Vitamin D: Rickets and Beyond

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December 12, 2008

Vitamin D

- Not really a vitamin
- Prohormone produced photochemically in the skin
- Closely related to classical steroids

Vitamin D Sources

- Sunlight
- Diet
  - Very few foods- best is fatty fish
- Dietary Supplements
  - In US dietary vitamin D is primarily from supplemented foods
    - Milk (100 IU / 8 oz)
    - Some dairy products
    - Some cereals
    - Calcium-fortified juices

Vitamin D Effects on Calcium and Phosphorus

- Vitamin D Sufficient State (> 20 ng/mL)
  - Net intestinal calcium absorption is up to 30%
    (60-80% during rapid growth)

Vitamin D Deficiency

- Intestinal absorption is 10-15%
- Decrease in phosphate absorption
- Low Ca++ → ↑ PTH → ↑ Ca++ reabsorption in kidneys and ↑ 1,25 dihydroxyvitamin D, ↑ phos in urine
- This leads to ↓ Calcium×Phosphorus product resulting in ↓ bone mineralization
- Low phosphorus causes failure of normal apoptosis in chondrocytes
**Vitamin D Deficiency Effects on Bones**

- Rickets
  - Defective mineralization of cartilage in epiphyseal growth plates of children
- Osteopenia/ osteoporosis
- Osteomalacia
  - Disordered mineralization of new bone matrix in adults

**Case 1**

- 17 month old African American male
- Rickets seen on skeletal survey done to r/o abuse
- Breastfed as infant, drinks juice instead of milk

**Labs**

- PTH 295 (12-72)
- Calcium 8.2
- Phosphorus 1.6
- Alkaline Phosphatase 1455
- 25 OH-vitamin D <7
- 1,25 dihydroxy vitamin D 64.8 (normal)
- Vitamin D started (4000 IU PO QD)

**Follow-up in Endocrine**

- Exam notable for short stature, rachitic rosary, metaphyseal flaring
- Repeat Labs on therapy
  - PTH 654
  - Calcium 7.8
  - Phosphorus 2.6
  - Alkaline Phosphatase 1992
- Calcium carbonate added to therapy

**Case 2**

- 2 ½ year old AA male presented to OSH in tetany
  - Calcium 5.7, Phos 6.7
  - Given IV Calcium
- Transferred to WCHOB
- History significant for
  - drinking juice instead of milk
  - complaint of foot pain for several days prior to admission
  - history of severe dental caries

**Exam**

- Poor enamel formation, numerous caries
- No bossing
- No rachitic rosary
- No metaphyseal flaring
Initial Labs at WCHOB

- Calcium 5.4
- Phos 5.9
- Alkaline Phosphatase 360 (74-270)
- PTH 164 (12-72)
- 25-hydroxy Vitamin D 10 (9-43)
- 1,25 dihydroxy Vitamin D 65 (15-65)

Treatment

- Vitamin D
- Calcium

Case 3

- 14 y/o white female complaining of knee pain
- X-ray demonstrated normal knees but severely demineralized
- PMD initiated bone work-up
- History significant for not drinking milk and no vitamin supplements. Does eat yogurt and cheese

Labs

- Alkaline phosphatase 119 (42-121)
- Calcium 10.1
- PTH 112 (12-65)
- 25-OH Vitamin D 9.3 ng/mL (32-100)

Exam

- Height at 50-75%
- Weight at 10-25%
- Normal exam

Therapy

- 50,000 IU vitamin D PO x1
- 400 IU vitamin D daily
- Calcium carbonate 1000 mg
Follow-up Labs

- iPTH 81 (12-72)
- Alkaline Phosphatase 98 (64-480)
- Calcium 10.1
- 25-OH Vitamin D 32 ng/mL (32-100)
- Vitamin D increased to 800 IU per day

Signs of Rickets

- Widening of the wrists and ankles
- Genu valgum or varum
- Rachitic rosary
- Craniotabes
- Frontal bossing
- Delayed fontanel closure
- Delayed tooth eruption
- Poor quality of enamel—caries
- Poor growth
- Increased susceptibility to infection

Symptoms of Rickets

- None
- Irritability
- Gross motor delays
- Bone pain

A 30-month-old girl had had progressive bowing of the legs since she began walking at the age of 11 months

Vitamin D-deficiency rickets at presentation and 3 mos after vit D and Ca therapy in a 1-year old black boy

Hypocalcemia Due to Rickets
- Seizures
- Tetany
- Hypocalcemia may also present with apnea, stridor, wheezing, hypotonia, muscle weakness or brisk reflexes
- Most frequent in infancy and adolescence when increased demand for calcium by rapid growth leads to hypocalcemia before bone demineralization

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Rickets
- Failure of mineralization of growing bone and cartilage
- First described in the 17th century
- Turn of the 20th century 80% of children with rickets
- Around the 1920’s, it was recognized that cod liver oil and sunlight prevented and treated rickets

Rickets continued
- Once Vitamin D identified rickets almost disappeared in industrialized nations
- 21st century- rickets has been re-emerging

Why the Resurgence in Vit D Deficiency
- Majority of Vitamin D from sunlight
- < 10% from diet
- Recommendations to avoid sun to prevent skin cancer
  - SPF 15 blocks 99% of vitamin D production
- Lifestyle
Sunlight & Vitamin D

- Concentration of melatonin regulates amount of UV-B penetrating epidermal cells
- MED minimal erythema dose – amount of UVR that causes slight pinkness
- Exposure of 40% of the body to ¼ MED generates 1000 IU vitamin D per day

Sunlight & Vitamin D - 2

- UV-B is shorter than UV-A and is prone to scatter before 10 AM and after 3 PM
- Exposure time in Southern states in the summer at solar noon to achieve 1 MED is 4-10 minutes for pale skin & 60-80 minutes for dark skin

Vitamin D as a function of latitude

Moan J. et al. PNAS 2008:105:668-673

Prevalence of low serum 25-hydroxyvitamin D concentrations from NHANES 2000-2004 by cut-off

Yetley, E. A Am J Clin Nutr 2008;88:558S-564S

20,000 individuals

Vitamin D in Breast Milk

- In a vitamin D sufficient mother 15-50 IU/L breast milk
- Assuming intake of 750 ml/day = 11-38 IU/day vitamin D

Vitamin D in Formula

- Infant formulas in US are mandated to contain 40 to 100 IU vitamin D per 100 kcal
- Assuming 750 ml/day this is 200-500 IU/day
Old AAP Guidelines

- 2003 AAP recommended 200 IU vitamin D per day for infants beginning at 2 months, children and adolescents

2003 AAP Guidelines

- 200 IU per day maintains 25-OH vitamin D at above 27.5 nmol/L (11 ng/dl) and prevented signs of vitamin D deficiency in older studies
- These recommendations were made despite knowing since 1918 that a teaspoon of cod liver oil prevented and treated rickets 1 tsp = 400 IU vitamin D

Redefining Vitamin D Deficiency

- New information from adults has redefined vitamin D deficiency as less than 50 nmol/L (20 ng/ml)
- Vitamin D insufficiency is >50 nmol/L to 80 nmol/L (32 ng/ml)
- Normal values in children are unknown, but 400 IU per day of vitamin D will maintain 25-OH vitamin D levels above 50 nmol/L

New AAP Guidelines for Vitamin D

- Breastfed / partially breastfed infants-supplement with 400 IU/day of vitamin D within first few days of life
- Continue until taking 1 liter vitamin D fortified formula/ milk
- All children/ adolescents ingesting less than 1 L vitamin D fortified milk should take 400 IU vitamin D supplement

New AAP Guidelines for Vitamin D - 2

- 25-OH vitamin D should be > 50 nmol/L (20 ng/ml)
- Children with chronic fat malabsorption or taking antiseizure medications may need higher doses of Vitamin D

Growth in the number of articles published each year with the term vitamin D in the title or abstract, as reported in PUBMED

Norman, A. W Am J Clin Nutr 2008;88:491S-499S
Tissues that express the vitamin D receptor for the steroid hormone 1, 25-dihydroxyvitamin D₃

- Adipose
- Muscle, embryonic
- Adrenal
- Muscle, smooth
- Bone
- Osteoblast
- Bone marrow
- Ovary
- Brain
- Pancreas β cell
- Breast
- Parathyroid
- Cancer cells
- Parotid
- Cartilage
- Pituitary

Causes and consequences of vitamin D deficiency

Immune Roles

- VDR is present in activated human mononuclear leukocytes and lymphocytes
- 1,25-dihydroxyvitamin D₃ regulates release of cytokines from lymphocytes
- 1,25(OH)₂D₃ induces cathelicidin in macrophages
- Toll-like receptor activation of human macrophages upregulates expression of the VDR and the 25(OH)D₃-1-hydroxylase genes
- Skin injury enhances antimicrobial peptide synthesis through the VDR and the 25(OH)D₃-1-hydroxylase in keratinocytes

Vitamin D & Autoimmune diseases

- Polymorphisms in the VDR are associated with –
  - T1DM
  - Addison’s disease
  - Hashimoto’s thyroiditis
  - Graves disease
**Vitamin D & T1DM**

- Norwegian study found the use of cod liver oil but not other vitamin D supplements during 1st year of life decreased risk of T1DM RR = 0.74 (95% CI 0.56-0.99)
- Meta-analysis Vit D supplementation may provide protection against T1DM
  - No randomized control studies
  - 5 observational studies

**Birth-cohort study in Northern Finland**

- All children expected to be delivered in 1966 were enrolled (n=12,058)
- Recommended dose of Vitamin D = 2,000 IU/day
- 88% of children were given vitamin D regularly during the 1st year of life
- Children receiving the recommended dose of Vit D had a RR of 0.22 (95% CI 0.05-0.89) for developing T1DM before 1998

**Role in Pancreatic β cells**

- Vitamin D deficiency inhibits pancreatic secretion of insulin and 1,25(OH)2D3 restores it
- 25(OH)D concentration positively correlates with insulin sensitivity
- Calbindin-D28K protects β cells from cytokine mediated cell death
- Vitamin D deficiency in early life accelerates development of diabetes in NOD mice

**Cancer incidence and death rates as a function of latitude**

Moan J. et.al. PNAS 2008;105:668-673
Vitamin D Deficiency and Cardiac Disease

Incidence of CVD event and low total vitamin D levels

- Low circulating 25-hydroxyvitamin D levels
- Low cellular calcitriol concentrations

Matrix GLA Protein Synthesis
Renin-Angiotensin System

Relation between Serum 25-Hydroxyvitamin D Concentrations and Mean (+/-SE) Serum Concentrations of Parathyroid Hormone in the Study Patients


Vitamin D Levels Associated With CVD

1789 Offspring from Framingham study w/o CVD F/U 5.4 yrs

- HTN


Role in Brain

- The VDR and 1-hydroxylase are distributed in human brain
- Vitamin D deficiency in utero alters adult behavior in mice
- Fetal deprivation of vitamin D₃ could be associated with adverse neuropsychiatric outcomes
- Prenatal and chronic postnatal vitamin D deficiency in rats impairs prepulse inhibition of acoustic startle

Vitamin D and Blood Pressure

- In humans 1,25 (OH)₂ vitamin D inhibits renin which may decrease BP
- Increasing UVB radiation by tanning 3 times per week for 3 months ↑ 25(OH) vitamin D 180% and ↓ SBP 6 mm Hg
- In a small RCT in pts T2 DM with low vitamin D levels administration of 100,000 IU vitamin D ↓ SBP 14 mm Hg and improved forearm blood flow

Conclusions

- Vitamin D plays important roles in general health beyond bone health
- Old AAP recommendations for Vitamin D supplementation were too low
- Experts disagree on the proper level of Vitamin D required for optimal health
- At least 400 IU per day of Vitamin D is optimal
- 800-2000 IU per day may be necessary