Literature Review

Osteoporosis: An Increasing Concern in Pediatric Dentistry

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Abstract: *Increasing numbers of children are being affected by low bone density and osteoporosis. Bone fractures are the main reason for hospitalization between 10 and 14 years of age and, over the past 3 decades, there has been an increase in the incidence of fractures in children. Childhood factors such as lifestyle, diet, chronic illness, and medications have a vital short-term impact on bone health and a long-term effect on the achievement of peak bone mass, with the potential for morbidity in adulthood. The primary forms of osteoporosis consist of rare inherited conditions, but the secondary forms are becoming more common given that chronically ill children are surviving longer. This subject should be of interest to pediatric dentists, because low mineral density and osteoporosis, together with drugs used to treat them (eg, bisphosphonates), may cause adverse effects in the oral cavity. Furthermore, the pediatric dentist is an important health care professional to counsel patients about healthy lifestyles that can help prevent the condition from an early age. (Pediatr Dent 2011;33:241-5) Received November 3, 2009 / Last Revision January 13, 2010 / Accepted January 29, 2010*

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Increasing numbers of children are being affected by low bone density, which has become an important issue in contemporary pediatrics. Bone fractures are the main reason for hospitalization between 10 and 14-years-old, and over the past 3 decades there has been an increase in the incidence of fractures in children.[1,2] It has become clear that childhood factors such as lifestyle, diet, chronic illness, and medications can have a vital short-term impact on bone health and a long-term effect on the achievement of peak bone mass, with the potential for morbidity in adulthood.[3] Unmodifiable intrinsic factors (eg, race, genetics, gender) are responsible for determining 75% to 80% of an individual's peak bone mass, while potentially changeable extrinsic factors (eg, diet, hormones, illness, physical activity) make up a significant component of the variability in ultimate bone mass.[3] Adequate calcium and vitamin D intake, which play important roles in bone formation, and regular physical activity, with its positive effects on bone size and mineralization, are among the most important extrinsic factors in gaining optimal bone mineral mass and density.[3,4]

Osteoporosis is classically defined as a systemic skeletal disease characterized by low bone mass; alteration of ultrastructural quality of bone; deterioration in trabecular architecture; increased cortical porosity; reduced cortical thickness and decreased bone width putting the individual at risk for fractures.[2,3] The primary forms of osteoporosis are rare, inherited conditions, but the secondary forms are becoming more common given that chronically ill children are surviving longer (Table 1). Several pathophysiologic mechanisms have been implicated in secondary osteoporosis, including poor nutrition; reduced physical activity; delayed puberty; and the effects of medications on the body. These can lead to inhibition of bone formation; increased bone resorption; and decreased responsiveness to mechanical stimulation.[2,3]

This subject should be of interest to pediatric dentists, because growing numbers of children and adolescents are being diagnosed with low bone mineral density (BMD) and osteoporosis and are being treated with drugs that may cause adverse effects in the oral cavity. Furthermore, the pediatric dentist is in an important position to counsel patients about healthy lifestyle habits that can help prevent the condition from an early age.

Defining osteoporosis in children and adolescents. A child's skeleton is constantly changing in size and shape with dramatic increases in bone mass and bone density, a process influenced by genetic, hormonal, and environmental factors. The rate of bone mass acquisition tends to mirror height velocity and is great during puberty; by the end of adolescence, 90% of peak bone mass has been acquired.[1,4] Girls start the pubertal spurt and the growth process earlier than boys, but males present a greater duration of growth spurt and maximal peak of growth than females.[4] Failure to achieve peak bone mass is associated with increased risk of adult osteoporosis and fractures. Excess or deficiencies in growth hormone, thyroid hormone, parathyroid hormone, and sex steroids also can lead to decreased BMD.[3]

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As often seen in pediatrics, definitions and therapies for osteoporosis are based on clinical experiences with adults. Although the classical definition of osteoporosis should be valid at any age, its applicability to children and adolescents remains controversial. No present consensus exists on an osteoporosis diagnosis based on BMD values which predict increased bone fragility and risk of fractures.[1] An adult is considered to have osteoporosis if the BMD value is less than 2.5 standard deviations (**SD**) below the average of healthy young adults (T-score <-2.5).[4,5] A T-score between -1 and - 2.5 SD is defined as osteopenia (ie, bone mass or BMD that is lower than normal).[5]

Although this definition was originally intended for the management of postmenopausal osteoporosis, it has been inappropriately extended to other situations.[5] The problem in defining pediatric osteoporosis arises when one considers that a child is a growing body. Pediatric BMD values are constantly changing with age and depend on many variables such as gender, body size, pubertal stage, skeletal maturation, hormone action, bone size, and ethnicity.[2,3] To complicate matters, many cases of low BMD in pediatric patients are secondary to highly variable pathological conditions and anomalies that affect height, weight, and pubertal development, and may even affect some areas of the skeleton more than others.[1,6] Hence, the definition and treatment of osteoporosis in children and adolescents are much more complex than in adults.

Using T-scores is inappropriate for children because they have not yet reached peak bone mass.[4] Pediatric BMD is assessed by an index called Z-score whose reference population is one of ethnicity-, gender-, and age-matched controls—data that is unfortunately limited.[1,3] The Z-score is the difference between the measured BMD value and the reference value, expressed in SD units.[4] It does not, however, take into account some of the aforementioned variables (gender, body size, pubertal stage, skeletal maturation, hormone action, bone size, and ethnicity). This poses a problem of diagnostic accuracy because serial measurements in a single child may be difficult to interpret. Thus, the diagnosis of pediatric osteoporosis should not be made based on densitometry alone.[1] Z-score values below -2 are generally considered a serious warning for osteoporosis, but most specialists do not make that diagnosis until at least 1 fragility fracture has been observed.[1]

A clinically significant fracture history is defined as long bone fracture of the lower extremities, vertebral compression fracture, and/or 2 or more long bone fractures of the upper extremities.[1,2,5] Other factors that lead to suspicion of osteoporosis in young patients include the presence of chronic bone pain and/or radiographic evidence of rarefied bone.[6] The term "low bone mass for chronologic age" should be used if the Z-score is ≤-2; the term "osteopenia" should not appear in pediatric bone reports.[1,2]

Given the issues in obtaining an accurate BMD measurement, the concept of osteoporosis has evolved over the years. Since fragility fractures constitute the clinical hallmark of osteoporosis, the focus has shifted from low BMD to compromised bone strength, underlining that the risk of fractures is related to complex factors and not only to one single quantitative measure.[1] In pediatrics, a novel approach to the definition of osteoporosis is based on the relationship between a child's BMD or bone mineral content (**BMC**) and muscle mass because the action of muscular work on bone increases its strength.[1] There are models that have examined the definition of osteoporosis as the presence of an altered ratio between BMC and muscular mass, but larger studies need to be done to confirm their accuracy.[1] Thus, BMD remains the diagnostic parameter for now.

Measuring bone mineral density in growing subjects. There are many available methods to measure BMD, but the most widely used and the principal tool for diagnosis and management of adult osteoporosis is dual energy X-ray absorptiometry (**DEXA**).[3] DEXA provides low radiation dose, good precision, and good reproducibility but does not measure volumetric bone density nor distinguish between cortical and trabecular bone.[3] DEXA can be particularly deceptive when used on a growing subject because it can underestimate the

Primary bone disorders	*heritable disorders of connective tissue*
	idiopathic juvenile osteoporosis
	osteogenesis imperfecta
	Marfan syndrome
	Ehler – Danlos syndrome
	Bruck syndrome
	osteoporosis pseudoglioma syndrome
	homocystinuria
Secondary causes	*inflammatory diseases*
	inflammatory bowel disease
	celiac disease
	juvenile idiopathic arthritis
	cystic fibrosis
	systemic lupus erythematosus
	dermatomyositis
	chronic immobilization
	cerebral palsy
	neuromuscular disorders
	epidermolysis bullosa
	spina bifida
	spinal cord injury
	head injury
	endocrine disturbances
	Turner syndrome
	anorexia nervosa
	hypogonadism

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Secondary causes	*endocrine disturbances*
	growth hormone deficiency
	juvenile diabetes mellitus
	hyperthyroidism, hyperparathyroidism
	Cushing syndrome
	delayed puberty
	hematologic-oncologic disorders
	childhood cancer
	thalassemia
	sickle cell disease
	inborn errors of metabolism
	protein intolerance
	glycogen storage diseases
	galactosemia
	Gaucher disease
	iatrogenic etiologies
	glucocorticoids
	anticonvulsants
	chemotherapy
	cyclosporine
	tacrolimus
	bone and/or cranial irradiation
	others
	chronic renal disease
	solid organ and hematopoietic stem cell tx
	anorexia nervosa
	steroid-dependent asthma

true density value for smaller bones while overestimating it for larger ones.[1,5] This means, for example, that a child who is short for his age will have smaller bones. Therefore, his areal bone density will be below the mean value for a child of the same age, leading to a misdiagnosis of osteoporosis.[1,3,5]

Other problems with interpreting DEXA results for pediatric patients include 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; and effects of gender, race, height, and puberty on BMD readings.[3] Furthermore, DEXA, being a projectional technique, can only collect a 2-dimensional areal measurement of a 3-dimensional object (bone), which certainly presents a problem.[3] Thus, bone mineral apparent density seems to be the most accurate representation of bone density within the pediatric population due to its ability to generate volumetric measurements, but DEXA continues to be the preferred method for assessing BMC and areal-BMD.[1,2] The most appropriate and reproducible sites for densitometry in children are the posterior/anterior spine and total body minus head.[2] Bone metabolism markers, such as alkaline phosphatase and osteocalcin, also can be measured in the pediatric population, but accuracy concerns and lack of pediatric reference ranges for newer markers have hampered its widespread use.[3]

Once treatment begins, DEXA is useful to monitor bone mass accrual at clinically appropriate intervals. The minimal interval that may detect actual changes in a growing skeleton is 6 months; longer intervals are appropriate for patients with mild disease and those not receiving any bone-active therapy.[3] Other methods for measuring BMD include quantitative computerized tomography; quantitative ultrasound; and magnetic resonance imaging, which is only used for special research purposes.

Treating osteoporosis in children and adolescents

Anticipatory guidance regarding healthy lifestyle habits, such as regular physical activity, a balanced diet, and avoidance of tobacco, alcohol, and illicit drugs, are of great importance to prevent bone loss and should start from an early age. This is an area where the pediatric dentist can make an impact on the patient's health and, thus, should be addressed at least at every recall visit.

Effective control of the underlying problem is the best approach to prevent low BMD and osteoporosis. In less severe cases of reduced BMD, correcting poor nutrition and calcium, taking vitamin D, and promoting weight-bearing physical activity can provide benefits with minimal risk.[3,10] Vitamin D deficiency can be caused by lack of exposure to sunlight and by a negative effect of some diseases and commonly used drugs (eg, steroids, anticonvulsants, heparin, cyclosporine, tacrolimus) on its metabolism and function.[9] Low vitamin D levels can cause an increase in secretion of the parathyroid hormone, which leads to increased osteoclast-mediated bone resorption.[3] Although calcium and vitamin D supplementation is instinctively felt to be an appropriate response to a child with low BMD, there is no evidence in pediatric practice to support such an approach.[3] Moreover, long-term compliance is extremely difficult to obtain in children, and the gastrointestinal symptoms of calcium supplements, such as constipation and abdominal pain, are serious limitations to their use.[10]

Soft drink consumption negatively influences bone mineral accrual in adolescent girls more than in boys, while eating fruits and vegetables is positively associated with BMD in girls.[8] Growth retardation, pubertal delay, or hypogonadism must be corrected with appropriate hormonal therapy. The new drug teriparatide (recombinant human parathyroid hormone), which stimulates bone formation, has not been studied in pediatric patients and may increase the risk of osteosarcoma in this age group.[3,16] Regarding physical activity, the type, quantity, and quality must be tailored to the patient's gender, age, and health status.[9] Not all patients should exercise intensely, because a negative effect on bone may appear after a certain threshold, as is the case in anorexia nervosa, for example.

As a general rule, DEXA must always precede bone-specific therapy, which is a delicate and controversial issue in children.[3] Antiresorptive agents, such as bisphosphonates,

Table 2. COMMERCIALLY AVAILABLE BISPHOSPHONATES

Generic name	Brand name (manufacturer)	Route	Potency
First generation			
Etidronate	Didronel (Procter&Gamble, US)	oral / IV	1
Clodronate	Bonefos (Berlex Inc, US)	oral / IV	10
Tiludronate	Skelid (Sanofi-Aventis, France)	oral	10
Second generation			
Pamidronate	Aredia (Novartis, Switzerland)	IV	100
Alendronate	Fosamax (Merck, US)	oral	1000 - 10000
Third generation			
Ibandronate	Boniva (Roche, Switzerland)	oral / IV	1000 - 10000
Risedronate	Actonel (Procter&Gamble, US)	oral / IV	1000 - 10000
Zoledronic acid	Reclast and Zometa (Novartis)	IV	> 10,000

slow bone resorption while allowing bone formation to continue (Table 2). Their use is mostly based on clinical experience with adults and should be considered only in pediatric patients who have very low BMD (Z score <-2), especially when fractures occur after minimal trauma and after all preliminary measures (diet, exercise, etc.) fail to lead to a reversal of bone loss.[3,6]

Bisphosphonates strongly bind to hydroxyapatite crystals and reduce bone resorption by inhibiting cell functions and inducing accelerated osteoclast death, especially in trabecular bone and bone with a high turnover rate.[3,6] Although the efficacy and safety of bisphosphonates in children require further evaluation with carefully designed studies, their clinical use in pediatrics has become increasingly accepted. Concerns for long-term safety of the drug have not materialized in over 10 years of pediatric use.[4]

Bisphosphonates have been mostly studied in young subjects as therapy for osteogenesis imperfecta (OI), leading to a marked reduction in the incidence of radiographically confirmed fractures, disappearance of bone pain and a significant increase in bone mass.[6] The drug does not eliminate fracture risk, however, and is not a cure for OI.[9] Although there is no consensus regarding the optimal bisphosphonate agent in children as well as optimal dosage and duration of therapy, its use should probably be continued until growth is fully or nearly completed.[10] Fever, malaise, nausea, diarrhea, and muscle or bone pain are common adverse effects and tend to be mild, last only for a few days, and rarely recur with subsequent doses.[9,10] The more serious effects seen in adults, such as uveitis, thrombocytopenia, and esophageal or oral ulcerations, are rare in children.[10]

Due to the lack of long-term efficacy and safety data, many experts recommend prescribing bisphosphonates only to those children with recurrent extremity fractures, symptomatic vertebral collapse, and reduced bone mass.[10,11] At this point, evidence does not support use of bisphosphonates as standard therapy for pediatric patients with secondary osteoporosis.[11] The use of bone-specific therapy as prevention in cases of low BMD (Z-score between -1 and -1.5) and in the absence of fractures is very controversial.[6]

Implications of osteoporosis and its treatment in pediatric dentistry. Pediatric dentists have to be meticulous when taking the medical history of children and adolescents with special health care needs. In the case of patients with a diagnosis of low BMD and osteoporosis, it is important to know:

1. how low the patient's BMD is—transferring patients from wheelchairs to the dental chair, physical restraint, and extractions, especially of permanent teeth, may lead to bone fractures if not done carefully;
2. what has caused the patient's low BMD or osteoporosis (Table 1)—the patient's underlying condition and medications may warrant other special considerations in the delivery of dental care;
3. what treatment is being provided for the bone condition in order to prevent other problems such as bisphosphonate-related osteonecrosis of the jaws (BRONJ). Because bisphosphonates may be administered every few weeks or months, patients and caretakers may not remember they took it if they are not clearly asked. It is important to add a specific question about it in the medical history form and to be aware of the drug's potential long-term oral complications given that its half-life may be several years.

Children and adolescents at risk for developing osteoporosis often have other chronic health issues that may make oral health a low priority in their everyday life. In the particular case of bisphosphonate therapy, dental care to optimize oral health and decrease the likelihood of its side effects is important before, during, and after therapy. Educating patients and caretakers about the importance of oral health and the potential long-term side effects of the drug is a must. Elimination of all potential sources of odontogenic and mucosal infection must be done before the patient starts therapy with bisphosphonates. Routine dental care can be provided without antibiotic prophylaxis. Avoiding oral surgical procedures, especially in patients who have had or are being given intravenous (IV) bisphosphonates, is crucial to decrease the risk of BRONJ.

Individuals receiving the oral form of the drug are at a considerably lower risk of BRONJ than those who receive IV infusions.[12] There is insufficient evidence to suggest that implant placement, tooth extraction, and other surgical treatments should be routinely avoided for patients receiving oral forms of the drug. Duration of oral therapy (ie, older than 3 years), however, may correlate with development and severity of BRONJ.[13] In our institution, several primary and permanent tooth extractions have been performed in pediatric patients using bisphosphonates, and no complications have been observed.

One can speculate that extraction of primary teeth may not pose a risk for the development of BRONJ given the relatively small wound and the porosity and vascularity of the jaw bones at such a young age. Another reason may be

the smaller dose given to children vs adults. The condition has not been reported in children and adolescents to this date. The published studies,[14-17] however, present design flaws (eg, small numbers of patients, lack of randomization, short follow-up period, differing drugs and doses used, etc.) which must be taken into account when interpreting their results. As more pediatric patients are referred for orthodontically related extractions, removal of impacted teeth and third molars, and tissue biopsies, the risk of BRONJ could increase, especially in adolescents and young adults. Before proceeding with invasive procedures in this population, the pediatric dentist must consult the patient's physician and obtain a detailed informed consent that clearly states the possibility of complications. The pathophysiology, diagnosis, and treatment of BRONJ have been described in detail elsewhere.[12] Although there are no known studies on the effects of osteoporosis on the craniofacial bones of pediatric patients, radiographic exams of postmenopausal women affected by the condition showed presence of erosion and heavy endosteal cortical residues in the mandible's inferior cortex.[18]

Bisphosphonates can inhibit tooth movement, posing a problem for orthodontic therapy—which depends on osteoclastic activity to move teeth. It has been suggested that orthodontic treatment be avoided in patients with high risk/high level of osteoclastic inhibition such as those who are receiving or have received IV BIS.[19] The drug also is associated with delayed tooth eruption in children with OI[20] and with ulcers when the pills come in direct contact with the oral cavity, although this has not been reported in pediatric patients.[21-23]

In summary, the pediatric dentist must be constantly alert to diseases and conditions that once were not recognized in their patient population as well as their treatment, as they may present compromises to the delivery of dental care. Low BMD or osteoporosis in children and adolescents is going to become more common given lifestyle changes and the increasing success of medical technology that has allowed chronically ill children to survive longer. Pediatric dentists should make extensive use of their important role in counseling families on how to live healthier lives.

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