Calcium, Vitamin D, Exercise and Bone Health

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Regulation of Serum Calcium
Key principle #1

Hormonal mechanisms keep the serum calcium within normal limits “at all times” under general homeostatic conditions—even if calcium balance is negative.
Normal Function

Serum Ca (mg/dL)

Time (hrs)

Feeding

Fasting
Hormonal regulation of the serum calcium level

- Parathyroid hormone
- Vitamin D
• 24 healthy post-menopausal women
• 500 mg oral Ca load from each of 3 equivalent supplement preparations

PTH Responsiveness

Serum Total Calcium (mg/dL)

- 1%–2% rise in serum Ca
- ~40% drop in serum PTH

iPTH (as Fraction of Baseline)

PTH: Effect on Serum Calcium

Bone → Blood → Kidney

↑ Calcium
Hormonal regulation of the serum calcium level

• Parathyroid hormone
• Vitamin D
Storage form: index of vitamin D sufficiency or insufficiency
1,25(OH)$_2$D: Effect on Serum Calcium
Principle #2

• Osteoporosis is a state of *skeletal* calcium deficiency; not of abnormalities in the serum calcium.

• The serum calcium in osteoporosis is typically:
  - Normal
  - High
  - Low
Osteoporosis: Identifying the Problem

“A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.”

Osteoporosis

- A skeletal calcium deficiency state (not a state of abnormal serum calcium concentration) associated with bone loss and microarchitectural deterioration
Osteoporosis

A GLOBAL PROBLEM
Projected Number of Hip Fractures

Projected to reach 3.250 million in Asia by 2050

Estimated no. of hip fractures: (1000s)

<table>
<thead>
<tr>
<th>Year</th>
<th>1950</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>378</td>
<td>629</td>
</tr>
<tr>
<td>2050</td>
<td>742</td>
<td>668</td>
</tr>
</tbody>
</table>

Total number of hip fractures:
1950 = 1.66 million
2050 = 6.26 million

Osteoporosis: Worldwide Prevalence

- Affects 200 million women worldwide\(^1\)
  - 1/3 of women aged 60 to 70
  - 2/3 of women aged 80 or older
- Approximately 30% of women over the age of 50 have one or more vertebral fractures\(^2\)

1. International Osteoporosis Foundation Osteoporos Int 1996, 6:233
2. Dennison, 2000
Predicted Number of Hip Fractures Worldwide

Assuming 1% increase in fracture rate per year

Over 6 million hip fractures worldwide by 2050

Socioeconomic impact of hip fractures will increase markedly, particularly in Asia.

Gullberg, Osteoporosis Int. 1997;7:407-413.
Projected number of hip fractures worldwide

Total no. hip fractures
1990 = 1.66 million
2050 = 6.26 million

Cummings et al, 2002
BY THE YEAR 2050, MORE THAN HALF OF THE WORLD’S 6 MILLION HIP FRACTURES WILL OCCUR IN ASIA

Cooper C et al. Hip fractures in the elderly
Osteoporosis Int’l 1992;2;285-289
Morbidity After Hip Fractures

One year after a hip fracture:

- Death within one year: 20%
- Permanent disability: 30%
- Unable to walk independently: 40%
- Unable to carry out at least one independent activity of daily living: 80%
6459 postmenopausal women ages 55-81 years followed for an average of 3.8 years

Relative Risk of Death Following Clinical Fractures
Fracture Intervention Trial (FIT)*

Any Symptomatic
Non-spine
Hip
Spine
Forearm
Other

Age-Adjusted Relative Risk (95% CI)

*6459 postmenopausal women ages 55-81 years followed for an average of 3.8 years

Importance of the Hip Fracture

- Increased morbidity and mortality
- Without treatment, the risk of another fracture with the first year is significant
- Another fracture leads to another fracture
- Impaired Quality of Life
Human Costs of Osteoporosis

- Impaired function, decreased mobility
- More bone loss due to decreased activity
- Compressed abdomen, reduced appetite
- Reduced pulmonary function
- Sleep disorders
- Shortened survival
- Poor self esteem

Photo courtesy of the National Osteoporosis Foundation
Primary Goal of Therapy Is to Stop the Fracture Cascade
The key epidemiological message:

“Osteoporosis is one of the most dangerous diseases of the 21st century”

*Narine Mamikonyan, Armenian Osteoporosis Association, 2015*
Osteoporosis

• A skeletal calcium deficiency state (not a state of abnormal serum calcium concentration) associated with bone loss and microarchitectural deterioration

• Childhood nutrition is a key element in the disease that is seen in adulthood
Osteoporosis is a problem that has its roots in **CHILDHOOD!**
Increase in Bone Mass with Age in Children

Peak attained in early 20s-30
Maintained until 30s or 40s

Peak bone mass is a major determinant of bone density and strength throughout life
The beginning of the end result: Failure to Achieve Optimal Peak Bone Mass

A. Optimal Peak Bone Mass

B. Low normal peak bone mass
The beginning of the end result:
Failure to reach even low normal peak bone mass

A. Optimal Peak Bone Mass
B. Low normal peak bone mass
C. Failure to acquire bone mass even in the low normal range:
   • small size
   • heredity
   • late or missed puberty
   • Stunting?
Patient seen by Dr. Bilezikian on May 11, 2016: Case in point?

53 YO Caucasian woman with strong family history of osteoporosis (mother and father)
Menopause 2 years ago. No estrogen Rx
G1 P1
No fragility fractures
No other risk factors
No secondary causes
BMD done because of FH
T-scores: LS -3.0; TH -1.1; FN -2.1; distal radius -0.8
Labs including Chem screen, serum calcium, 25-OH D, PTH, P, BTMs are all normal. Celiac screen- neg
Patient seen by Dr. Bilezikian on May 11, 2016: 
Case in point?

Is this postmenopausal bone loss? (It is hard to imagine that her bone density would fall so quickly in the two years since menopause)

It would seem more likely that her bone density was low well before the menopause

It is possible that she did not achieve the desired optimal peak bone mass in her young adult years
Principle #3

Strongest predictor of bone mineral density in the later years is low bone mineral density at younger ages.
Determinants of Peak Bone Mass

• Factors that determine peak bone mass
  – Genetic (approximately 60-80%)
    • Disease susceptibility genes, “high BMD” gene
  – Exercise
  – Nutrition - calcium, vitamin D and protein
  – Body size and weight
  – Smoking
  – Sex hormones during adolescence
EXERCISE

Childhood
• Stay active
• Stay active
• Stay active
• Stay active
• Stay active

Adulthood
• Walking
• Jogging
• Treadmill
• Weight training
• Tai Chi
• Swimming
Effect of Exercise on Bone Mass

Childhood
- Exercise has been clearly shown to increase bone mass in the growing skeleton

Adulthood
- Exercise has not been clearly shown to increase bone mass in the adult skeleton
- Exercise, though, is helpful for muscle strength, balance, and overall fitness
Background: Exercise increases bone mass in children

Question: Does it influence fracture risk?

Design: 40’ of exercise/school day x 8 yrs in 1339 children (6-8 yrs old). Control: 2,195 children in other schools 60 minutes/school week.

Results: RR for fx fell every year: at end RR reduction 0.48 (CI 0.25-0.91). Bone mass higher in the exercisers. Muscle strength greater.

Conclusion: EXERCISE LEADS TO BETTER SKELETAL HEALTH IN CHILDREN.
Physical Activity and Calcium Intake work together to increase bone density

Roles of Exercise in Bone Health

- induces growth of larger bones in children and influences peak bone mass

- important for bone health in young adults

- increasingly important with aging
  - slows but does not prevent bone loss
  - maintains muscle strength
  - decreases risk of falling
Children and Adults are not getting enough exercise: Why?

Children
- Urban environment
- Television
- The computer
- Limited exercise programs in schools

Adults
- Urban environment
- Television
- The computer
- The Automobile
- Fewer bicycles
CALCIUM
Calcium intake in Childhood in Armenia

• By UN survey in 2005, the average intake of dairy was 2.5 servings per week (8% of caloric intake) and well under nutritional recommendations.
<table>
<thead>
<tr>
<th>RDA</th>
<th>mg/d*</th>
<th>Upper Limit (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 yr</td>
<td>700</td>
<td>2500</td>
</tr>
<tr>
<td>4–8 yr</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>9–18 yr</td>
<td>1300</td>
<td>3000</td>
</tr>
<tr>
<td>19–50 yr (Male)</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>51–70 yr (Female)</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>71+ yr</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>Pregnant or lactating (Female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–18 yr</td>
<td>1300</td>
<td>3000</td>
</tr>
<tr>
<td>19–50 yr</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>200</td>
<td>1000</td>
</tr>
<tr>
<td>6–12 months</td>
<td>260</td>
<td>1500</td>
</tr>
</tbody>
</table>

*Intake that covers needs of ≥97.5% of population

Calcium

- Preferably, calcium intake should come from natural sources (i.e., dairy)

- Calcium supplementation is used only to make up the difference between amount in foods (including calcium-supplemented foods) and what is needed.

- Only 500-600 mg advised at a time for better absorption

- Should be taken with food (protein meal) for better absorption efficiency
The best sources of Calcium

- **Dietary**
  - Dairy products
  - Green vegetables
  - Certain nuts like almonds

- **Calcium Supplements**
  - Calcium carbonate (40% calcium)
    - Requires a source of acid (gastric or food)
    - Absorption is enhanced by food
  - Calcium Citrate (20% calcium)
    - Does not require acid for absorption
    - Absorption is enhanced with food
    - Is thought to cause fewer GI issues
Calcium is a Threshold Nutrient (Heaney, 2006)

Caucasian Women In New York*

Chinese Women In New York*

Armenian Women in Armenia?
DRINK YOUR LOW OR NON-FAT MILK; EAT YOUR LOW OR NON-FAT YOGURT, CHEESE; USE CALCIUM SUPPLEMENTS ONLY TO SUPPLEMENT!
Recent Claims: Calcium may be bad for your cardiovascular health and will not improve your bone mineral density! (Bolland, Reid et al, 2006)

Why this view is not correct:

- The reports are based upon retrospective and meta-analyses
- The CV end points are not consistent
- Little attention has been paid to the amounts of calcium in these reports: often greater than recommended (<2.5 g/day)
Calcium is good for you!

• In moderation
• Dietary calcium is preferred
• Supplements should be used to supplement dietary calcium
• There is no evidence that dietary and supplemental calcium less than 2.5 g/day is harmful
VITAMIN D
Without sufficient vitamin D

- Calcium absorption is reduced
- Even a calcium sufficient diet, therefore will not be adequate, in the presence of vitamin D deficiency
Vitamin D: What is the metabolite to measure?
In Armenia

• It is very expensive to measure 25-hydroxyvitamin D: ($25-US per sample)
• Essentially no data, therefore, on vitamin D adequacy here
• Abundant data, though, throughout the world
VITAMIN D DEFICIENCY IS COMMON
• How common is vitamin D deficiency?
• What are common sources of Vitamin D
  – The sun?
  – Dairy? What dairy?
  – Other sources
• How is Vitamin D deficiency defined?
• The stages of Vitamin D deficiency
  – Early, moderate, severe
Sources of Vitamin D: THE SUN
but why is it difficult to get sufficient Vitamin D from the sun?

- Seasonal
- Latitude dependent
- Concerns:
  - Skin cancer
  - Melanoma
  - Skin health
- Cultural
- Environmental
- Official Dermatological recommendations to avoid sun exposure

THE SUN IS NO LONGER A MAJOR SOURCE OF VITAMIN D THROUGHOUT THE WORLD
If we do not get our Vitamin D from Sunlight…

Is food an alternative source of Vitamin D?
Vitamin D is Rare in Food; as a Result, Intake is Low At All Ages

<table>
<thead>
<tr>
<th>Food</th>
<th>IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod Liver Oil, 1 Tsp</td>
<td>400</td>
</tr>
<tr>
<td>Salmon, 3.5 oz</td>
<td>360</td>
</tr>
<tr>
<td>Mackerel, 3.5 oz</td>
<td>345</td>
</tr>
<tr>
<td>Milk, 1 cup fortified</td>
<td>100</td>
</tr>
<tr>
<td>Fortified cereal, 3/4 cup</td>
<td>50</td>
</tr>
<tr>
<td>Liver, 3.5 oz</td>
<td>30</td>
</tr>
<tr>
<td>Egg, one whole</td>
<td>25</td>
</tr>
</tbody>
</table>

NHANES III data; mean vitamin D intake from food plus supplements

Moore, et. al., Am Diet Assoc, 104;980-983, 2004
Without sunlight as a source
Without food as a source...

We are all likely to be deficient in Vitamin D
Low Vitamin D Status is Endemic

**Diagram:**

- **X-axis:** Serum 25(OH)D (ng/ml)
- **Y-axis:** Percent of 71 Women

- **Key Point:** 59% of women have levels < 30 ng/ml.
Vitamin D Inadequacy is Common Worldwide

A convenience sample of 2,589 postmenopausal women with osteoporosis from 18 countries from 64° N to 38° S latitude

Overall, 64% had serum 25(OH)D < 30 ng/ml

Adapted from Lips, et. al., J Intern Med, 260; 245-254, 2006
Vitamin D inadequacy was defined as serum 25(OH)D <30 ng/mL.

Study Design: Cross-sectional, international study of 2589 women with osteoporosis from 18 countries to evaluate serum 25(OH)D distribution to evaluate serum 25(OH)D distribution


*Vitamin D inadequacy was defined as serum 25(OH)D <30 ng/mL.

Study Design: Cross-sectional, international study of 2589 women with osteoporosis from 18 countries to evaluate serum 25(OH)D distribution

How does one determine what is a normal and what is abnormal re 25-hydroxyvitamin D?

What value of circulating 25-hydroxyvitamin D should we aim for?

- >20 ng/mL (50 nmol/l)?
- >30 ng/mL (75 nmol/l)?
Vitamin D Status: Impact on Calcium Absorption and PTH

Fasting PTH

Calcium Absorption*

Mean serum 25(OH)D level, nmol/L

*P<0.001.

Calcium absorption plateaus at serum 25(OH)D levels ≥32 ng/mL.

Calcium absorption rises as 25(OH)D increases within the range of 25(OH)D values commonly encountered.
25-hydroxyvitamin D: what is recommended by most professional societies?

- Lower limit: 30 ng/mL (75 nmol/L)
- Upper limit: 50-80 ng/L (125-200 nmol/L)
25-Hydroxyvitamin D: Threshold values for adequacy

(nmol/l)

Inadequate levels  Adequacy
0  20  40  60  80  100

(ng/ml)

Inadequate levels  Adequacy
0  8  16  24  32  40
The IOM Report (November 2010)*

- Recommended daily intake: 600 IU (under 70 yrs); 800 IU (over 70 yrs old)
- Maximal daily intake: 4,000 IU
In Armenia

Since Vitamin D measurements are not practical because of expense, how should we ensure vitamin D adequacy in the population?
In Armenia- a suggestion

- Perhaps larger doses 2,000 IU per day for 2 months is advisable

- Then nutritional intake according to the Institute of Medicine guidelines is reasonable
Vitamin D Supplementation and Fracture Risk

- Some studies have found a reduction in fractures with supplementation
- Others have not seen an effect
- Conflicting results may relate to differences in baseline vitamin D status of participants, range of doses used, and compliance
Major points

• Good nutrition in childhood (and throughout life) is a key to optimal skeletal health
• Poor calcium intake and vitamin D deficiency in childhood could lead to suboptimal skeletal calcium and contribute to osteoporosis later in life
• Vitamin D sufficiency is a key element to good skeletal health
• There is an epidemic of vitamin D deficiency, and thus calcium deficiency, throughout the world
What can we do?

- Pediatricians and Nutritionists in Armenia:
  Pay attention to calcium and vitamin D!
  Make sure your children are getting enough exercise!

- Primary care physicians in Armenia:
  Pay attention to calcium and vitamin D!
  Make sure your patients are getting enough exercise!
Shnorhagatalutyun!