Part 1:
Essential Nutrients for Bone Health

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Outline

- Key nutrients for bone health
- Nutrient needs across the life span
  - Dietary Reference Intakes (DRIs)
  - How much is too much?
- How do Canadians measure up in nutrition for bone health?
- Osteoporosis prevention with early nutrition
Critical Stages of Bone Mass Accretion & Loss

Peak bone mass

Factors Affecting Peak Bone Mass

- Genetics – VDR gene, estrogen/PTH receptor genes
- Fetal/neonatal programming
- **Nutrition** – Ca, P, vitamins D & K, protein, etc
- Weight bearing activity – from infancy
- Diseases – malabsorption, inflammation, cancer, genetic
- Drugs – glucocorticoids, methotrexate, antiepileptics
Nutrients for Bone Health

- Calcium
- Vitamin D
- Energy, Protein, Vitamin K
- Phosphorus, Copper, Magnesium, Zinc
- Homocysteine, Folate, B6, B12, Fatty Acids, Boron
- Carbohydrates, Fluoride
- Amino Acids, Acid-Alkaline
- Ash, Iron, Vitamins A, C
- Phytoestrogens, Fiber
- Herbals-Botanicals
- Sodium, Oxalates
- Caffeine, Alcohol
Nutrients for Bone Health

Potential deficient nutrients
• Calcium
• Vitamin D
• Protein
• Vitamin K
• Folate & B12

Potential excess components
• Vitamin A
• Fibre
• Sodium
• Oxalates
• Caffeine
• Alcohol
How much nutrient to eat for bone health?

Food and Nutrition Board, National Academy of Sciences & Office of Nutrition Policy and Promotion, Health Canada
DRI Basic Concepts

- 3 reference values
  - **Population – EAR** – Estimated Average Requirement
    - Used to **assess diet adequacy** in groups of people
  - **Individual – RDA** – Recommended Dietary Allowance
    - target intake for individual
  - **Upper level – UL**
    - too much leads to adverse health effect

- Nutrient need varies by age/gender
- Indicator of adequacy:
- Bone health only for calcium & vitamin D
Nutrient DRIs for Bone Health

Possible EAR/RDA
• Calcium
• Vitamins D, K & C
• Magnesium

Considered in UL
• Vitamin A
• Fluoride
• Phosphorus

Neither EAR/RDA nor UL
• Protein
• Magnesium
• Vitamins K, C, folate, B6 & B12

+ve

-ve
Facts for Calcium

- 99% body calcium in bone

Factors affecting Ca bioavailability:

- Age
  - children absorb 60% vs adults 30% dietary Ca

- Dose consumed
  - higher intake → lower absorption
    (not > 500 mg supplement at once)

- Vitamin D status

- Enhancing/inhibiting effects of food substances
Ca bioavailability for absorption: Factors

- **Enhancing factors** – chelates that keep Ca soluble in intestine
  - Lactose
  - Citrate and amino acids

- **Inhibiting factors** – precipitate or render Ca insoluble so that it is excreted in feces
  - High fat diet → Ca soaps
  - Oxalic acid in spinach, rhubarb, broccoli
  - Phytic acids in grains such as soy
  - Excess of other divalent cations – Mg++, Zn++
Substances that interfere with calcium

- **High salt intake**  \(\rightarrow\) urinary Na and Ca loss
  - Solvent drag effect of Na on Ca
  - Only a problem at high Na and low Ca intake

- **High caffeine intake**
  - Caffeine induces  \(\rightarrow\) small decrease in absorption and increase in excretion
  - 1 cup regular coffee  \(\rightarrow\) 2–3 mg Ca excretion
    - \(> 2-3\) cups coffee/d)  \(\rightarrow\) possible bone loss but only if Ca intake very low

- **High alcohol intake**
  - Reduces Ca absorption & interfere with metabolism of vit D in liver
    (J Nutr 2003;133:855S; J Nutr 2003;133:862; AJCN 1999;69:147)
DRI for Calcium: Adults

19-50 yr
- Balance studies (Hunt and Johnson 2007)
- EAR = 800 mg/day for essentially “0” balance
- RDA 1000 mg/day.

51-79 yr
- Analysis of fracture risk and BMD data → higher value best for women 51-70 & adults > 70 yr
- EAR 1000 mg/d
- RDA 1200 mg/d
UL for Adults – Risks of excess calcium

UL for DRI
To age 50: 2500 mg/d; > 50 y: 2000 mg/d

Basis:
- Kidney stones
- Interference with microminerals – Fe, Zn, Mg

Not Considered
- Risk of cardiovascular disease (CVD)
- Calcium supplements – good or bad?
Calcium and CVD

- Calcium proposed to reduce risk by:
  - decreasing intestinal absorption of lipids
  - increasing lipid excretion
  - lowering blood cholesterol
  - promoting calcium influx into cells

- Calcium proposed to increase risk by:
  - abrupt changes in plasma Ca concentrations after starting Ca supps might cause the adverse effects.

http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#h8
## Calcium Intakes & CVD Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Ca/Vit D</th>
<th>No Risk</th>
<th>Risk Increase</th>
<th>Risk Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wang 2010, SR</strong> N=12,000</td>
<td>1 g Ca ± Vit D</td>
<td>No effect Ca or Ca+D sups</td>
<td></td>
<td>For CVD Vit D @ 1000 IU/d</td>
</tr>
<tr>
<td><strong>Bolland 2010, SR</strong> N=20,072</td>
<td>Ca sups</td>
<td></td>
<td>For MI RR 1.27 for Ca sups – vit D</td>
<td></td>
</tr>
<tr>
<td><strong>Bolland 2011, WHI, N=36,282</strong></td>
<td>Ca sups ± Vit D</td>
<td></td>
<td>For MI - RR 1.24 for Ca sups</td>
<td></td>
</tr>
<tr>
<td><strong>Samelson 2012</strong> N=1278</td>
<td>Total Ca intake</td>
<td>Artery calcification</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Li 2012 EPIC</strong> N=23,980</td>
<td>Ca sup vs diet/dairy Ca</td>
<td></td>
<td>For MI HR 1.86/2.39 for Ca sup only</td>
<td>For MI HR 0.69 for total &amp; dairy Ca</td>
</tr>
<tr>
<td><strong>Michaelsson 2013</strong> N=61,443</td>
<td>High vs low Ca intakes ± Ca sups vs 666-1000 mg</td>
<td></td>
<td>For CVD/IHD HR 1.49/2.14 if total Ca &gt; 1400 or &lt; 600 mg/d</td>
<td></td>
</tr>
</tbody>
</table>
Critique: Calcium & CVD Risk

• Data not rigorous nor consistent \( (\text{Heaney R et al. Adv Nutr 2012}) \)
  – inadequate compliance with Ca sup intervention
  – use of non-trial Ca sups
  – potential bias in event ascertainment
  – lack of adjustment for known CVD determinants

In light of current evidence on Ca intake & CVD:

• Recommend a daily calcium intake
  – within DRI recommendations for age
  – preferably from dietary sources
  – if supplements, give calcium and vitamin D together

http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#h8
Vitamin D & Bone Health

**Figure 1. Human vitamin D synthesis pathways. Reproduced with permission from [7].**

1. **7-dehydrocholesterol in skin**
   - (SPF ≥ 8, clothes, glass)
   - (-)
   - UVB (290-315 nm)

2. **Major Source: Sun**
   - Minor Source: Dietary
   - Vitamin D₂ (ergocalciferol):
     - Plants/supplements - D₃
   - Vitamin D₃ (Cholecalciferol):
     - Fish (cod liver oil), meat, fortified milk, egg yolk, butter

3. **25-hydroxylase**
   - 25-hydroxyvitamin D₃
   - 25(OH) D₃
   - Parathyroid hormone
   - (+)

4. **1-hydroxylase**
   - 1,25-dihydroxyvitamin D₃
   - ↑Calcium absorption (small intestine)
   - ↑Urinary calcium reabsorption (kidney)
   - ↑Bone mineralization

Wagner CL et al. Nutrients 2012 (Breastfeed Med 2008)
Vitamin D: Key DRI indicator

Target to set DRI $\rightarrow$ serum 25OHD to optimize bone health by indicators:

- Calcium absorption
- Rickets
- Fracture risk: RCTs
- Fracture risk: Observational
- Falls
Vitamin D: Development of Requirement Distribution

Serum 25-OHD

- 40 nmol/L (16 ng/mL) → EAR
- 50 nmol/L (20 ng/mL) → RDA

Why not 75 nmol/L (30 ng/mL)?

Other lines of evidence did not support:

- Calcium absorption not higher at > 20-50 nM
- Prevention of falls
- PTH Suppression
# DRI for Vitamin D

<table>
<thead>
<tr>
<th>Age Group</th>
<th>EAR (IU/day)</th>
<th>RDA (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants to 1 yr</td>
<td>(AI=400)</td>
<td></td>
</tr>
<tr>
<td>1-70 yr</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>&gt;70 yr</td>
<td>400</td>
<td>800</td>
</tr>
<tr>
<td>Preg/lactation</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>14-50 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UL – Risks of Vitamin D

**UL**

9 yr+ : 4000 IU/d (100 µg)

**Basis**

- Hypercalcemia of hypervitaminosis D
Conundrums.....

Why different vitamin D recommendations from other sources???
# Recommended Intakes for Vitamin D, IU/d

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<tr>
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</thead>
<tbody>
<tr>
<td>0-1</td>
<td>400</td>
<td>400-800</td>
<td>-</td>
<td>400-1000</td>
</tr>
<tr>
<td>1-3</td>
<td>600</td>
<td>400-800</td>
<td>-</td>
<td>600-1000</td>
</tr>
<tr>
<td>4-8</td>
<td>600</td>
<td>400-800</td>
<td>-</td>
<td>600-1000</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>800</td>
<td>-</td>
<td>800-1000 (2000)</td>
<td>1500-2000</td>
</tr>
<tr>
<td>Pregnancy/lactation</td>
<td>600</td>
<td>2000</td>
<td>-</td>
<td>1500-2000</td>
</tr>
<tr>
<td>UL</td>
<td>&gt; 9 y 4000</td>
<td>-</td>
<td>-</td>
<td>1-18 y – 4000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;19 y – 10,000</td>
</tr>
</tbody>
</table>
Conundrums of Vitamin D Recs

• DRIs for general **healthy** populations not therapeutic guidelines

• CPS for **children and pregnant/lactating** women – not evidence-based

• Osteoporosis Canada – target is adults at risk of **osteoporosis** – systematic review

• US Endocrine Society – **not based on systematic review** – different targets for vitamin D status and deficiency criteria and populations at risk

(Rosen LJ & IOM DRI committee. JCEM 2012)
Other Nutrients for Bone Health

Possible EAR/RDA
- Vitamins K & C
- Magnesium

Considered in UL
- Vitamin A
- Fluoride
- Phosphorus

Neither EAR/RDA nor UL
- Protein
- Magnesium
- Vitamins K, C
- Folate, B6 & B12
Protein & Bone: Excess vs adequate

Excess protein intake
• Higher acid load requires buffering by bone
• Increases urine Ca especially at low Ca intakes


Adequate protein intake: Systematic review
• Protein intake > 75 g/day → higher hip and spine bone (Shapese & Sukumar 2010)
• Important for older persons who have low protein intakes
• No proven impact on fracture risk

http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#h8
Vitamin K and Bone Health

• Role in formation of osteocalcin, an essential protein in bone-matrix that binds to calcium

• Postulated protective against age-related bone loss \( \rightarrow \) lower risk of fractures

• **Diet sources**: green–leafy veggies like kale, lettuce, and spinach — as well as asparagus, broccoli, brussels sprouts, watercress, parsley, or okra
Vitamin K and Bone Density in Adults
Fang et al. Meta analysis of RCTs. JBMR 2012

Systematic review

– Modest overall treatment effect of vitamin K supplements on change in BMD at lumbar spine but not femoral neck
– No difference by ethnicity, gender or type or dose of vitamin K (1 or 2)
– Cautious interpretation due to study heterogeneity

DRI – Adequate Intake for Adults
Males – 120 ug/d  Females – 90 ug/d
DRI - ULs Related to Bone Health

• **Fluoride** – UL = 10 mg/d
  – Skeletal fluorosis > 8 yr

• **Vitamin A** – UL = 600-3000 ug/d
  – Infants/children: Intracranial bulging fontanel
  – Adults: Skeletal abnormalities, bone tenderness
    • High vs low Vit A excess (s- retinol >80 ug/dl)
      → 8x greater risk OP in women *(Mata-Granados et al 2013)*
    • Vit A excess + vit D defic → higher risk OP

• **Phosphorus** – UL = 3-4 g/d
  – Skeletal porosity
  – Interference with calcium absorption/PTH
How do Canadians measure up to the DRIs and nutrient status for bone health?

Data from the Canadian Community Health Survey and Canadian Community Measures Survey, Statistics Canada, 2004-2013

http://www.hc-sc.gc.ca/fn-an/surveill/nutrition/commun/art-nutr-adol-eng.php#a331
% Adults > Age 19 with a Usual Calcium Intake < EAR, Canada, 2004
% Females > 19 yr with a Usual Calcium Intake < EAR, Canada, 2004

% Females > 19 yr with a Usual Vitamin D Intake < EAR, Canada, 2004

Bone Nutrients Missing in Diet: Intakes < EAR in adults

**CALCIUM**
- Females: 47.5% to 86.9%
- Males: 26.5% to 80.1 %

**VITAMIN D**
- All: 80-90%  - Caution: data have large CVs
  - Apparent high prevalence of inadequate dietary vitamin D is NOT supported by wide-spread vitamin D deficiency in Canadians

**MAGNESIUM**
- All: 34% - 40%
Bone Nutrients Missing in Diet: Intakes < EAR in adolescents

http://www.hc-sc.gc.ca/fn-an/surveill/nutrition/commun/art-nutr-adol-eng.php#a331

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Age 9-13 yr % &lt;EAR</th>
<th>Age 14-18 yr % &lt;EAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>66.9%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>93.1%*</td>
<td>93.5%*</td>
</tr>
<tr>
<td>Magnesium</td>
<td>10-30%</td>
<td>66.3%</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>10-30%</td>
<td>42.2%</td>
</tr>
</tbody>
</table>

* Vitamin D dietary intake data cannot stand alone and consideration must be given to serum 25OHD levels.
Measurement of Vitamin D Status

Inconsistency in defining reference cut-offs

![Graph showing serum 25(OH)D levels and cut-off values for vitamin D status]

- Severe Deficiency
- Insufficiency
- Optimal

**RDA > 50 nM** for bone health

*Cut-off Values by IOM DRIs (2011)*

*IOM. DRI for calcium and vitamin D. NAP, Washington. 2011*
Vitamin D Status in Canadians: 2009-11

Chart 1
Percentage of Canadians above and below selected vitamin D cut-off (50nmol/L), by age group

Note: 1. Data are from Cycle 2 of the Canadian Health Measures Survey, collected from August 2009 to November 2011.
Source: Statistics Canada, Canadian Health Measures Survey.

Vitamin D Blood Levels of Canadians
http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11727-eng.htm
Vitamin D Status in Canadians by Milk Consumption

Note: 1. Data are from Cycle 2 of the Canadian Health Measures Survey, collected from August 2009 to November 2011.
Source: Statistics Canada, Canadian Health Measures Survey.
Chart 4
Average vitamin D levels of adults, by age group and body mass index category

Notes: 1. Data are from Cycle 2 of the Canadian Health Measures Survey, collected from August 2009 to November 2011. Obese category includes obese, very obese, and severely obese respondents.
Source: Statistics Canada, Canadian Health Measures Survey.
Vitamin D Status in Canadians by Season

Chart 3
Percentage of Canadians at selected vitamin D levels, by season

Season

- Summer (April to October)
  - Above vitamin D cut-off: 75%
  - Below vitamin D cut-off: 25%
  - Deficiency: 6%

- Winter (November to March)
  - Above vitamin D cut-off: 60%
  - Below vitamin D cut-off: 40%
  - Deficiency: 15%

Notes: 1. Data are from Cycle 2 of the Canadian Health Measures Survey, collected from August 2009 to November 2011.
   'Deficiency' is a subset of the below vitamin D cut-off category.
   Source: Statistics Canada, Canadian Health Measures Survey.
Summary: Vitamin D Status (2009-11)

Adequate – serum 25OHD > 50 nmol/L
  - a level sufficient for healthy bones for most people
  • 68% of all Canadians; 89% children 3 to 5 yr
  • 85% vitamin D supplement users (34% of all)
  • 59% non-supplement users

Inadequate – serum 25OHD < 50 nmol/L
  • 40% in winter
  • 25% in summer

Deficient (< 30 nmol/L) – 10% Canadians

Vitamin D Blood Levels of Canadians
http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11727-eng.htm
Summary

Most (~70%) Canadians have sufficient vitamin D status to maintain healthy bones

→ despite > 80% adults & > 90% adolescents consume < EAR of 400 IU vitamin D/d

Vitamin D Blood Levels of Canadians
http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11727-eng.htm
Clinical Utility of Vitamin D Testing

Ontario Health Technology Advisory Committee (OHTAC)*

Vitamin D tests in Ontario
- mostly requested by patients soared over 5 years
  - 2004 - 30,000
  - 2008 - 400,000
  - 2009 - over 730,000

COST
- 2008 - $21.0M
- 2009 - $66 M

Testing of Vitamin D Status

OHTAC – 2010 Recommendations

– No routine vitamin D testing in general population
– Vitamin D intake and supplementation as recommended by Health Canada through education
– Excludes patients with conditions such as osteoporosis, rickets, osteopenia, malabsorption syndromes, and renal disease or drugs that affect vitamin D metabolism.

Report at:
http://www.health.gov.on.ca/english/providers/program/ohtac/tech/recommend/rec_vitamin%20d_201002.pdf
Osteoporosis Prevention

http://www.osteoporosis.ca/index.php/ci_id/8867/la_id/1.htm

Osteoporosis
“a paediatric disease with geriatric consequences”

Building strong bones in childhood is best defence against developing OP later

http://www.osteoporosis.ca/multimedia/tools.html
Epidemiological Evidence

Maternal influences in pregnancy on fetal/child bone outcomes

http://www.gettyimages.com/detail/dv385038/Photodisc
Determinants of Child Bone Mass

- Vitamin D & Ca intake (maternal – meet DRI)
- Protein intake (maternal/infant)
- UV-B exposure (maternal/infant)
- Maternal Smoking
- Gestational weight gain
- Physical activity (maternal/infant)
- Infant birth weight/prematurity
- Adiposity (leptin)
- SES

Ponsonby AL et al. Nutrients 2010

http://www.gettyimages.com/detail/dv385038/Photodisc
Pregnancy Vitamin D Status & Fetal/Child Somatic Growth

MATERNAL VITAMIN D STATUS

Fetal long bone growth

Child femur length

Birth weight, length & bone mass

Muscle mass

Child height & bone mass to 16 yr

Infant/Child Bone Mass

Fetal femur length

http://www.gettyimages.com/detail/dv385038/Photodisc
Vitamin D in Pregnancy: What to recommend (IU/d)?

Vitamin D Supplementation in Pregnancy

De-Regil LM et al Cochrane Review – 2012

n=3 trials in 463 women

- Vitamin D supplements in single or continued dose during pregnancy increases 25OHD in mother
- Clinical significance undefined due to limited trials; may protect against low birth weight
- Need RCTs with long-term outcomes in child
- Ensure mothers receive RDA = 600 IU/d
Simple Nutrition for Bone Health

• Dietary Goals
  – Intakes of all bone nutrients at RDA
  – Avoid intakes > UL → calcium, vitamins D & A, fluoride, sodium and phosphorus
  – Primary source: natural or fortified foods
  – If low milk intake/older age
    → Calcium supplements - up to 1000 mg/d
    → Vit D supplements – at least 400 IU/d

• Identify risk groups
  – vegan, adolescents, obese, non-white