Pediatric Bone Health

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Objectives

- To identify risk factors for a low bone density among children and adolescents
- To review the effects of vitamin D on different tissues and factors associated with vitamin D deficiency
- To consider strategies to optimize vitamin D status and bone health in a pediatric practice
Osteoporosis

- preventable disease
- no cure
- new interest in childhood and adolescence as critical years for bone acquisition
Peak bone mass: accrued during adolescence
Determinants of Bone Mass

**Extrinsic**
- Diet
- Body mass/habitus
- Hormonal milieu
- Illnesses
- Exercise
- Lifestyle choices

**Intrinsic**
- Gender
- Family History
- Ethnicity
Promoting healthy bones – and identifying ones “at risk”!
Gender and Race

- Males:
  - higher bone mass at all ages
  - higher peak bone mass
  - slower decline of sex steroids

- Osteoporosis/Fractures:
  - lower among African Americans (higher peak bone mass in both males and females)
Genetic Factors

- Striking patterns within families
- Premenopausal daughters of postmenopausal women with osteoporosis: lower BMD
- Candidate genes:
  - Vitamin D receptor
  - Estrogen receptor
  - IGF-I receptor
  - TGF-β
  - Alleles involved in collagen synthesis
At-Risk Children and Adolescents

- Obesity
- Poor diet/little sun exposure
- Anorexia nervosa/chronic amenorrhea/delayed puberty
- Turner syndrome
- Growth hormone deficiency
- Medications: glucocorticoids, anticonvulsants, depot medroxyprogesterone, GnRH agonists
- Gastrointestinal disease (IBD)
- Cerebral palsy/neuromuscular diseases

- Rheumatologic diseases: SLE, JRA, dermatomyositis
- Cystic fibrosis
- Celiac disease
- Renal failure
- Diabetes mellitus
- Hemoglobinopathies (sickle cell, thalassemia) + hemophilia
- Immobilized patients
- HIV
- Hyperprolactinemia
Organ Transplant Recipients

- All transplant recipients at increased risk for osteoporosis
  - kidney, liver, heart, bone marrow
- Mechanisms of injury (to bone):
  - Poor nutrition
  - Low body weight and weight loss
  - Chemotherapy
  - Irradiation
  - Immunosuppressive agents
Calcium

- Optimal calcium intake:
  - maximize and maintain peak bone mass
- Requirements increase during periods of rapid growth
- Supplemental intake appears to improve BMD in children and adults
- Area of controversy!
  - *Pediatrics* 2005;155:736-743
Vitamin D

- Critical for normal calcium absorption from diet
- Risk factors for deficiency:
  - Inadequate diet
  - Inadequate sunlight
  - Adolescent lifestyle, including the above!
  - Obesity
  - Anticonvulsant therapy
  - Malabsorption
- RDA = 600 IU (AAP recommendation = 400 IU)
Vitamin D Metabolism

- Sunlight
- Skin
- 7-Dehydrocholesterol
- Cholecalciferol (vitamin D₃)
- Liver
- 25-hydroxyvitamin D₃
- Kidney
- 1,25-dihydroxyvitamin D₃

Dietary intake:
- Vitamin D₃ (fish, meat)
- Vitamin D₂ (supplements)

Maintains calcium balance in the body
Vitamin D: Who’s Who?

- Vitamin D2 = ergocalciferol
- Vitamin D3 = cholecalciferol
- 25(OH)D = calcidiol
  - Relatively inactive, very stable
  - Reflects vitamin D status, low in vitamin D deficiency, longer half-life than other metabolites
  - The one to measure!
- 1,25(OH)D = calcitriol
  - ‘active’ metabolite, highest affinity + activity at nuclear VDR, short half-life
  - Concentrations 1000-fold < 25(OH)D
Sunlight and Vitamin D

- **Melanin**: absorbs UVB radiation + competes with 7-dehydrocholesterol for photons in skin of darkly pigmented individuals
- **SPF8**: reduces vitamin D₃ production by 97.5%
- **Latitude**: Skin unable to produce any vitamin D₃ at all in Boston: Nov-February (*JCEM* 1988;67:373-378)
- **Individuals in extreme latitudes** (northern or southern) may require supplementation (*JCEM* 1999;84:1839-1843; *J Bone Miner Res* 1993;20:99-108)
Should children and adolescents be supplemented with Vitamin D?

- 200 IU, 400 IU, 600 IU or 1000 IU daily?
- Vitamin D2 or D3?

Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents

Carol L. Wagner, MD, Frank R. Greer, MD, and the Section on Breastfeeding and Committee on Nutrition

*Pediatrics* 122:1142, 2008
Dietary Sources of Vitamin D

- D3 in fatty fishes and fish (cod) liver oils
- Fortified milk and juice has approx 100 IU/8 oz.
- Survey of vitamin D content of milk samples in U.S. found:
  - approximately 15% had no detectable vitamin D and >50% had <80% of vitamin D content stated on label (Chen et al. *NEJM* 1993)
Prevalence of Vitamin D Deficiency among Healthy Adolescents in Boston (n=307)

- Higher prevalence
  - Winter vs summer
  - Black vs white adolescents

- Vitamin D deficiency (25OHD < 15 ng/mL)
  - 75/307 = 24%

- Vitamin D insufficiency (25OHD < 20 ng/mL)
  - 124/307 = 42%

Gordon et al., Arch Ped Adol Med 2004
Rickets is back! 1915 versus 2011
Subclinical Vitamin D Deficiency in Healthy Infants and Toddlers

- 12% healthy 8-24 month old’s (<20 ng/mL)
- 40% suboptimal (< 30 ng/mL)
- Did not vary by season or race/ethnicity
- Significant predictors
  - Breastfeeding without supplementation
  - Lack of milk consumption
- Demineralization (33%) on x-rays
**Prevalence in Children with Chronic Disease**

- **Inflammatory bowel disease**
  - *Pediatrics* 2006;118(5):1950
- **Cystic fibrosis**
- **Seizure disorders**
  - Anticonvulsants, ketogenic diet
- **Anorexia nervosa**
  - More compliant with calcium + vitamin D; low prevalence
  - Low body fat; more bioavailable?
How do we define “deficiency”?  

- Or is it “insufficiency”?  
- And what about “optimal levels”?  
- 11, 12 or 15 ng/mL = deficiency  
  - Expressed as nmol/L 27.5, 30, or 37.5  
- 21-30 ng/mL = insufficiency  
- > 30-32 ng/mL = optimal  
- Accepted definition (deficiency)  
  - 25(OH)D₃ < 20 ng/mL  
  - Recommended threshold of IOM
How much is enough?
Guidelines for Vitamin D Intake

<table>
<thead>
<tr>
<th>Age</th>
<th>RDA (recommended daily allowance)</th>
<th>Safe upper limit**</th>
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<tbody>
<tr>
<td>0 - 1 yr</td>
<td>400 IU</td>
<td>1000 - 1500 IU</td>
</tr>
<tr>
<td>1 – 3 yr</td>
<td>600 IU</td>
<td>2500 IU</td>
</tr>
<tr>
<td>4 - 70 yr</td>
<td>600 IU</td>
<td>4000 IU</td>
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_Institute of Medicine 2010_
Estimates of optimal vitamin D status

Bess Dawson-Hughes · Robert P. Heaney
Michael F. Holick · Paul Lips · Pierre J. Meunier
Reinhold Vieth

- RE: fracture prevention in adults, for 5/6 authors, the minimum desirable 25(OH)D clusters between 70 and 80 nmol/l (28-32 ng/mL)
- Considering all health endpoints (BMD, risk falls, fracture, colon cancer), 75-100 nmol/L (30-40 ng/mL) optimal
Biomarkers for Vitamin D Sufficiency

- 25(OH)D
- PTH
- Bone mineral density (BMD)
- Fracture + falls
- Intestinal calcium absorption
- Blood pressure
- Dental health
- Insulin sensitivity
- Beta cell function
- Immune function
- Respiratory disease, wheezing, TB
Extraskeletal Role for Vitamin D?

- People living closer to the equator are at decreased risk of developing MS
- Similar trends: cancer, hypertension, SAD
Work-up for Vitamin D Insufficiency

- Serum 25(OH)D
- PTH
- Calcium
- Magnesium
- Phosphorus
- Alkaline phosphatase (total)
- Urine calcium/creatinine ratio
  - Start with spot sample
  - If abnormal, 24-hour sample
Rickets in an 18 month old
(before and after treatment)
Treatment of Vitamin D Deficiency

- **Vitamin D2 or D3:** 2000-5000 IU/D or 50,000 IU once weekly
  - provide calcium supps to prevent “hungry bone”
- **Malabsorption**
  - Larger doses of vitamin D: 10,000-25,000 IU/d
- **Anticonvulsant therapy**
  - vitamin D - 800 - 2000 IU/d

- **Impaired production of vitamin D:** calcitriol
  - Liver disease: 25(OH)D or 1,25(OH)₂D
  - 1α-hydroxylase deficiency: 1,25(OH)₂D

- **Hereditary 1,25(OH)₂D resistant rickets** - large doses of vitamin D – treatment is not very effective
How Much is Too Much?
Vitamin D Intoxication

- Intoxication: Case series of 8 children with high vitamin D levels (731 +/- 434 nmol/L)
- Symptoms hypercalcemia or hypercalciuria
- All 8 drank milk from same local dairy
- Milk at local dairy had vitamin D concentration ranging from undetectable to 245,840 IU/L
- Intoxication only seen at total daily doses of 10,000 IU or greater

Jacobus et al. NEJM 1992
Body Weight and Weight-Bearing

- Positive correlation between body weight and BMD
- Low body weight (from many conditions)
  - independent risk factor for fracture
- Weight-bearing exercise may have positive effect on bone size and mineralization
  - In vitro: osteoblasts respond positively to strain
Female Athlete Triad
Weight Loss
Amenorrhea
Bone Loss

How do we prevent stress fractures in this young group?
- hormonal factors
- training factors
- nutrition
- family history*
Remember: growth, puberty, and bone accrual go hand in hand!
Measurement of Skeletal Status – 2011

**Bone density**
- Dual energy x-ray absorptiometry (DXA) – 2D
- Quantitative ultrasound (QUS)
- Quantitative CT – 3D (including pQCT)
  - High-resolution pQCT (XtremeCT)
- Peripheral vs. axial (central) measurements

**Bone quality**
- High-resolution MRI
- Micro-CT (from biopsy specimens)
- Hip structural analysis (bone geometry)
- Fracture rates
DXA Terminology: Consider Different Regions of Skeleton

- Central skeleton (axial skeleton plus hips and shoulders):
  - Spine, ribs, pelvis, hips, shoulders

- Peripheral skeleton (appendicular skeleton minus hips and shoulders):
  - Extremities (arms and legs)
DXA scanner – open configuration
DXA Results: rate-of-change curve
Definition of “osteoporosis” in children

- No WHO definitions in children and teens
- Concern for low bone mass
  - BMD Z-score by DXA ≤ -2.0 SD
  - Slightly low if Z-score between -1.0 and -2.0
- “Diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of BMD alone.”

- Int’l Soc Clinical Densitometry 2007
Radial and Tibial Measurements

Peripheral QCT

Quantitative Ultrasound
Peripheral quantitative computed tomography of radius and tibia

Tibia

Radius
Bone Turnover Cycle – hormonal balance enables appropriate activity of osteoblasts vs osteoclasts

Bone Resorption
- Estrogen
- PTH
- Cortisol

Bone Formation
- GH
- IGF-1
- DHEA
- Androgens
What can we do as health care providers?

- Rule out systemic disease, endocrinopathy ⇒ bone loss
- Amenorrhea in young woman ⇒ be concerned!
- Consider BMD measurement in *at risk* patients and ones with strong family history
  - Recall role of genetics in BMD determination
- Encourage:
  - Regular exercise
  - Maintenance of normal weight
  - Good nutrition, with adequate calcium and vitamin D
  - Wean of glucocorticoids as primary disease allows
Diagnostic Work-Up

- Rule-out systemic disease
- Consider insidious celiac disease
- 25-hydroxyvitamin D
- PTH
- Calcium, phosphorus, magnesium

- Other:
  - Ceruloplasmin, copper, IGF-I, DHEAS
- Bone age
- Urinary calcium/creatinine (spot/24 h)
- If amenorrhea: thyroid function, FSH, prolactin
When should you order DXA scans?

- Patients with multiple fractures
- Pathologic (atraumatic fractures)
- Diseases associated with skeletal deficiency states
- Hypothalamic amenorrhea: after 6 months of amenorrhea
- Be suspicious of low BMD if strong family history
- Repeat scans only annually (except as part of research protocol)
US Office of Women’s Health Campaign: Best Bones Forever

www.bestbonesforever.gov for girls

www.bestbonesforever.gov/parents for parents and partners
Clinical Report—Bone Densitometry in Children and Adolescents

Laura K. Bachrach, MD, Irene N. Sills, MD, and THE SECTION ON ENDOCRINOLOGY
Thank you!

Questions/Comments?