Bone Health in Children: Guidelines for Vitamin D and Calcium Intake

Cemre Robinson, MD & Thomas Carpenter, MD

The evil men do lives after them, the good is often interred with their bones.

—William Shakespeare

Learning Objectives:
1. Review vitamin D metabolism, specifically as it relates to calcium homeostasis
2. Discuss recommendations regarding vitamin D and calcium intake by the American Academy of Pediatrics (AAP) and the Institute of Medicine (IOM)
3. Identify situations in which screening for vitamin D deficiency is necessary
4. Understand the implications and controversies surrounding vitamin D deficiency and its treatment

Primary References:

CASE ONE:
Mindy Vita is a 2-month-old infant who is coming in for a well visit on a cold winter day. This adorable infant is breastfeeding well, but her mother hasn’t yet given the multivitamins you prescribed at the two week visit.

1. What is the metabolism of vitamin D, and what are its effects on bone growth?
Vitamin D is a sterol formed in the skin by irradiation of 7-dehydrocholesterol by ultraviolet light from the sun. Thus, exposure to sunlight is important in the maintenance of vitamin D stores, particularly when dietary sources of vitamin D are limited. Vitamin D is converted to 25-hydroxyvitamin D (25-OHD) in the liver, then, in renal proximal tubule cells, 25-OHD is converted to 1,25(OH)2D, the activated form of vitamin D. This conversion is stimulated by parathyroid hormone (PTH), low blood phosphorus, and other factors. This activated form of vitamin D promotes the absorption of calcium and phosphate by the intestine. Vitamin D is one of several calcitropic hormones that, together with mineral nutrients, particularly calcium and phosphorus, are important in the construction of a normal skeleton. Deficiency of serum calcium or phosphorus can result in defective mineralization of cartilage in the growth plate, a syndrome known as rickets.

2. What are the recommendations for vitamin D intake for healthy children?
The AAP has steadily increased the recommended amount of daily vitamin D for children, and endorsed the 2011 guidelines from the Institute of Medicine of the National Academy of Sciences (IOM) for the “Recommended Dietary Allowance” (RDA) for vitamin D intake. These guidelines suggest providing 400 IU per day for infants less than 1 year, and 600 IU per day after one year of age, with a goal 25-OHD level of at least 20 ng/ml. Preterm infants should be given 400 to 800 IU per day, as premature infants have higher calcium and phosphate needs for bone mineralization, which occurs most rapidly in the third trimester. To meet these intake goals, the AAP recommends that infants (both breast and formula-fed) initiate vitamin D supplementation in the first few days of life, and continue to do so until consuming at least 1L of vitamin D fortified milk or formula a day. Children should also receive supplementation if consuming less that this amount of milk to meet the RDA.

The recommendations were chosen to achieve a target threshold for serum 25-OHD levels of 20 ng/ml, which is the level that has been shown to prevent increases in serum alkaline phosphatase activity (a biochemical marker of rickets). The IOM reported that serum 25-OHD values higher than 20 ng/ml were
not consistently associated with greater benefit for any health measures, and for some outcomes U-shaped associations were observed with the lowest risk for morbidity and mortality at moderate 25-OHD levels and increased risk at both low and high levels of 25-OHD. Moderators should highlight the IOM summary table listed as a primary reference above.

Some laboratories do offer higher reference values (such as 32 ng/ml) based on data collected in older adults that examined the relationship between 25-OHD levels and parathyroid hormone levels, but no clear evidence of skeletal benefit has been shown. Moreover, this relationship does not appear to be relevant in children. Furthermore, targeting higher values may lead to toxicity.

Vitamin D supplements are available in two forms; D$_2$ (ergocalciferol), which is plant derived and D$_3$ (cholecalciferol), which is the form made by vertebrates. There is some evidence that cholecalciferol may be more potent, but either form may be used. Tri-vi-sol contains cholecalciferol. Intake guidelines can be met through diet, and where dietary intake is insufficient, with supplementation.

**CASE TWO:**

The next patient on your schedule is Ricky Otts, a 9-month-old male whom you sent for admission for several days of coughing and wheezing; you were concerned because he had had multiple episodes of bronchiolitis and had recently not gained weight for several months, leading to a weight at less than the 5$^{th}$ percentile for age. During the admission, a chest radiograph showed normal heart size with several areas of atelectasis. The radiologist noted that the proximal humerus had a widened metaphysis, with cupped, hazy and indistinct edges. His biochemical evaluation in the hospital revealed a serum calcium of 7.0 mg/dl, phosphorus of 3.4 mg/dl, alkaline phosphatase activity of 750 U/L, a PTH of 65 nEq/ml (moderately elevated), and a 25-OHD of 12 ng/ml. Due to the history of failure to thrive, and multiple respiratory infections, a sweat test was ordered. The sweat test results were >60 meq/L, indicating the likely diagnosis of cystic fibrosis, which predisposed Ricky to vitamin D deficiency due to malabsorption of fat soluble vitamins.

3. **What signs and symptoms would make you suspect vitamin D deficiency?** What other risk factors besides CF might predispose Ricky to nutritional vitamin D deficiency?

Chronic vitamin D deficiency can present with rickets, in which patients can have enlarged wrists and knees, bowing of the long bones, rachitic rosary, craniotabes, delayed tooth eruption, and frontal bossing. Typical radiographic findings of rickets include widening, cupping, and fraying of the metaphysis with uncalcified and poorly mineralized epiphyses (Figure 1).

Signs and symptoms of acute hypocalcemia can include paresthesias, muscle cramping, and carpopedal spasm. In infants, hypocalcemia can present with apneic spells, stridor, wheezing, hypotonia, muscle weakness, and brisk reflexes. Rarely, in its most severe presentation, hypocalcemia can present with mental status changes, seizures, and cardiac effects including impairment of myocardial contractility and prolongation of the QTc interval. Cardiac function will correct with treatment of hypocalcemia. Normalization of serum calcium levels will alleviate acute symptoms.

Vitamin D deficiency is commonly seen in periods of rapid growth velocity, particularly infancy, toddlerhood, and adolescence. In adolescence, more of half of adult bone mass is acquired, but the increased calcium requirements are frequently not met through the typical adolescent diet. In addition, there are disease related risk factors such as poor nutrition, malabsorption, immobilization, diseases of muscle function, sex steroid or growth hormone

Figure 1: Left wrist x-ray in a 3-month-old boy with concern for nutritional rickets. Flaring of the distal left radial and ulnar metaphyses (white arrows) and cupping of the ulna (black arrow) are present. Bones appear osteopenic (white arrowhead).
deficiency, drugs (such as glucocorticoids), and chronic inflammation. A regimen of consistent weight-bearing activity that is sustained from childhood through adolescence would be a protective factor for overall bone health. The predisposing factors for Ricky include age, season, malabsorption, and lack of vitamin D supplementation.

4. Identify situations in which measurement of markers of bone health is useful. What testing should be performed?

Children who should be tested are those:
- with poor growth, gross motor delays, unusual irritability, or other signs or symptoms of hypocalcemia
- receiving anticonvulsant or chronic glucocorticoid therapy
- with malabsorptive disorders (e.g., cystic fibrosis, inflammatory bowel disease, celiac disease)
- with frequent fractures and low bone mineral density
- with eating disorders

Recommended testing includes serum calcium, phosphorus (important to use age-specific normal values, as normal phosphorus levels in children are higher than in adults), alkaline phosphatase activity (normal value in neonates < 500 IU/L and children < 1000 IU/L up to 9 years), PTH and 25-OHD levels. If the results of these biomarkers present concern for bone health, radiographs of the distal radius and ulna or distal femur/proximal tibia should be obtained. A wrist radiograph may be most reliable test for detecting subclinical rickets.

5. How is vitamin D deficiency defined? What levels necessitate therapy?

The most accurate measure of the body’s vitamin D stores is the serum 25-OHD level; assays should measure the total 25-OHD (i.e., that derived from both vitamin D₂ and vitamin D₃ derivatives because both may be present, based on dietary and/or supplement sources of the vitamin). Deficiency is defined as 25-OHD levels less than 20 ng/ml; a level less than 5 ng/ml indicates severe deficiency, with a high risk of rickets. Note that a level greater than 50 ng/ml indicates excess, but there is still controversy regarding the tolerable values. Levels of circulating 25-OHD greater than 80 ng/ml raise concern for hypercalcemia.

An asymptomatic child greater than 1 year of age with a serum 25-OHD level less than 20 ng/ml should receive 600 IU per day of vitamin D, and children less than 1 year should receive 400 IU per day; the same as for children with normal serum levels. However, higher doses of vitamin D are required for infants and children who manifest clinical features of rickets, osteomalacia, or hypocalcemia as a result of vitamin D deficiency.

There is a wide range of currently recommended treatment regimens for symptomatic vitamin D deficiency. Due to the risk of toxicity, a conservative approach with frequent biochemical monitoring is suggested, especially in younger children; 1000 IU/day for infants less than 1 month of age, 2000 IU/day for older children. As lack of adherence can be an issue, an alternative approach for older children is to use high doses of vitamin D in weekly administration of 50,000 IU for 6 to 8 weeks, followed by a maintenance dose of 600 to 1000 IU/day. Therapy may need to be repeated every 3 months if families are non-adherent with maintenance dosing. Hungry bone syndrome, when movement of calcium into healing bone is rapid enough that the serum calcium decreases dangerously, can necessitate supplementation with calcium as well. The recommended oral dose of elemental calcium is 35-75mg/kg/day divided into three separate doses. Vitamin D therapy must be closely monitored by sampling calcium, phosphorus, and alkaline phosphatase levels no longer than one month after initiating treatment, with infants being sampled within 2 weeks. Radiologic evidence of healing should be seen in 2-4 weeks, at which time the dose could be reduced to the standard 400 IU/day for infants and 600 IU/day for older children. Even recommended treatment doses have the potential to cause toxicity if administered inappropriately or for too long a period of time, without the necessary biochemical monitoring.

Treatment doses should only be given under supervision of a qualified health-care provider and with close follow-up, to avoid hypervitaminosis or hypercalcemia that can manifest as hypercalciuria, confusion, polyuria, polydipsia, anorexia, vomiting, muscle weakness, or bone pain.
CASE THREE:

Still in your office, you see Noah Dairy, a 16-year-old who was recently treated in the Emergency Department for a wrist fracture and has come for follow-up. He tells you that he fell on the ice in his driveway. Looking in his chart, you note that he has had 2 other fractures over the last 2 years; he fractured his right arm after wrestling with his brother and fractured his left tibia after he was tripped by another player while playing soccer. On further review of systems, he tells you he used to get stomachaches after eating pizza. He thought he was lactose intolerant and so has been avoiding dairy products for the last 3 years. He does not take any vitamin or mineral supplements. Biochemical evaluation reveals a serum Ca of 9.1 mg/dl, phosphorus of 3.1 mg/dl, a PTH of 28 nEq/ml (10-25) and a 25-OHD of 17 ng/ml.

6. How would you advise this patient regarding his lactose intolerance with respect to his dietary calcium intake?

According to the Panel Statement issued by the NIH Consensus Development Conference on Lactose Intolerance and Health, lactose intolerance is defined as the onset of gastrointestinal symptoms following a blinded, single-dose challenge of ingested lactose by an individual with lactose malabsorption, which are not observed when the person ingests an indistinguishable placebo. Current management of lactose intolerance often relies on reducing lactose exposure by avoiding milk and milk-containing products, or by drinking milk in which the lactose has been prehydrolyzed with lactase enzyme. Alternatively, lactase non-persisters (individuals with a genetically programmed decrease in lactase which occurs after weaning) may tolerate moderate amounts of dairy products ingested with other foods.

Studies have shown that children with a history of long-term avoidance of cow’s milk have very low dietary calcium intake, poor bone health, decreased bone mineral density on dual-energy x-ray absorptiometry (DXA), and therefore an increased susceptibility to fracture. Furthermore, children with low calcium intake may reach adulthood with a low peak bone mass, making them more vulnerable to osteoporotic fractures later in life when bone mass decreases as an effect of aging. Many individuals with real or perceived lactose intolerance avoid dairy and ingest inadequate amounts of calcium and vitamin D, which may predispose them to decreased bone accrual, osteoporosis, and other adverse health outcomes.

Of great concern is that many individuals mistakenly ascribe symptoms of a variety of intestinal disorders to lactose intolerance without undergoing testing. This misconception becomes intergenerational when parents with self-diagnosed lactose intolerance place their children on lactose-restricted diets, sometimes in the absence of symptoms, in the mistaken belief that they will develop symptoms if given lactose. Even in persons with lactose intolerance, small amounts of milk, yogurt, hard cheeses, and reduced-lactose foods may be effective management approaches. Individuals with lactose malabsorption probably can ingest 12 grams of lactose (the equivalent of 1 cup of milk) without significant symptoms, particularly if ingested with other foods. Lactase-treated products may be tolerated better than nontreated products.

Therefore, it is important to distinguish lactose intolerance from other etiologies of gastrointestinal symptoms. Targeting the specific underlying condition likely will optimize outcomes and help avoid unnecessary food group restriction. For example, people who remain symptomatic on a dairy exclusion diet may have other causes for their gastrointestinal symptoms, such as irritable bowel syndrome, celiac disease, inflammatory bowel disease, or small bowel bacterial overgrowth. Formal lactose challenge testing may be required in patients with other gastrointestinal illnesses, or in situations where the etiology of gastrointestinal symptoms remains unclear.

Teenagers, as a group, tend not to take in enough calcium to meet recommended needs. In fact, not only has milk consumption declined among teenagers since the 1970s, but soda consumption has increased; teenagers are drinking twice as much soda per day as they do milk according to U.S. Department of Agriculture data from the Continuing Survey of Food Intake of Individuals (CSFII). Soda intake, especially in excessive amounts, can negatively impact bone health in multiple ways. High
phosphorus content in soda can alter calcium homeostasis while both caffeine and sugar can lead to increased urinary calcium excretion.

Inadequate dietary calcium intake is exacerbated by dairy avoidance in individuals who consider themselves lactose intolerant, regardless of whether they have undergone objective testing. It is important to obtain a diet history to assess daily calcium intake for those patients at risk for nutritional deficiency. Nutritional guidance should be provided to patients who do not meet RDA guidelines, using calcium supplementation if necessary. The IOM summary table provides recommendations for daily calcium intake by age group.

Links to tools to assist health care professionals in obtaining dietary calcium intake history and providing counseling to patients can be found in the Resources section.

On a related note, children and teenagers have also become more sedentary. Both limited intake of dietary calcium and decreased weight-bearing activities are risk factors for poor bone health, particularly in adolescence when peak bone mass is accrued. Physical activities with high strain (e.g., gymnastics) or weight-bearing (e.g., soccer) are particularly useful to increase peak bone mass throughout growth. In terms of bone health, physical activity should start in the prepubertal years when the skeleton is sensitive to the mechanical stimulation elicited by exercise.

CASE continued:

Noah’s father is concerned about all these fractures. He asks, “My mother was told by her doctor that she has osteoporosis, and was told to have a DXA scan to evaluate her bone density, should Noah should have one too?”

7. What is the utility of DXA scans in children? Are there any precautions to interpretation?

The use of DXA should be reserved for individuals at significant risk for fragility fractures. The National Osteoporosis Foundation lists the following indications for DXA in children: chronic use of systemic steroid medications, chronic inflammatory conditions, hypogonadism, prolonged immobilization, osteogenesis imperfecta, idiopathic juvenile osteoporosis, and recurrent low trauma fractures. The National Institutes of Health also recommends a baseline DXA for patients expected to receive systemic corticosteroids for longer than 2 months.

When interpreting the results of a DXA, the diagnosis of osteoporosis should not be made on DXA results alone, but should take into account other patient factors such as gender, ethnicity, height-age, weight, body composition, and physiologic maturity. The commonly used T-scores (SD’s below peak bone mass) that are used to classify osteoporosis and osteopenia in adults should not be used in the pediatric patient.

Since its original use in the evaluation and management of adult bone diseases, DXA has gained wide use in pediatrics. However, the use of DXA in measuring bone mineral density (BMD) in the pediatric population requires special considerations. Specifically, the interpretation of DXA results requires comparison to standardized reference data of BMD for several areas of the skeleton that traditionally reflect the effect of age-related bone loss, which, in adults, include the lumbar spine (L1-L4), the hip, the wrist/forearm, and a total body measurement. In children, the preferred sites of measurement are the spine and total body scores, avoiding use of the wrist/forearm and hip as reference sites. However, comparing the bone mineral density of children to the reference data of adults will underestimate the BMD of children, because children have less bone mass than fully developed adults, which would lead to an over-diagnosis of osteopenia and osteoporosis for children. Therefore, to avoid an overestimation of bone mineral deficits, BMD scores need to be compared to reference data for the same gender and age, a practice prevalent only in centers with experience in performing pediatric DXA scans.

The second important confounding variable is bone size. DXA has been shown to overestimate the bone mineral density in individuals with larger bone size, and underestimate the bone mineral density of those with smaller bone size. To some extent this is evident when comparing taller and shorter subjects of the same age. As BMD is based on the two-dimensional projected area of a three-dimensional structure, the depth of the bone is unknown. This third dimension, depth, cannot be measured directly because it is in the same plane as the x-ray beams. Therefore, the BMD is an areal measurement, rather than a true
volumetric density, with smaller bones appearing to have a lower density when compared to larger bones even when the volume is the same. Thus, in certain situations, children of the same chronologic age who have a lower height-age appear to have lower BMD than those with a taller height-age, as the Z (or standard deviation) scores are based on chronologic age. Standard pediatric reference data for bone mineral density were established with the Bone Mineral Density in Childhood Study (BMDCS); a multicenter, longitudinal study of bone accrual in healthy children and adolescents performed at five U.S. clinical centers. An online tool that health care providers can use to calculate BMD Z scores for their patients based upon the BMDCS reference data was created, taking into account the age, sex, ethnicity (African American or non-African American) and height of the patient.

CASE continued:

Noah’s mom has heard that vitamin D can prevent autoimmune diseases like type 1 diabetes, multiple sclerosis, and cancer. She wants to know if she should give Noah extra vitamin D to prevent these diseases.

8. What is the relationship between vitamin D and health, other than that related to bone and calcium?

In recent years, research has shown that vitamin D is associated with physiologic functions other than its well-established role in calcium homeostasis and bone health. The vitamin D receptor (VDR) is present in the small intestine, colon, osteoblasts, activated B and T lymphocytes, pancreatic islet cells, and several other locations in the body such as the brain, heart, skin, gonads, prostate, breast, and mononuclear cells. Although these findings may provide possible new therapies for diseases such as cancer, causality remains to be established. The Institute of Medicine’s review regarding these non-classical effects found the evidence at this time to be inconclusive with respect to a causal role for vitamin D. Further clinical trials are needed to elucidate the relationship between vitamin D and immune mediated diseases. Unfortunately, overzealous administration of vitamin D supplementation by the public may lead to toxicity, especially in children. Health care providers should therefore discourage the use of unmonitored high-dose supplementation.

Additional References:

Resources:
1. Links to handouts and guidelines regarding vitamin D from the AAP: http://www.aap.org/healthtopics/vitamind.cfm
3. Link to Bone Mineral Density in Childhood Study (BMDCS) and height-adjusted BMD Z-score calculator: https://www.nichd.nih.gov/research/supported/bmdcs

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