

Osteoporosis & Vitamin D

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Vitamin D

A VERY HOT TOPIC!!

But all the facts may not yet be in!

Functions of Vitamin D

- Traditionally, prevents rickets in children and osteomalacia in adults
 - Effects on calcium and phosphate absorption and metabolism, integrity of bone
- More recently, seems to be very important in optimal muscle function
 - Myopathy may be associated with deficiency
 - Repletion associated with fewer falls, thus fewer fractures, in some studies of nursing home patients
 - Better levels correlate with improved strength, even athletic abilities in teens!
- Role in cellular metabolism
 - Antiproliferation; prodifferentiation

Possible Associations with Diabetes (more investigation needed!)

- Meta-analysis of 5 studies suggests that Vit D supplements in young children may be associated with lower risk of type 1 diabetes!* (29% lower!) (6,455 cases)
 - Apparently through improved function of immune system, minimizing risk of autoimmune destruction of pancreas
- Mini-Finland Health Survey suggests that adequate 25-OH vitamin D may reduce the risk of onset of DM 2.°
- Possible improved insulin sensitivity with adequate 25-OH vitamin D#

*CS Zipitis, AK Akobeng: Arch Dis Child 93: 512-517, 2008.

° C Mattila et al: Diabetes Care 30: 2569-2570, 2007.

KC Chiu et al: Am J Clin Nutr 79(5):820-825, 2004.

Further Speculation about Vitamin D

- Deficiency associated with all kinds of musculoskeletal aches and pains!
- Deficiency a possible CVD Risk Factor
- Deficiency a cause of depression?
 - Data not yet clear, under investigation

Case #1

- 16 y-o Inupiat male from far north community, referred for suspected rickets
- CC muscle weakness and cramps which awaken him at night
 - Tetany in hands; no calf cramps
 - Eats salt to relieve sx
- Too weak for PE at school; studies sports rules instead
- Diet: exclusively corn dogs, chicken nuggets, pizza, french fries. Nothing else ever per hx.

Case #1, cont

- Ht 5'2" Wt 50.7 kg or 111.7 #
- BP 118/75 P 83
- + Chvostek +Trousseau Skin dry
- Some pubertal delay suspected
- Strengths 3 ½ -4/ 5 throughout
- Serum Ca 5.9 (8.4-10.2) PO4 4.9 (2.7-4.5)
- ionized Ca 0.74 (1.12-1.32)
- 25-OH vit D undetectable PTH 182 (high)
- Alk phos 840 (adults 42-128)
- X-rays: fraying of distal bones c/w rickets

Case #1

- After three months of therapy (same diet):
 - Cramps gone, somewhat stronger
 - Ca 8.7 ionized Ca 1.16
 - 25-OH vit D 73/ D3 6/ D2 67 PTH 78
- After six months of therapy (same diet):
 - More vigorous, participating in whaling with uncles
 - Labs similar

Case #2

- 25 y-o mother of one referred re nephrolithiasis and increased PTH
- Hx renal tubular acidosis, type 1
 - Nephrocalcinosis and stones, on Rx
 - Intermittent hypokalemia
- Main problem is difficulty walking, weakness x sev mos; planning muscle bx
- Low wt, poor appetite, very little dairy
- Recent hairline fx pelvis after fall in kitchen
- Started on alendronate

Case #2

- Ht 4'11" Wt 43.9 kg/ 96.7#
- BP 100/74 P 86
- Gait very abnl, difficulty getting onto table
- Strengths all decreased 3-4/ 5
- PTH 109 (high)/Ca 8.1 (low)
- ionized Ca 1.11 (1.12-1.32)
- 25-OH vit D 14/ D3 14/ D2 <4

Case #2, course

- Almost immediate improvement in sx's with ergocalciferol and OsCal+D; stop alendronate
- Gait and strength much improved at 6 weeks, muscle bx cancelled
- PTH 78/ Ca 8.7 ionized Ca 1.17
- 25-OH vit D 70/ D3 6/ D2 64
- Longer term follow-up has been scant.

Deficiency May Be Very Common

- Experts concluded that 50% of individuals >age 50 in North America failed to maintain healthy bone density and/or tooth attachment because of inadequate vitamin D*
- 93% of patients with persistent, nonspecific musculoskeletal pain were deficient in vit D at an inner city primary care clinic in Minneapolis^o

* AW Norman et al: 13th Workshop Consensus for vitamin D Nutritional Guidelines. J Steroid Biochem Mol Biol. 2007; 103(3-5):204-205.

^o Plotnikoff GA and Quigley JM: Mayo Clinic Proc. 2003; 78: 1463-1470.

Deficiency Very Common

- 57% of all patients admitted to Massachusetts General Hospital general medical service were vit D deficient, many with associated 2° hyperparathyroidism*

* MK Thomas et al 1998 NEJM 338: 777-783

Vitamin D Deficiency

- Deficiency: serum 25-OH vitamin D < 20 ng/ml (50nmol/l)
- Insufficiency: 20-30 ng/ml (50-75 nmol/l)
- Optimal: >32 ng/ml (cease to see increase in PTH at this level)

Two Main Forms of Vitamin D

- D3: cholecalciferol.
 - Most synthesized in skin with UVB exposure
 - Very little during Alaskan winter!!
 - Some in diet but mainly found in oily fish and fortified dairy products
- D2: ergocalciferol.
 - Found in plants after radiation with UVB
 - Not many food sources of D2

Additional Steps in Vitamin D Metabolism

- Liver: 25-hydroxylation to 25-OH vit D (calcidiol)
- Kidney: 1-hydroxylation to biologically active 1,25 di-OH vit D (also called calcitriol).
 - Also occurs in colon, breast, prostate.

Assessment of Vitamin D Status

- Measure 25-OH vitamin D to assess body stores.
- 1,25 di-OH vitamin D is not the best measure of body repletion
 - can be affected by secondary hyperparathyroidism due to vitamin D deficiency!

But we need not measure vitamin D in most patients!

- Current craze to measure this is probably somewhat wasteful
- May be more appropriate (especially in Alaska) to simply supplement

Vit D Requirements somewhat controversial

- DV (Daily Value) per Institute of Medicine:
 - 200 IU for infants, children, young adults
 - AAP recommends 400 IU for infants, children
 - 400 IU after age 50
 - 600 IU after age 70
- These amounts may be too low to maintain adequate levels; final word probably not in yet!
- National Academy of Science states little risk of toxicity up to 2,000 IU/day

Vitamin D in Diet

- Very little in most foods except oily fish
- Milk, cereal, OJ may be fortified to 100 IU/serving
- Canned tuna: 230 IU / 3.6 oz
- Canned salmon: 300-600 IU / 3.5 oz
- Fresh wild salmon: 600 – 1,000 IU / 3.5 oz
- Fresh farmed salmon: 100-250 IU / 3.5 oz
- Egg yolk: 20 IU
- Breast milk: 20 IU / liter

Optimal Calcium Intake Uncertain

- US National Academy of Science:
 - 1000 mg/day for adults < 50 years
 - 1200 mg/day for adults \geq 50 years
- NIH suggests 1500 mg for adults \geq 65 years
- European guidelines call for less
 - 800 mg/day for women ages 50-65
- May be more side effects with higher intake
 - Note 17 % increase in nephrolithiasis in Womens Health Initiative with 1000 mg/day + vit D 400 IU/day
 - Possible increase in cardiovascular endpoints in New Zealand study 2008
- Average post-menopausal woman consumes < 500 mg/day, and absorption declines with age!
 - Daily obligatory losses 200-300 mg/day

Some Ca/D Supplement Options

- OsCal + D: 500 mg Ca + 200 IU vit D3
- Citracal: 315 mg Ca + 250 IU vit D3
- Viactiv: 500 mg Ca + 500 IU vit D3 + 40 mcg vit K
- MVI (Centrum): 400 IU D3 + 200 mg Ca
- Vitamin D3: 400, 800, 1000, 2000 IU
- Calcium carbonate, 1250 mg
- Ergocalciferol: 50,000 IU

One Possible Regimen

- Repletion (“refill the tank”): ergocalciferol, 50,000 IU weekly X 8 – 12 weeks
- Maintenance (to replace obligatory, ongoing losses): OsCal + D, one TID with meals or two BID with meals
 - If not well tolerated, try Citracal, two BID
- Note that Ca carbonate may cause intestinal gas
 - requires stomach acid for absorption
 - not as well absorbed on proton pump inhibitors where Ca citrate may be preferred

Other options

- D3 1000 – 2000 IU/day + plain Ca carbonate or Ca citrate
- Viactiv Chews
- 2 MVI provides 800 IU vitamin D

- MGH recommends 800 IU vit D + Ca for all postmenopausal women

Special Notes

- Ca and vitamin D are necessary but not sufficient for prevention and management of osteoporosis
- Bis-phosphonates may precipitate hypocalcemic tetany in setting of vitamin D deficiency
- Alendronate is not as effective in the setting of vitamin D deficiency

Osteoporosis

- Generalized skeletal disorder
- Compromised bone strength and increased predisposition to fracture
 - Bone density and bone quality both important
- Present in most patients (male and female) over the age of 80

Osteoporosis

- Affects 44 million Americans or 55% of people \geq age 50
 - Another 34 million with osteopenia
- Only half of fractures occur in patients with T scores suggesting osteoporosis
 - Quality of bone important
 - Likelihood of falling/frailty
 - 98% hip fractures result from falls
 - Other Risk Factors for fracture

Osteoporotic Fracture

- 50% lifetime risk of osteoporotic fracture in white women age 50
 - 60% of hip fxs in women occur after age 80
 - Median age for hip fx in women is 83
- Lifetime risk of fx in men approx one-third the risk in women
 - Hip fxs occur later in men than women but are twice as likely to be associated with mortality within one year

Risk Factors for Osteoporosis

- Age
- Gender (female > male)
- Caucasian or Asian
- Small Body Size (Wt < 127# or BMI <20 - 25) or Loss of > 10% Body Wt
- Family hx osteoporosis
- Premature menopause in female or hypogonadism in male
- Corticosteroid Therapy
- Rheumatoid Arthritis
- Diabetes
- Smoking
- Excessive Alcohol
- Inactivity
- Certain Medical Conditions and Medications

Medications associated with Osteoporosis

- Glucocorticoids (virtually guarantee bone loss!)
- Heparin
- Anticonvulsants
- Aromatase Inhibitors (for breast CA) (profound reduction in estrogen synthesis throughout the body)
- Androgen deprivation therapy (for prostate CA)

Medical Conditions as causes of osteoporosis

- Primary Hyperparathyroidism
- Hyperthyroidism
- Vitamin D Deficiency (which causes 2° hyperparathyroidism)
- Cushings Syndrome
- Chronic Renal Failure
- Nutritional Malabsorption (including after bariatric surgery)
- Hematopoietic Disorders (multiple myeloma, other)
- Genetic Disorders (Turners, Klinefelters)
- Connective Tissue Disorders (such as osteogenesis imperfecta)

Osteoporosis Prevention

- Adequate Calcium and Vitamin D
 - New data suggests higher requirements to maintain optimal vit D level and bone density
- Exercise
- Treatment of Underlying Predisposing Conditions: hypogonadism, hyperthyroidism, etc
- Smoking cessation
- Fracture Prevention through Fall Prevention
- Limitation of alcohol and caffeine
- Medications

Osteoporosis/Osteopenia Therapy

- This should not consist of simple reflex prescription for bis-phosphonate based on dxa score
- More thorough and thoughtful approach is needed
- Comprehensive assessment of modifiable risks
- Consider bis-phosphonates or other meds

Osteoporosis/Osteopenia Therapy

- ALWAYS optimize Calcium and Vitamin D
 - 800-1000 IU vitamin D/day
 - Recommended amounts are tending to increase (up to 2000 IU/day seems to be quite safe)
 - If outright deficient need to replete stores in addition to ongoing maintenance supplements (think of a water tank with the drain a bit open!)
 - Consider ergocalciferol 50,000 U/week X 8-12 weeks for repletion
 - 1200-1500 mg Ca/day as supplements plus diet (with plenty of H₂O)
- Note that Ca and Vit D are necessary but not sufficient for prevention and management of osteoporosis

Osteoporosis/Osteopenia Therapy

- ALWAYS check TSH, gonadal status, meds, other conditions & correct what can be corrected
- ALWAYS wt bearing exercise
- ALWAYS smoking cessation
- ALWAYS moderation of etoh
- ALWAYS attention to risk of falling
 - Railings, safety bars, ice grippers, walkers, etc
 - Consider hip protectors which may reduce risk of fx by 60% (see www.safehip.com)
- ALWAYS ask yourself whether these issues have been adequately addressed!

Osteoporosis/Osteopenia Therapy

- Consider actual risk of fracture to determine whether anti-fx medication is indicated
- Bis-phosphonates should not be a “reflex” based on slightly low T score alone.

FRAX

WHO Fracture Risk Assessment Tool

- Integrates risks associated with clinical risk factors along with BMD measurement
- Also available in downloadable chart form for use with BMI (no BMD needed)
- Gives the 10-year risk of fracture at hip and for major fracture (hip, shoulder, forearm, clinically evident spine fx)
- www.shef.ac.uk/FRAX
- or simply search FRAX

FRAX

WHO Fracture Risk Assessment Tool

- Suggests that anti-fracture therapy (usually bis-phosphonate) be considered if:
 - Prior hip or vertebral fx
 - T score ≤ -2.5
 - T score between -1.0 and -2.5 (“osteopenia range”) plus 10-yr risk hip fx $\geq 3\%$ or 10-yr risk major fx $\geq 20\%$.
 - Clinical judgment

Case #1

69-y-o woman referred for palpitations on high dose levothyroxine (hx thyroid ca 2000) Feeling better on lower dose.

Hx bilat Colles fxs

Smokes 2 cigs/day

Meds: HCTZ, lisinopril, simvastatin, thyroid, OsCal/D

Undetectable TSH since 2000 (for CA)

Ht 5'1" Wt 61.9 kg BMI 26

25-OH vit D 40/ D3 40/ D2 < 4

Case #1 Dexa

- L femur 0.609 g/cm² T -2.2
- AP spine 0.75 g/cm² T -2.5
- L hip 0.754 g/cm² T -1.5

Case #2

- 68 y-o woman referred to optimize osteoporosis risk; to take anastrozole
- Has breast ca, doing well
- No prior fxs ever
- Mom age 89, no fxs known (?shrinking)
- No steroids ever
- Regular exerciser
- Meds: 3200 IU D3/day + OsCal+D BID + two dairy/day
- Ht 5'0" Wt 60 kg BMI 26
- 25-OH vit D 75/ D3 75/ D2 <4

Case #2 Dexa

- L Fem neck 0.725 gm/cm² T -1.1
- AP spine 0.941 gm/cm² T -1.0
- L hip 0.849 gm/cm² T -0.8

Case #3

- 64-y-o woman to optimize osteoporosis risk for anastrozole therapy for breast CA
- Ductal carcinoma in situ
- Nasal fx when fell on ice last year (no others)
- Lactose intolerant; eats fish 1x/wk, started OsCal+D last wk
- Menopause around age 40
- Ht 4'11 ½" Wt 64.3 kg BMI 27.5
- TSH < 0.005 FT4 1.43 PTH 69(hi) /Ca 9.0
- 25-OH D 23/ D3 23/ D2 <4

Case #3 Dexa

- L Fem neck 0.0.514 gm/cm² T -3.5
- AP spine 0.664 gm/cm² T -3.0
- L hip 0.686 gm/cm² T -2.1

Case #4

- 64 y-o- woman, wheel chair bound
- NH resident due to CVA, hemiparesis
- Hx bilat hip fxs
- Severe hyperthyroidism, on methimazole
- Hx heavy etoh, none now
- Recently started ergocalciferol and OsCal+D
- Ht 5'4" Wt 67.1 kg
- 25-OH vit D 17/ D3 17/ D2 <4
- PTH 38/ Ca 9.0

Case #4 Dexa

- L Fem neck 0, 430 gm/cm² T -3.8
- AP spine 0.827 gm/cm² T -2.0
- L hip 0.429 gm/cm² T -3.7

Case #5

- 61 y-o woman with remote hx 1° hyperparapara (surg resection), subsequent vit D def with 2° hyperparapara (on Rx with D)
- Severe RA with deformities, uses cane
- No fxs ever
- No FH fx
- No steroids ever
- Ht 5'0" Wt 75.5 kg BMI 33

Case #5 Dexa

- L Fem neck 0.669 gm/cm² T -1.6
- AP spine 0.817 gm/cm² T -2.5
- L hip 0.712 gm/cm² T -1.9

FDA Approved Therapies

- Oral bisphosphonates (approx \$1100-\$1400/yr)
 - Alendronate
 - Risedronate
 - Ibandronate (not proven for non-spine fxs)
- IV bisphosphonate
 - Zoledronic acid (single annual infusion, approx \$1350)
- Raloxifene (approx \$1500/yr)
 - (does not reduce hip fx risk)
- Teriparatide (synthetic PTH) (approx \$11,000/yr)
 - Limit to two years
- Calcitonin (intranasal, efficacy less certain; may help with pain)

Bis-Phosphonates

- Decrease bone resorption
 - Carbon-substituted analogs of pyrophosphate
 - Bind tightly to hydroxyapatite crystals
 - Taken up by osteoclasts and inhibit ability to resorb bone
- Remain in bone long-term
- May precipitate hypocalcemia if vitamin D deficient
- Require adequate vitamin D level for optimal effectiveness

- Osteonecrosis of Jaw (ONJ) seen primarily with high-dose therapy for malignancy, not with doses used for osteoporosis.
 - NOT a valid reason to withhold therapy for osteoporosis

Raloxifene

- Selective Estrogen Receptor Modulator (SERM)
- Reduces risk of vertebral fxs by 30-50%
- No effect on nonvertebral fxs
- Reduces LDL cholesterol
- Reduces risk of breast cancer
- Increases risk of DVT, possibly fatal stroke

Teriparatide

(human PTH 1-34)

- First anabolic agent approved for use in osteoporosis
- Reduced risk vertebral fx by 70%, non-vertebral fx by 54%
- Should be used alone, followed by anti-resorptive therapy
- Limit to two years (due to teratogenic effects observed in rats)
- Very expensive

Calcitonin

- Efficacy less convincing than bis-phosphonates
- May help with pain in some patients
 - Especially with acute vertebral fx
- Generally given intranasally at bedtime
 - Work up gradually with dose to avoid side effects, nausea and flushing
 - Start at 25 IU QHS, increase to 100 IU daily or QOD
- Often reserve for pts who cannot tolerate bisphosphonates