fibrosis now are living well into adulthood due to improvements in management. Unfortunately, the recognition of osteoporosis as a complication of cystic fibrosis is becoming more common as these patients reach adulthood. A number of factors are believed to be causal, including growth retardation, malabsorption with compromised nutrition, delayed puberty, and the effects of glucocorticoids used in treatment.

Systemic glucocorticoid therapy can be very beneficial in severe asthma, but systemic therapy also is associated with significant adverse effects, including osteoporosis. Inhaled glucocorticoid therapy can provide effective therapy of asthma with fewer adverse effects and has become a mainstay in the treatment of chronic asthma. However, recent data suggest that inhaled glucocorticoid therapy may have more negative effects than previously appreciated, such as adrenal suppression or reduction in bone mineral density. A study of children using inhaled glucocorticoids for at least 3 years recently demonstrated a negative association between the duration of inhaled steroid use and total body bone mineral density.

Malignancy and Organ Transplant

Osteoporosis, including the occurrence of pathologic fractures, is seen with increasing frequency in pediatric malignancies as survival rates improve. Factors such as aggressive chemotherapy, high-dose chronic glucocorticoid treatment, irradiation, poor nutrition, and decreased physical activity are postulated to affect bone mineral density adversely. In addition, the underlying illness may promote poor bone development; several studies have shown impaired bone formation with normal or increased bone resorption at the time of initial

diagnosis. The potential effect of childhood illness on long-term bone health is underscored by the finding of widespread osteoporosis in a study of long-term survivors of acute lymphocytic leukemia treatment who were mostly in their late 20s and had been diagnosed and treated during childhood. Finally, exposure to cranial irradiation has been shown to be a particularly important predictor of persistent low bone mass density.

Recipients of organ transplants are also at increased risk for osteoporosis, which has been reported in cases of renal, hepatic, cardiac, and bone marrow transplantation. Transplant patients share many of the same osteoporosis risk factors as patients who have malignancies, including poor nutrition, chemotherapy treatment (including glucocorticoids), and irradiation effects. Treatment with immunosuppressive agents represents an additional risk factor for this population.

Anorexia Nervosa

A variety of factors can lead to osteoporosis in anorexia nervosa. Malnutrition with a low BMI has been shown to impair bone formation directly and increase bone resorption. Amenorrhea resulting from undernutrition and excessive exercise leads to chronically low estrogen production, which further increases the osteoporosis risk. Most worrisome is the finding of persistently low bone mineral density in young adult women who have a history of long-term anorexia, despite establishment of regular menses and attainment of a normal BMI. This observation supports the concern that impairment of bone mineral accretion during the critical period of adolescence may have long-term consequences for bone health. The athletic triad is a condition in young women associated with osteoporosis. It is within the spectrum of anorexia nervosa and is comprised of amenorrhea, eating disorders, and osteoporosis.

Collagen-Vascular Diseases

The direct inflammatory effects of illness, as well as the use of glucocorticoids in treatment, play a role in osteoporosis associated with collagen-vascular disease. A study in 62 children who had juvenile rheumatoid arthritis showed decreased bone mineral density in 50% to 60% of the population, with a strong correlation between the loss of bone mineral density and disease duration.

Chronic Renal Disease

Impaired vitamin D hydroxylation and secondary hyperparathyroidism are well-recognized complications of chronic renal disease. Osteoporosis results from both impairment of bone formation due to a relative defi-

ciency of vitamin D and from increased bone resorption from secondary hyperparathyroidism.

Central Nervous System (CNS) and Neuromuscular Disease

A variety of factors place children in this heterogeneous group at risk for osteoporosis. As mentioned previously, mechanical stress forces (weight-bearing and impact exercises) increase bone size and mineralization. Impaired mobility, hypotonia, and decreased weight bearing are more likely to be encountered in CNS or neuromuscular diseases. These factors can diminish the important influence of mechanical stress forces on bone growth and mineralization. In addition, chronic anticonvulsant therapy used to treat a seizure disorder increases the risk of vitamin D deficiency.

Evaluation

A National Institutes of Health-sponsored panel of experts met in March 2000 to discuss issues of prevention, diagnosis, and therapy of osteoporosis. Some of the more important conclusions reached included:

1. Optimization of bone health is a process that must occur throughout life.
2. Certain risk factors exist in adults (many of the same risks cited in children) that increase the probability of osteoporosis.
3. Osteoporosis screening should be considered strongly in individuals who have one or more osteoporosis risk factors.

Radiographic Studies

Adult osteoporosis has been diagnosed on the basis of either radiologic or laboratory studies. Radiologic studies, in particular dual-energy x-ray absorptiometry (DEXA), appear to be superior to laboratory studies and have become the established diagnostic modalities. Mul-

tiple adult studies using DEXA to measure bone mineral density have shown correlation between decreased bone mineral density at specific bone regions (such as the hip or spine) and increased fracture risk in those bone regions.

DEXA technology measures the transmission of x-rays of two different photon energies through the body. The attenuation of these transmitted energies depends on the composition of the tissues through which the beam passes. A detector measures the energies passing out of the body, and computer-calculated values of bone mineral content and bone mineral density are reported. Table 6 summarizes some terms commonly seen on DEXA reports.

Although the availability of bone mineral density measurement by DEXA and pediatric software packages for various DEXA scanners has expanded rapidly in the pediatric population, results must be interpreted carefully. Interpretation of pediatric DEXA results has been hampered by several factors (Table 7). The lack of diagnostic criteria for osteoporosis in the pediatric population represents the greatest barrier to the clinical application of DEXA scans in pediatrics. Misdiagnosis of osteoporosis or the degree of osteoporosis may lead to increased anxiety and unnecessary treatments or unnecessary alterations in current treatments. Pediatricians should strongly consider contacting a pediatric specialist who has expertise in bone metabolism before ordering a DEXA scan and for assistance in interpretation.

Interpretation of DEXA data in pediatrics always must be relative to age-specific and gender-specific normal values (Z scores). T score values relate the reported bone mineral density to the peak bone mineral density attained for a person's gender and are not useful in pediatric patients. Furthermore, if old and new DEXA data are being compared, it is critical to verify that the same brand of DEXA machine was used in both readings. Bone

Table 6. Common Terms Seen in a DEXA Report

Term	Units	Comments
Bone mineral content	Grams of hydroxyapatite	A calculated calcium content of a specific bone region that is based on the attenuation of photon energy passing through that bone region
Bone mineral density	Grams of hydroxyapatite per cm ² of bone region	Bone mineral content per area for a specific bone region
T Score	—	A standard deviation score for a subject's bone mineral density relative to the peak bone mineral density attained for his or her gender. <i>Not useful in pediatrics</i>
Z Score	—	A standard deviation score for a subject's bone mineral density relative to age- and gender-matched controls

Table 7. Common Pitfalls in DEXA Interpretation

- Comparatively small numbers of reference range studies
- Predominance of Caucasian subjects used to generate normal reference ranges
- Differences between readings from the different brands of DEXA machines
- Lack of a definition of pediatric osteoporosis
- Effects of gender, race, height, and puberty on bone mineral density readings

mineral density values obtained by different machine brands cannot be compared directly. Lastly, short stature, delayed skeletal maturity, and delayed puberty can influence interpretation of DEXA scan results.

Calcium content (bone mineral content) for a specific bone region is calculated based on attenuation of x-rays passing through that bone region. Bone mineral density readings are reported in two-dimensional units of grams of hydroxyapatite per cm^2 area of a particular bone region. These readings are affected strongly by a person's height, with greater bone heights giving relatively larger bone area values. Therefore, a child who has short stature and smaller bone heights will have a downward skew in bone mineral density reading relative to a peer of average height. Similarly, a child who has significantly delayed skeletal maturation or puberty (as reflected by a delayed bone age) likely will have a bone mineral density reading more appropriate for his or her skeletal maturation than for chronologic age.

Several studies have proposed approaches to address the biasing influences of short stature, delayed skeletal maturity, and delayed puberty on DEXA readings. For example, analysis of bone mineral density relative to "height age" (the age at which the child's height would be at the 50th percentile) has been proposed to mitigate the effects of short stature on bone mineral density readings. Alternatively, calculation of a three-dimensional volumetric bone mineral density value (grams of hydroxyapatite per cm^3 of a particular bone region) by using a mathematical model has been proposed to correct for short stature bias. Mathematically calculated volumetric bone mineral density readings correlate well with actual three-dimensional bone mineral density readings obtained by quantitative computed tomography. Lastly, analysis of bone mineral density readings relative to the gender-specific normals for the patient's bone age

rather than chronologic age may correct for the biases of delayed skeletal maturation or delayed puberty.

Laboratory Studies

Laboratory measures of bone metabolism markers in serum or urine, believed to reflect the activity of either osteoblasts or osteoclasts, have been studied in adults as a means of screening for osteoporosis and monitoring osteoporosis treatment. Adult studies have shown that the accuracy of these markers for osteoporosis diagnosis and monitoring is inferior to bone mineral density measurements. Bone metabolism markers also can be measured in the pediatric population, but the accuracy concerns noted in adult studies as well as other problems hamper their widespread use. Many of the markers have diurnal variation, and all are influenced strongly by puberty. Furthermore, there are no pediatric reference ranges for many of the newer markers. Measurement of these markers in conjunction with clinical evaluation and radiologic findings may aid in the initial investigation of pediatric osteoporosis and possibly assist in monitoring therapy. Due to their multiple limitations in pediatrics, bone metabolism markers should not be relied on exclusively to make important clinical decisions. Measurement of several indices at once, as well as serial measurements, may help to overcome some of these limitations. Table 8 summarizes several laboratory assays for bone metabolism markers.

Management Prevention

One of the goals of routine health supervision visits is anticipatory guidance regarding healthy lifestyle habits. Components of healthy lifestyle habits include regular physical activity, a healthy diet, and in the adolescent years, avoidance of smoking and other tobacco products. The AAP has created specific policy statements outlining recommendations to achieve each of these goals. Promotion of these healthy lifestyle habits during a health supervision visit also may decrease the risk of future osteoporosis.

The general pediatrician may be relegated to a minor role in the care of a chronically ill child. However, complications arising from a disease or its treatment may be overlooked, especially when the child is receiving care from multiple subspecialists. By maintaining regular contact with the family and remaining informed of current treatment, the general pediatrician may be in the best position to perceive the "big picture" of potential risks of chronic illness and therapy, including the risk of osteoporosis. The promotion of a healthy lifestyle within

Table 8. Bone Metabolism Markers

Marker	Location	Notes
Bone Formation		
Alkaline phosphatase	Serum	Most widely used test; 80% of activity is derived from bone
Bone-specific alkaline phosphatase	Serum	Assay not widely available
Osteocalcin	Serum	Product of osteoblast function; specificity of test reportedly is good
Procollagen type I carboxyterminal propeptide	Serum	Cleavage product from formation of type I collagen; other sources of type I collagen besides bone hamper test specificity
Procollagen type I amino terminal propeptide	Serum	Cleavage product from formation of type I collagen; other sources of type I collagen besides bone hamper test specificity
Bone Resorption		
Tartrate-resistant acid phosphatase	Serum	Produced by osteoclasts; assay not widely available; data on normal values are scarce
Hydroxyproline	Urine	Amino acid component of collagen; wide variation in day-to-day values as well as effects from dietary sources hamper specificity
Pyridinoline/Deoxypyridinoline	Urine	Cross-linking peptides within collagen; specificity reported to be good
Collagen type I cross-linked C-telopeptide	Serum	A fragment from cross-linking peptides within collagen; assay not widely available, and data on normal values scarce.
Collagen type I cross-linked N-telopeptide	Urine	A fragment from cross-linking peptides within collagen; values strongly affected by puberty; specificity reported to be good.

limitations imposed by the chronic illness may be particularly important in preventing avoidable long-term problems in at-risk populations. The prevention of osteoporosis is an excellent example of this principle.

Diagnosis

Subsequent to the experience in adults, DEXA rapidly is becoming an established modality for the measurement of bone mineral density in children and adolescents. As with adults, screening of children or adolescents who have one or more osteoporosis risk factors should be considered strongly, particularly in the setting of fractures associated with minimal trauma. In addition, a report of osteopenia on plain film radiographs in an individual who has one or more osteoporosis risk factors should be followed up with a quantitative measurement of bone mineral density by DEXA.

Treatment

After critical examination of data in an individual at risk for osteoporosis, including physical examination, DEXA scan readings corrected for statural or pubertal variation, and any additional studies, the clinician must decide whether and how to treat low bone mineral density.

Three major limitations affect such decisions. First, there is no standard definition for osteoporosis in the pediatric age group. Second, there is no consensus on the degree of bone mineral deficit that places children or adolescents at risk for fractures. Third, there are no large, well-controlled studies to assess the efficacy and safety of potential osteoporosis treatments in children and adolescents.

Review of the relatively small amount of literature (prospective studies and case reports) published on the treatment of pediatric osteoporosis provides some perspective about the criteria considered diagnostic for osteoporosis, as well as a sense of the severity of bone mineral deficit present in at-risk populations. The majority of patients reported in these articles had bone mineral density Z scores below -2 (range, -2 to -5.5) and had a history of one or more fractures. Based on these data, treatment should be strongly considered in children and adolescents who have severely low bone mineral density (Z scores below -2), especially in the setting of fractures with minimal trauma.

There is little debate over the likely benefits and minimal risks associated with some treatments. In less severe cases, interventions such as ensuring adequate

calcium and vitamin D intake, optimizing general nutrition, and promoting weight-bearing physical activity within the limits of the patient's illness will provide benefit with minimal risk. Similarly, replacement of estrogen, testosterone, or growth hormone in proven deficiency is appropriate and widely supported. Serum calcium and urinary calcium excretion normalized to creatinine should be monitored regularly in individuals receiving supplemental calcium and vitamin D to help avoid the pitfall of nephrocalcinosis from overtreatment.

Antiresorptive agents slow bone resorption while allowing bone formation to continue, theoretically leading to a net gain in bone mass. Although the efficacy and safety of the two most common types of antiresorptive agents, the bisphosphonates and calcitonin, have been established in large, well-controlled adult treatment studies, these agents have not been used in large numbers of children or adolescents. Consequently, there are no large, well-controlled studies to assess their efficacy and safety. However, cautious and thoughtful use of these agents should be considered in children or adolescents whose bone mineral density is severely low or who have failed to improve after receiving more conventional treatment or who have suffered multiple fractures.

Bisphosphonates are taken up rapidly by the bone, where they prevent bone mineral hydrolysis and exert direct inhibitory effects on osteoclast activity. They are available in oral and intravenous forms and have been used in a variety of adult conditions, including Paget disease, postmenopausal osteoporosis, fibrous dysplasia, glucocorticoid-induced osteoporosis, and hypercalcemia of malignancy. Gastrointestinal upset and the consequent need for relatively complicated oral dosing regimens are the biggest obstacles to oral bisphosphonate therapy.

Most clinicians have been extremely reluctant to use bisphosphonate treatment in children because of theoretical concerns about negative effects on growth, based on animal studies showing inhibition of bone calcification by some of the first generation of bisphosphonates. Bisphosphonate treatment has been used successfully in small numbers of pediatric patients for a variety of conditions, including fibrous dysplasia, hypercalcemia of malignancy, and miscellaneous forms of severe osteoporosis. The largest and most successful use of bisphosphonates to date has been in children who had osteogenesis imperfecta, very low bone mineral density, and fractures, who were treated for 1 year with intravenous bisphosphonate. Treatment resulted in significantly fewer frac-

tures, improved mobility, and improved growth. A number of additional controlled trials of bisphosphonates in pediatric osteoporosis are underway.

Calcitonin is produced by C cells in the thyroid gland and acts in opposition to parathyroid hormone. It has been approved for use in postmenopausal women unable to take estrogen replacement and is available in nasal spray. However, its efficacy in adult studies has been no better than that of bisphosphonates, and waning effectiveness (tachyphylaxis) may be seen with prolonged use. Successful osteoporosis treatment with calcitonin has been reported in small numbers of children who had thalassemia and renal disease.

Summary

The morbidity and mortality from adult osteoporosis continues to grow as the United States population ages and lives longer. Although the condition manifests many years later, the roots of osteoporosis begin in childhood and adolescence. The efforts of pediatricians to promote healthy life choices—sensible diet, regular exercise, and avoidance of tobacco—may help to decrease the prevalence of osteoporosis when the current generation of children reaches old age. Furthermore, the recognition of childhood osteoporosis as a consequence of chronic illness and its treatment can help pediatricians screen for this condition, institute preventive measures, and refer for appropriate treatments when necessary.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

9. Which of the following statements regarding bone mass in children is *true*?
 - A. African-Americans have a higher risk of osteoporosis than Caucasians because of lower bone mass.
 - B. Extrinsic factors, such as diet and chronic illness, are the primary determinants of a child's bone mass.
 - C. Increased calcium intake has not been proven to improve peak bone mass.
 - D. Males have a higher bone mass than females.
 - E. Peak bone mass is not achieved until early adulthood.

10. Which of the following has been shown to improve bone mass and decrease the risk of osteoporosis?
 - A. Limited sun exposure.
 - B. Smoking cigarettes.
 - C. Use of corticosteroids.
 - D. Use of whole milk rather than low-fat milk.
 - E. Weight-bearing exercises.

11. You are the pediatrician for a child who has cerebral palsy and epilepsy. You recognize that this child is at risk for osteoporosis, and you order a DEXA scan to make the diagnosis. Which of the following statements regarding DEXA scans in children is *true*?
 - A. Criteria for diagnosing osteoporosis in children have been well established.
 - B. Data must be interpreted relative to a child's age and gender.
 - C. Delayed puberty has no effect on DEXA results.
 - D. Results are easy for the pediatrician to analyze.
 - E. The information obtained is less useful than laboratory markers such as osteocalcin and alkaline phosphatase.

12. You are caring for an adolescent who has a history of chronic steroid use for systemic lupus erythematosus, and her radiographs show evidence of osteopenia. Findings from a DEXA scan are consistent with osteoporosis. You want to help her prevent fractures. Which of the following statements regarding treatment of osteoporosis in adolescents is *true*?
 - A. Bisphosphonates may help prevent bone resorption but have gastrointestinal side effects.
 - B. Calcitonin has been proven effective in preventing fractures in children who have osteoporosis.
 - C. Increasing intake of calcium and vitamin D has not been shown to be beneficial.
 - D. The patient is not at increased risk for fractures if her osteoporosis is mild.
 - E. Weight-bearing activities should be discouraged.