Pediatric and adolescent care professionals have increasingly recognized the importance of understanding the skeletal health of their patients. Peak bone mass, the “bone bank” on which an individual will draw for their entire adult life, is likely achieved by late adolescence, with the critical window for accumulation occurring much earlier. This review outlines the known conditions that are associated with impaired bone mineral accrual and clinical settings in which the evaluation of “at-risk” adolescents should be considered. We describe the methods available to the health care professional for evaluating bone density, along with the limitations of each technology. Potential therapeutic options for patients identified to have a low bone mineral density are discussed. Finally, current recommendations regarding physical activity and nutrition, beneficial interventions for all adolescents, are presented.

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sity (BMD). Recent studies have demonstrated that overweight children have an increased incidence of fractures, suggesting a deleterious effect of excess adiposity on skeletal development and resilience. At the other end of the spectrum, illnesses that are characterized by weight loss, such as anorexia nervosa, illustrate the detrimental effect of malnutrition on bone density in teenagers. Questions have arisen regarding the applicability of findings from such studies of malnourished youth with chronic disease to the bone health of well adolescents. In particular, the skeletal effects of calcium and vitamin D in all children and adolescents is an issue that has received attention in many recent reports, including a position statement by the American Academy of Pediatrics.16,24-30

The effect of calcium intake during adolescence is one of the most intensely studied areas of pediatric bone health. Calcium is needed for normal mineralization of the bone and cartilage matrix. Once calcium intake is adequate to prevent rickets (disordered organization of the cartilage matrix) or osteomalacia (defective bone mineralization), provision of additional calcium may increase bone density by affecting bone turnover and the size of the remodeling space. Controversy arises because some, but not all, studies of calcium intake and measures of bone health show a positive relationship. However, because adolescence is the most critical period for bone mineral accrual, experts currently advocate for the provision of optimal calcium intake to maximize peak bone mass. These recommendations are driven by the fact that calcium absorption is known to be enhanced during puberty, with an optimal calcium balance achieved at an intake of approximately 1300 mg/d. Few data are available regarding the appropriate intake level for racial groups other than white adolescents. One study showed that compared with white adolescent girls, black teenagers exhibit more efficient calcium absorption and may achieve the same PBM with less calcium intake. Because of the potential skeletal benefits of calcium, it is concerning that the majority of adolescents fail to achieve the recommended daily intake.

Several research papers and policy statements have also examined the role of vitamin D, which is needed for efficient bodily absorption of calcium, on the bone health of children and adolescents. Vitamin D deficiency has been linked to fracture and a low bone mass in elderly men and women. Recent research has documented vitamin D deficiency to be a common problem among otherwise healthy young patients, including adolescents, but have not definitively correlated this deficiency with decreased bone density in youth, often because of the lack of BMD measurements in some studies.

### Hormonal Status

A number of hormones affect bone formation and remodeling. Endogenous circulating estrogens and androgens exert independently positive effects on bone growth, development, and mineral acquisition among both male and female adolescents. Patients with hormonal deficiencies or receptor abnormalities demonstrate lower than expected BMD. Similarly, growth hormone deficiency negatively impacts bone size and mass. Other endocrinopathies (Figure 2) affect the bone remodeling cycle by influencing osteoclasts and osteoblasts directly (eg, thyroid or parathyroid hormone, cortisol) or indirectly via their effects on the sex steroids (eg, hyperprolactinemia, hypopituitarism). Finally, ongoing studies are investigating the role of leptin as a primary or secondary messenger that modulates bone remodeling.

### General Health and Genetics

In addition to exercise, proper nutrition, and maintaining a normal hormonal milieu, avoidance of excessive al-
cohab and any tobacco use is beneficial to bone health. The vast majority, between 60% and 80%, of the variance in BMD can be attributed to inherited and, likely, polygenic factors, including putative, but unproven, receptor polymorphisms for vitamin D, estrogen, type I collagen, insulin-like growth factor I, transforming growth factor-β, and IL-6.

WHICH PATIENTS ARE AT RISK FOR POOR SKELETAL HEALTH?

Important conditions that are currently believed to place adolescents at risk for poor skeletal health—other than intrinsic bone diseases such as osteogenesis imperfecta—are listed in Figure 2. Some diseases (such as cystic fibrosis and inflammatory bowel disease) are associated with increased secretion of proinflammatory cytokines such as IL-1β, tumor necrosis factor α, and IL-6 that may directly inflict harm to the skeleton by increasing bone resorption. Many of these illnesses also require use of medications with deleterious skeletal effects (Figure 2). Finally, any condition that negatively affects the factors described previously (Figure 1) could impair bone mineral accrual.

Although the concept of “athletic amenorrhea” and its detrimental skeletal effects had been described earlier, it was not until 1992 that the term female athlete triad was coined (definition in Figure 2). Estimates of the prevalence of the triad have varied dramatically depending on the population studied; it may remain elusive until, as some experts have recommended, the skeletal component “osteoporosis” is redefined to allow for a more meaningful assessment in young athletes. While the earlier term implicated the stress of exercise to be the cause of menstrual irregularity and a consequent hypoestrogenic state, more recent work has demonstrated that even subtle imbalances between caloric intake and energy expenditure alter luteinizing hormone pulsatility and amplitude, triggering the cascade that results in luteal phase defects or frank hypothalamic amenorrhea. Those who exhibit the female athlete triad may be at increased risk for stress fracture, but it is yet to be determined if this injury is a sentinel event for low BMD, warranting further evaluation.

HOW TO EVALUATE SKELETAL STATUS

Measures of BMD

Bone mineral density has been the most commonly used outcome measure to address skeletal status because bone mass predicts 80% to 90% of its strength in vitro, which translates into a high predictive value for osteoporotic fractures in postmenopausal women. Among children and adolescents, the association is not as strong, although the majority of case-control studies of healthy children suggest that the BMD z score (number of standard deviations higher or lower than the mean of peers matched for age, sex, and ethnicity) is predictive of fractures of the distal forearm (the most common fracture site during the pubertal growth spurt), with each standard deviation decrease from the mean significantly associated with an increased risk. The relationship is less clear among children and adolescents with chronic illness.

Dual-Energy X-ray Absorptiometry (DXA)

Dual-energy x-ray absorptiometry (DXA) is the current standard for assessing BMD in children and adolescents. The scans are relatively rapid to perform and involve low radiation exposure. Because of their use in screening postmenopausal women, DXA scanners are often geographically accessible to pediatric professionals and demonstrate high precision. Pediatric software algorithms and reference data are increasingly available, allowing for BMD evaluations in young patients from early childhood up through adolescence. Using x-ray beams at 2 photon energies to differentiate soft tissue from bone, DXA can measure bone mineral content (in grams) and areal BMD—a 2-dimensional measurement of bone mineral per unit of area (grams divided by centimeters squared)—and estimate total body lean vs fat mass.

There are several caveats that arise as DXA is used in adolescents. A pediatric normative database must be used to interpret properly the measurement for either bone mineral content or BMD. The normative data must have been generated on a similar instrument and should account for sex and ethnicity, as each can influence bone mass. Since the z score is based on chronologic age, “correcting” the BMD for an adolescent with a delayed bone age (interpreting for that age) can be a helpful maneuver to avoid the overestimation of skeletal deficits. Even with appropriately matched databases and age adjustment, DXA does not adequately account for the influence of bone shape and size on its measurements. In essence, DXA estimates bone mineral content by measuring the “shadow” cast by bone within a fan-shaped x-ray beam. This shadow is influenced not only by the composition of the bone, but its depth, which is not measured, and the distance of the bone from the beam. Attempts to correct for these limitations include obtaining 2 orthogonal scans (ie, anteroposterior and lateral), mathematical formulas to estimate volumetric BMD (eg, bone mineral apparent density), and more advanced regression models of bone that have been adopted uniformly. The bones of an adolescent are also changing continuously because of growth, which only further complicates the BMD interpretation.

In recognition of these challenges, a 2004 position statement of the International Society for Clinical Densitometry issued guidance for the use of DXA in the diagnosis of osteoporosis in children (Table 1). Perhaps the most pertinent recommendation was that T scores, which compare bone density to PBM (assumed to occur between ages 20-29 years) and which are the basis of the World Health Organization definition of postmenopausal osteoporosis, should not appear in DXA reports for children and adolescents. Therefore, the diagnosis of osteoporosis in children requires evidence of skeletal fragility; it should not be made based on DXA measurements alone.

Quantitative Computed Tomography

The current “gold standard” for noninvasive bone evaluation is quantitative computed tomography (QCT), which can evaluate bone in 3 dimensions, thereby providing a
direct measure of “true” volumetric BMD (in grams per centimeters cubed).71 Differentiating cortical from trabecular bone, QCT can also precisely track the pubertal changes in bone size and shape that occur during adolescence.72 Performed on standard computed tomography scanners, QCT requires specific software algorithms that are not widely available, in part because of cost. The greatest drawback to QCT is its moderately high radiation dose. As a consequence, normative pediatric data are sparse, with their use reserved predominantly for research. Peripheral QCT, which only evaluates BMD of the extremities, uses much lower radiation doses than those associated with axial QCT but is hindered by the same factors.73

Ultrasound

Quantitative ultrasound is attractive in that it involves no radiation exposure, is portable, and potentially allows for inexpensive, office-based bone health screening.74 Unfortunately, not all quantitative ultrasound devices are appropriately sized for use in children and younger adolescents, and most devices do not have adequate normative pediatric databases.75 Furthermore, correlation with BMD as measured by DXA or QCT has been inconsistent. Further research is needed to determine if this technique captures intrinsic qualities of bone (eg, elasticity, trabecular separation) that are not detected by other modalities but still may affect fracture risk.76,77

Assessment of Bone Strength

One of the most clinically relevant properties of bone is its strength, which is dependent not only on bone mass, but size, geometry, and microarchitecture. Quantitative computed tomography is able to measure all of these parameters and is capable of generating numeric estimates of bone strength.78 Magnetic resonance imaging is also being investigated as a radiation-free modality to evaluate both bone geometry and quality,79 and there are mathematical models that use DXA data to estimate bone strength at the hip (ie, hip structural analysis).80

Measurement of Bone Turnover

Serum and urinary markers of bone turnover are sensitive to changes in bone formation and resorption. They are increasingly available for clinical use in reference laboratories, but normal growth and development during adolescence increase the variability in these measures such that their use should be restricted to monitoring treatment effects, not diagnosis.17 Common measures of calcium homeostasis such as serum calcium, magnesium, phosphorus, 25-hydroxyvitamin D, parathyroid hormone, and urinary spot calcium-creatinine ratio do not directly reflect bone turnover. They may be useful, however, when evaluating low BMD, but only to complement thorough medical, menstrual, and family histories; a complete review of systems; and a directed objective examination, including body mass index calculation and Tanner staging. Finally, bone biopsy to obtain computer-assisted histomorphometric information may rarely be

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Table 1. Guidance on Dual-Energy X-ray Absorptiometry Interpretation in Children and Adolescents Younger Than 20 Years*

<table>
<thead>
<tr>
<th>Class</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Z score ≤ -2.0</td>
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<tr>
<td>2</td>
<td>Z score -2.0 &gt; -2.0</td>
</tr>
<tr>
<td>3</td>
<td>Z score ≤ -2.0</td>
</tr>
<tr>
<td>4</td>
<td>Z score -2.0 &gt; -2.0</td>
</tr>
</tbody>
</table>

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; PBM, peak bone mass.

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When should one consider a bone density measurement?

At the present time, no evidence-based clinical guidelines exist to help health care professionals determine when BMD screening is warranted, although a number of groups have published recommendations. The Cystic Fibrosis Foundation recently published an official position regarding bone health18 including an assessment and treatment protocol with baseline DXA scans obtained as young as 8 years. The British Paediatric and Adolescent Bone Group has also published guidelines for bone density screening and treatment in adolescents who they consider to be at risk, including those who have sustained recurrent fractures or a low-impact fracture, back pain, spinal deformity, loss of height, or a change in mobility or nutrition.73 The varied recommendations of these and other groups reflect the fundamental uncertainty over what constitutes a “fracture threshold” for children and adolescents at this time. Our clinical practice is to consider DXA scanning for an adolescent who has an underlying chronic condition that predisposes to a low BMD (Figure 2), with the presence of multiple risk factors or a strong family history of osteoporosis lowering our threshold for evaluation.

An example of the complexity of the decisions facing health care professionals regarding appropriate BMD screening practices is the debate stimulated by the recent Food and Drug Administration decision to issue a “black box” warning label on depot medroxyprogesterone acetate because of bone loss attributable to this agent.81,82 There is some evidence to suggest that adoles-
There are few skeletal agents (medications designed to augment BMD by either inhibiting bone resorption and/or increasing bone formation) available for potential use in adolescents. The unknown effects of some of these medications on a growing skeleton and the disappointing efficacy of others has hindered their use by pediatric professionals. Bisphosphonates are prescribed commonly to adults for postmenopausal and glucocorticoid-induced osteoporosis and offer a life-changing therapy for children with osteogenesis imperfecta and low bone mass and fractures secondary to cerebral palsy. With the exception of recent information on oral alendronate use, there is little experience with agents other than recent information on oral alendronate so-called girls with anorexia nervosa or hypothalamic amenorrhea is yet another area of both controversy and active investigation. Several reports have documented no significant change in BMD in this group after estrogen therapy, often provided in the form of an oral contraceptive. Some subgroups of patients may be protected from bone loss with this therapy, especially young women with an extremely low body mass index (<70% of ideal body weight). The balance of data from several research studies suggests that the lack of efficacy of estrogen therapy in this population is because the observed bone loss may be attributable to other abnormalities beyond that of estrogen deficiency. Recent studies have explored the roles of insulin-like growth factor 1, alone or in concert with an oral contraceptive, and androgen therapy (dehydroepiandrosterone and transdermal testosterone).

**USE OF SKELETAL AGENTS IN ADOLESCENTS**

There are few skeletal agents (medications designed to augment BMD by either inhibiting bone resorption and/or increasing bone formation) available for potential use in adolescents. The unknown effects of some of these medications on a growing skeleton and the disappointing efficacy of others has hindered their use by pediatric professionals. Bisphosphonates are prescribed commonly to adults for postmenopausal and glucocorticoid-induced osteoporosis and offer a life-changing therapy for children with osteogenesis imperfecta and low bone mass and fractures secondary to cerebral palsy. With the exception of recent information on oral alendronate use, there is little experience with agents other than intravenous pamidronate for these diagnoses. Nonetheless, the apparent positive tolerability of bisphosphonates in these populations, there is interest in expanding their use to indications for which efficacy is currently unknown. For example, alendronate sodium and risedronate sodium have been investigated in small studies of adolescents and young women with anorexia nervosa. Information is lacking on the long-term (>10 years) adverse effects of these agents, optimal duration of treatment, or appropriate maximal dose. Because it is known that bisphosphonates remain in the skeleton for several years, perhaps indefinitely, and that they cross the placenta, health care professionals should proceed with caution until more definitive safety and efficacy data are available.

The role of estrogen and/or progesterin therapy in adolescent girls with anorexia nervosa or hypothalamic amenorrhea is yet another area of both controversy and active investigation. Several reports have documented no significant change in BMD in this group after estrogen therapy, often provided in the form of an oral contraceptive. Some subgroups of patients may be protected from bone loss with this therapy, especially young women with an extremely low body mass index (<70% of ideal body weight). The balance of data from several research studies suggests that the lack of efficacy of estrogen therapy in this population is because the observed bone loss may be attributable to other abnormalities beyond that of estrogen deficiency. Recent studies have explored the roles of insulin-like growth factor 1, alone or in concert with an oral contraceptive, and androgen therapy (dehydroepiandrosterone and transdermal testosterone).

**POTENTIALLY BENEFICIAL INTERVENTIONS FOR ALL ADOLESCENTS**

**Physical Activity**

If physical activity is to be prescribed for bone mineral accrual, the questions to be answered include "how" and "when"? suggest that the benefits of exercise may be most pronounced in premenarchal girls experiencing their peak height velocity and boys in comparably early puberty, or ages 10 to 12 years in girls and 12 to 14 years in boys, on average. call for further research to clarify this "critical window" for bone accretion, as well as to determine whether benefits persist into adulthood. Another important area of inquiry in this field includes the interaction between physical activity and hormonal status, particularly the effect of estrogen status on bone mass in young women. Finally, the optimal types and duration of exercise have yet to be defined, leaving the American College of Sports Medicine, in its recent position stand on "Physical Activity and Bone Health," unable to outline a prescription more detailed than high-intensity impact activities (such as running, jumping, gymnastics, or basketball) for 10 to 20 minutes, at least 3 days per week.

**Nutrition**

The minimal amount of calcium that results in bone accretion is unclear, and the effect of calcium intake also varies by skeletal site, with cortical bone appearing to respond more significantly than trabecular bone. Recommendations for teenagers are further complicated by the fact that the skeletal effects of calcium may be dependent on the level of physical activity. However, the best available evidence was summarized by the National Academy of Sciences in 1997 to produce the dietary reference intake ranges (Table 2).

In 2003, the American Academy of Pediatrics adopted the National Academy of Sciences recommendation that all children from infancy to adolescence receive 200 IU of vitamin D supplementation daily, a policy that has been met with some controversy. This recommendation was reiterated in the recent position statement by the American Academy of Pediatrics on bone health.

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Table 2. Recommended Dietary Intake of Calcium for Adolescents in the United States

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Calcium Al, mg/d</th>
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<tr>
<td>9-18</td>
<td>1300</td>
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<tr>
<td>19-50</td>
<td>1000</td>
</tr>
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Abbreviation: Al, adequate intake (used if sufficient scientific evidence is not available to derive a recommended daily allowance).

*Adapted from the Institute of Medicine and Food and Nutrition Board."
Adolescence is the most critical period across the life span for bone health because more than half of PBM is accumulated during the teenage years. Recent and ongoing studies have highlighted the increasing number of clinical settings in which an adolescent may potentially lose bone density and are beginning to fill gaps in knowledge regarding the roles of physical activity and calcium and vitamin D intake in healthy adolescents, as well as the appropriate use of pharmacologic skeletal agents in those with chronic illness. Unfortunately, research has not yet generated evidence to identify appropriate candidates for both baseline bone density screening and continued monitoring. Nonetheless, although there still seem to be more questions than answers in this new field, adolescent health care professionals are on the cusp of an exciting era in which they can have a major role in improving the skeletal health of our nation.

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