Osteoporosis has long been considered a health problem unique to older adults. Children and adolescents with chronic illness, primary bone disease, or poor nutrition, however, are also predisposed to impaired skeletal health. The present review discusses normal skeletal development, risk factors for low bone mineral density, and prevention and treatment strategies that can help optimize bone health in the pediatric population.

Osteoporosis is observed primarily in postmenopausal women and elderly adults—affecting 10 million men and women nationwide. However, these patient populations are not the only ones at increased risk for low bone mineral density (BMD). The condition has been increasingly recognized in children and adolescents. In fact, research suggests that osteoporosis seen later in life may originate in childhood or adolescence.

Multiple factors contribute to normal skeletal development and attainment of normal BMD. Well-balanced nutrition is essential, but adequate amounts of calcium and vitamin D in the diet are especially important, particularly in adolescence because puberty is a critical time for accruing bone mass.

The benefits of physical activity—especially weight-bearing exercise—on bone health are well established. Recent studies found that jumping-based activities resulted in substantial improvements in bone mass in prepubertal and pubertal children.

In addition, hormones such as growth hormone, thyroid hormone, and estrogen are essential to normal bone metabolism and mineralization. Good overall health is beneficial to the skeleton, as various chronic illnesses are known to predispose individuals to bone disease.

Bone Growth and Calcium Homeostasis

Skeletal patterning begins in utero, with the majority of calcium and phosphate deposition taking place in the third trimester. Normal bone mineralization occurs throughout infancy, childhood, and adolescence and is the result of two dynamic processes: modeling and remodeling.

Modeling allows for deposition of cortical bone beneath the periosteal surface and is the process by which bones grow wider and longer. This process is unique to growing skeletons. Remodeling, in contrast, occurs throughout life and consists of two opposing processes: resorption and formation.

Bone resorption is initiated by osteoclasts and has three functions:

- maintain normal skeletal mass
- repair microdamage to the skeleton
- participate in calcium homeostasis

This process is followed by bone formation, during which osteoblasts fill the resorption cavity with osteoid, which is later mineralized into new bone. Bone mineralization continues until peak bone mass is achieved sometime in early adulthood, usually in the third decade.

Calcium is important in achieving optimal bone mass. Serum calcium levels are finely regulated by complex interplay among the skeleton, intestine, kidneys, and parathyroid glands. Parathyroid hormone (PTH) is secreted by the four parathyroid glands posterior to the thyroid. This hormone directly affects the skeleton and kidneys and indirectly affects the intestine so that serum calcium levels can be maintained in the normal range.

The skeleton is the largest reservoir of calcium and phosphate in the body. When calcium levels fall, PTH levels rise and promote calcium resorption from the bones. In the kidneys, PTH has two distinct actions: (1) promote calcium reabsorption in the distal tubule and phosphorus excretion in the proximal tubule, and (2) facilitate the conversion of 25-hydroxyvitamin D, which is inactive and made in the liver, to 1,25-dihydroxyvitamin D, which is active, via 1α-hydroxylase. In turn, 1,25-dihydroxyvitamin D is necessary for active absorp-
Excessive levels of systemic hormones can negatively impact bone health. For example, growth hormone deficiency, diabetes mellitus, and hyperthyroidism are all risk factors for osteoporosis. Pubertal hormones, especially estrogen, play a critical role in bone mass acquisition. Because the majority of BMD is accrued during the peripubertal years, recognition and timely treatment of hypogonadism are key.

Decreased muscle development and impaired ambulation in children with cerebral palsy and muscular dystrophy contribute to increased risk of osteoporosis.

Primary Bone Disease

Osteogenesis imperfecta includes a spectrum of genetic disorders of collagen synthesis resulting in abnormal skeletal and connective tissues. Type III osteogenesis imperfecta is a severe form of the disease and is easy to identify because it is associated with obvious bony deformities and reduced BMD. Type II is lethal in the perinatal period. Although types I and IV are milder and less easily recognized, they should be considered in the differential diagnosis of children with multiple fractures.

Current Medication and Treatments

Glucocorticoids are well known for their potent anti-inflammatory effects in patients with chronic inflammatory disorders such as ulcerative colitis and cystic fibrosis. One adverse effect of glucocorticoid use is its detrimental impact on BMD. At pharmacologic doses, glucocorticoids impair the function and reduce the life of osteoblasts. Simultaneously, glucocorticoids accelerate the maturation and activity of osteoclasts while exerting antiapoptotic effects on these cells.

In addition, glucocorticoids reduce intestinal calcium absorption and promote renal calcium excretion. The resulting increase in PTH secretion and reduced levels of sex steroids caused by chronic glucocorticoid therapy promote bone resorption. Therefore, the combination of impaired bone formation and accelerated bone resorption increases risk of osteopenia or osteoporosis.

Low BMD resulting from anti-epileptic medication is multifactorial. Such medication can accelerate vitamin D metabolism in the liver and lead to a deficiency of this nutrient. Low BMD is also induced by the direct effects of anti-epileptic drugs on bone cells, resistance to PTH, inhibition of calcitonin secretion, and impaired calcium absorption.

Patients with seizure disorders who require combination therapy and may be taking more than one anti-epileptic agent at a time are at an even greater risk. In children with cerebral palsy who have decreased lean muscle mass and limited weight-bearing activities, anti-epileptic agents compound the risk for low BMD.

As the number of survivors of childhood cancer increases, the toxic effects of chemotherapy and radiation on the skeleton are becoming more apparent. Osteoporosis is one of many health issues in a long list of potential “late effects” caused by these therapies. Therefore, physicians must provide appropriate surveillance.

Nutrition

Most adolescent females consume less than half of the recommended daily allowance of calcium. Milk provides a substantial amount of calcium per serving, yet milk consumption has decreased while soft drink consumption has increased. Flavored water is another popular choice and is healthier than soft drinks, but it lacks important nutrients found only in milk.

For example, milk is a good source of protein and contains multiple vitamins and minerals (e.g., iron, magnesium, phosphorus, potassium, zinc) crucial for developing healthy bones.
The vitamin K found in milk is a cofactor for osteocalcin synthesis and the vitamin D used to fortify milk augments calcium absorption from the intestine.

In addition, specific components of milk directly promote bone formation and inhibit bone resorption. For example, lactoferrin stimulates osteoblasts and inhibits osteoclasts, resulting in an overall increase in bone mass. Other dairy products such as lowfat yogurt and cheese are also very nutritious and help boost dietary calcium intake.

Adolescents with severe malnutrition, such as those with anorexia nervosa, are at risk for developing osteopenia or osteoporosis caused by inadequate nutrition and, in women, estrogen deficiency.

In female adolescents, physicians should be aware of the “female athlete triad”—anorexia, amenorrhea, and osteoporosis—which can have a negative effect on overall health and athletic performance. Whereas exercise is generally anabolic for bones, the excessive exercise typical for these young women may exacerbate the insult to their bones.

Conversely, the obesity epidemic among our nation’s youth is staggering. Although the 9 million overweight or obese children in the United States do not meet the classic definition of malnutrition, most are, in fact, undernourished in the sense that their diets are generally poor and lack many important nutrients.

In addition, obesity itself is a risk factor for fracture in children. Although it seems counterintuitive, the data are convincing. Obese children are generally sedentary, causing poor musculoskeletal coordination and inadequate lean muscle mass to control their body mass. Because their bone development does not keep pace with their weight gain, their relatively immature skeletons must bear a disproportionate amount of weight when they fall and can result in fracture.

**Lifestyle**

According to 2005 data, approximately 43% of US high school students consume alcohol, while 4.5 million US adolescents smoke cigarettes. Such lifestyle habits, as well as lack of physical activity, can all contribute to poor bone health.

For example, chronic excessive consumption of alcohol is toxic to osteoblasts and results in impaired bone formation. Cigarette smoking can lead to bone resorption through alterations in calcium and vitamin D metabolism and perturbations in the vitamin D–PTH axis.

Sedentary individuals not only lack the important bone-building stimulus of exercise in their daily lives but also are more likely to be overweight and perhaps not as focused on good nutrition, all of which augment their risk for poor bone health.

**Diagnosis**

Osteoporosis was once defined as a disease of decreased bone mass that predisposes individuals to fragility fractures. A newer and more meaningful definition for this condition is a disease of decreased bone strength that predisposes individuals to fragility fractures.

Although bone mass contributes substantially to bone strength, several other components—bone size, shape, distribution, and composition—cannot be discounted. The most obvious clinical manifestation of weak bones is a fracture, especially if sustained after low-impact trauma. Chronic back pain may indicate vertebral compression fractures, but it is important to note that such fractures may also be asymptomatic, especially in those with increased risk for low BMD.

When a child with one or more risk factors for low bone density is identified, it is particularly important to measure BMD. Most subspecialists are aware of the risks to skeletal health posed by various chronic diseases in their given fields of practice and routinely screen such patients for evidence of low BMD using dual-energy x-ray absorptiometry (DXA) scans. If this screening is not done by the child’s subspecialist, however, it would be reasonable for a primary care physician to order a DXA scan when the patient’s history is indicative of a risk factor, including a history of fractures or a single fracture after low-impact trauma (Figure 1).

Dual-energy x-ray absorptiometry scanning is traditionally used to assess BMD. It is readily accessible, noninvasive, rapid, and painless. In addition, DXA scanning delivers a very low dose of radiation—less than the amount from a standard posterior-anterior chest radiograph. Unfortunately, there are multiple limitations of DXA scanning in children that can confound interpretation of the results.

Dual-energy x-ray absorptiometry provides a two-dimensional projected area of a three-dimensional structure. The

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**Figure 1. Indications for considering a dual-energy x-ray absorptiometry scan for pediatric patients.**

- **Risk factor for low bone mass density**
  - Chronic illness
  - Chronic renal insufficiency
  - Gastrointestinal diseases
  - Cystic fibrosis
  - Endocrine system disorders
  - Medications or treatments
    - Glucocorticoids
    - Anti-epileptic drugs
    - Chemotherapy
    - Radiation therapy
  - Primary bone disease (ie, osteogenesis imperfecta)
  - Poor nutrition
  - Lifestyle habits
    - Alcohol consumption
    - Cigarette smoking
    - Lack of physical activity
  - History of multiple fractures
  - Single fracture following low impact trauma
The impact of the growing skeleton on follow-up measurements must be taken into account. Unlike adult patients for whom bone volume does not change over time, when children grow, their bones change size and shape and, therefore, volume. Moreover, the growth of individual bones is not uniform in three dimensions. This can make comparison and interpretation of serial scans more challenging.

As with any numerical result, the patient’s measured value needs to be compared with data from appropriate normal controls so that the clinician can arrive at a meaningful interpretation.

There is an overall lack of consensus regarding which patient demographic and physiologic factors should be incorporated into normative databases. Some researchers recommend adjusting DXA results for height, weight, pubertal status, or lean body mass. Given the fundamental relationship between muscle contraction and increasing bone mass, correcting DXA-derived variables for lean mass may help distinguish among primary (bone), secondary (muscle), or mixed disorders leading to low BMD. Perhaps most importantly, the prognostic value of pediatric DXA with regard to reducing fracture risk or attaining peak BMD remains to be determined.

Before interpreting a DXA report, the clinician must be aware of the difference between a T score and a Z score. The T score is a standard deviation (SD) score relative to age and gender. This score is used to interpret DXA results from adult patients but should not be included in a pediatric DXA report.

Because the T score is essentially a measure of bone density loss since early adulthood, its use in children who haven’t yet reached peak BMD is meaningless. The Z score is the SD score for BMD relative to normal controls and is the only SD score appropriate for pediatric DXA results.

The World Health Organization defines osteopenia and osteoporosis based on T scores of -1.0 and -2.5, respectively. However, as T scores are not applicable in pediatrics, different terminology is recommended. Instead of osteopenia or osteoporosis, the phrase “low bone density” is preferred.

Still, some clinicians and researchers use the diagnostic terms osteopenia and osteoporosis for children when their Z scores meet these criteria. However, the diagnosis of osteopenia or osteoporosis in a child or adolescent should never be made on the basis of DXA scanning alone but should consider other patient factors, including history of fractures.

Researchers are increasingly using peripheral quantitative computed tomography scanning to assess BMD in children. This diagnostic tool has the distinct advantages of being able to differentiate between cortical and trabecular bone densities and to provide a true BMD measurement. As certain disease processes have a differential effect on cortical and trabecular bone, peripheral quantitative computed tomography scanning is useful in distinguishing between the two. Unfortunately, this technology is not widely available. In addition, the high dose of radiation and the current relative lack of pediatric normative data limit the utility of this device.

Prevention and Treatment Strategies

The medical approach to managing osteoporosis is consistent with the osteopathic philosophy of treating the whole patient. In children and adolescents as in older adults, physicians must apply two major concepts of prevention and patient care: (1) identify and address all threats to bone health to prevent osteoporosis or additional BMD loss, and (2) intervene as needed to treat established osteopenia or osteoporosis.

Diet

Patients should be encouraged to follow a well-balanced diet that includes sufficient calories, protein, and healthy fats as well as adequate amounts of calcium and vitamin D. This lists some common foods that are rich in calcium. Additional information, including recommended daily allowances per age group and a complete list of foods rich in calcium, is available at http://dietary-supplements.info.nih.gov/factsheets/calium.asp. A good rule of thumb is to recommend 3 to 5 servings of lowfat dairy foods per day.

As previously described, vitamin D is essential in calcium absorption. Until recently, the American Academy of Pediatrics recommended 200 IU per day of vitamin D, but
icians screen for underlying liver and kidney function abnormalities, vitamin D deficiency or insufficiency, and celiac disease. For example, strict adherence to a gluten-free diet in children with celiac disease can result in improved or normalized BMD after only 1 year of therapy.55 The impact this improvement may have on helping a child attain peak BMD, however, is unknown.

For other chronic illnesses, achieving good control of the disease may not be sufficient to optimize skeletal health, but minimizing disease severity remains a crucial element of preventing and improving low BMD.

For adolescents with delayed puberty, gonadotropins (ie, luteinizing hormone, follicle-stimulating hormone) and evaluation of estrogen or testosterone levels might yield a diagnosis of hypogonadism. In such cases, administration of exogenous sex steroids may be necessary to attain peak bone mass.

### Osteotoxic Medications
Every attempt should be made to minimize the insult to the skeleton caused by medications that are harmful to bones.

Many of the chronic illnesses that predispose patients to osteoporosis are characterized by inflammation that must be controlled by glucocorticoids. It is well known that inflammatory mediators, including cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor α, can have direct deleterious effects on the skeleton. Striking a balance between avoiding excessive doses of steroids and controlling inflammation, therefore, is a challenging task.56 The same is true when using any medication known to have potentially detrimental effects on the skeleton to manage disease activity. Baseline and follow-up DXA scans every 6 months are recommended for children treated with glucocorticoids for more than 2 months.57

### Exercise and Lifestyle Habits
Regularly engaging in weight-bearing exercise and maintaining a healthy weight are essential for bone health. Weight-bearing exercise, including activities that involve walking, running, and jumping, is best. Many young children do these things naturally, but older children and adolescents may need encouragement. Exercising as a family or in another group setting (eg, friend, class, team sports) may help children and young adults maintain motivation and consistency.

For those unable to bear weight or engage in exercise, vibration therapy may be an option for optimizing bone health.55,54

In addition, all patients should be educated about the importance of avoiding unhealthy habits like cigarette smoking and drinking alcohol in excess. Physicians should convey that in addition to the increased risk of heart disease, stroke, cirrhosis, and more, cigarette smoking and alcohol consumption increase lifetime risk of low BMD.

### Systemic Disease
It is important to identify any underlying systemic disease, such as those previously listed, that could contribute to low BMD. Various laboratory tests and measurements (Figure 4) can help clinicians screen for underlying liver and kidney function abnormalities, vitamin D deficiency or insufficiency, and celiac disease. For example, strict adherence to a gluten-free diet in children with celiac disease can result in improved or normalized BMD after only 1 year of therapy.55 The impact this improvement may have on helping a child attain peak BMD, however, is unknown.

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**Pharmacologic Intervention**

Bisphosphonates, also called diphosphonates, are antiresorptive agents that interfere with osteoclast-mediated bone resorption. By reducing the functional capacity of osteoclasts, these medications tip the balance between bone formation and resorption in favor of bone formation.

In pediatrics, these medications are generally reserved for patients with a chronic illness—such as cystic fibrosis, cerebral palsy, and osteogenesis imperfecta—that seriously impairs bone mineral accrual. Intravenous pamidronate, one of several bisphosphonates, has been most extensively studied in pediatric patients with osteogenesis imperfecta. It has been very effective in increasing BMD and reducing fracture rates, thereby improving quality of life.58

Bisphosphonates have also been used in several other settings, such as low BMD associated with fractures caused by immobilization or prolonged glucocorticoid therapy.69-70 Unfortunately, clinical trials61-63 to date have generally included small numbers of study subjects, leaving many questions unanswered. For example, there are several protocols for administration of intravenous pamidronate,64-66 but optimal dosing and therapy duration are not known.

Although excessive doses can lead to osteonecrosis in the short term, these medications appear to be safe when used at recommended dosages. However, certain adverse effects may still occur.

In our experience, intravenous bisphosphonates may cause flu-like symptoms, including fever and myalgia, that are most pronounced when treatment is initiated. Generally, these symptoms become much less severe or disappear after continued use. In addition, such symptoms are easily remedied by administration of analgesics or antipyretics.

Oral agents may lead to gastroesophageal reflux or esophagitis. Osteonecrosis of the jaw is a rare but severe and debilitating potential complication of bisphosphonate therapy that has been reported in some adults taking these medications. Many such cases followed dental trauma such as tooth extraction, but others occurred spontaneously.68 Although no cases of osteonecrosis of the jaw have been documented in children to date,69,70 physicians treating pediatric patients with bisphosphonates should be aware of this potential complication. Ideally, patients should have a thorough dental evaluation before beginning bisphosphonate therapy. Good oral hygiene and regular dental care are essential throughout treatment.

If bisphosphonate therapy is stopped before the completion of linear growth, the interface between treated bone and bone naive to bisphosphonate therapy is prone to fracture.71 Because patients with different etiologies of low BMD will not have a uniform response to this therapy option, sustained effects of these medications will likely vary with underlying disease and disease severity.

Long-term data on fracture rates after bisphosphonate therapy are needed to determine if such treatment has a lasting impact on reducing morbidity associated with fragility fractures.72 For example, bisphosphonates remain in bone for years, but it is not currently known if these agents will lead to health hazards for patients or their offspring. As a result, bisphosphonates are currently not recommended for prevention of osteoporosis. Rather, their use is reserved for treating patients with severe debilitating bone disease, including low BMD associated with fractures and chronic bone pain.

Because these agents are not approved by the US Food and Drug Administration for use in children and adolescents, and given the paucity of long-term outcome data from bisphosphonate therapy, these agents should be used judiciously and should be prescribed only by physicians experienced in managing low BMD and metabolic bone disease in pediatric patients.

**Conclusion**

Osteoporosis is increasingly considered an adult disease that originates in childhood. While this understanding may be true for the otherwise healthy child who simply needs more calcium and vitamin D in his diet, clearly children with certain chronic illnesses are experiencing the consequences of serious insults to the skeleton (ie, low BMD and fractures). The increasing prevalence of low BMD in the pediatric population necessitates appropriate evaluation, assessment, and intervention by physicians.

**References**


8. Henwood and Binkovitz  Review


(continued)


JAOA call for case reports

To advance the scholarly evolution of osteopathic medicine, JAOA—The Journal of the American Osteopathic Association invites osteopathic physicians, researchers, and others in the healthcare professions to submit case reports relevant to osteopathic medicine.

In preparing submissions, authors should adhere to the JAOA’s “Information for Contributors,” which is available at http://www.jaoa.org/misc/ifora.shtml.

For more information, authors can e-mail questions to jaoa@osteopathic.org.