Nutritional Strategies for Bone Health

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www.nbihealth.com

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Osteoporosis-Specific Publications

Since 2006

Lab Testing

Launched 2020
- Consumer lab testing
- Doctor order provided
Prevalence, Risks and Costs

- More than 53 million people either already have osteoporosis or are at high risk due to low bone mass.
- By 2025 the estimated cost of treating more than 3 million expected fractures is projected be $25.3 billion.
- Mortality rate during first year following a hip fx is 20%
- Among those who survive the first year, 20% require nursing home care.

Historical Context

- Osteoporosis: disease of low BMD first defined in 1940
  - decreased bone mass in ovariectomized pigeons.
- Diagnostic criteria created 1994 by the WHO:
  - Osteoporosis: T-score of $\leq -2.5$
  - Osteopenia: T-score of -1 to -2.5

What’s the real risk?
FRAGILITY FRACTURES

- Debilitating acute and chronic pain in the elderly is often attributed to fractures from osteoporosis
- Can lead to further disability and early mortality
- Caucasian women and men 50 years or older: lifetime risk of a hip, spine, or forearm fracture is 40% and 13%, respectively.


Fractures (cont’d)

- Of the nearly 2 million osteoporosis fractures in 2005 in the U.S:
  - 27% were vertebral fractures
  - 19% were wrist fractures
  - 14% were hip fractures
  - 7% were pelvic fractures
  - 33% were “other” fractures

Fractures (cont’d)

- 2005: Nonvertebral fractures:
  - 73% of total fractures
- 71% of all fractures occurred in women

Fx and Mortality Risk (cont’d)

- 2009 JAMA study: Increased mortality risk persisted for 5 years for all fractures and up to 10 years for hip fractures.

- Predictors of mortality:
  - Men and women: age, quadriceps weakness, and subsequent fracture;
  - Women: low BMD, having smoked, and sway were also predictors for women
  - Men: Lower physical activity.

Is BMD Predictive of Fractures?

- In 2006 the North American Menopause Society (NAMS) published a position statement on managing osteoporosis. Fracture risk “depends largely on factors other than BMD.”

- 2008 *Ann Intern Med*
  - Lumbar and Hip BMD predict:
    - 44% of elderly women who progress to fractures
    - 21% of elderly men who progress to fractures

- 1996: BMD explains less than half the risk for hip fx.


Is BMD Predictive of Fractures? (cont’d)

- Half of all hip fx occur in women who are not classified as osteoporotic (they had osteopenia)
- National Osteoporosis Risk Assessment (NORA): more than two-thirds of hip fractures occur during the first year of follow-up in women (with an average age of 65 years) who were not deemed to be osteoporotic (they had osteopenia)


What is bone?

- Complex, living tissue.
- Interacts with all other systems.
- Continually rebuilds and remolds itself.
  - Osteoblasts
  - Osteoclasts
- Two major components:
  - Cartilage
  - Minerals
Bone Cartilage

- Provides flexibility to bone.
- Provides a model for the formation of the bones.
Bone Throughout Life (cont’d)

- In women, an accelerated rate of loss occurs during menopause and for about 10 years thereafter.
- As people of both sexes age, the risk of osteoporosis and of osteoporotic fractures increases.


PPI and Fracture Risk

- Nested, case control study of hip fx risk PPI (eg, Prilosec, Prevacid, Nexium, Protonix, Aciphex)
- N = 13,556 hip fx cases and 135,386 controls; age: > 50 years.
- Risk was stronger for men than women (p = 0.04)
- Risk was dose-dependent; similar risks seen with H2 blockers (eg, Tagamet)

<table>
<thead>
<tr>
<th>Duration of tx (years)</th>
<th>Risk of hip fx (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22%</td>
</tr>
<tr>
<td>2</td>
<td>41%</td>
</tr>
<tr>
<td>3</td>
<td>54%</td>
</tr>
<tr>
<td>4</td>
<td>59%</td>
</tr>
</tbody>
</table>

Prevention and Tx Approaches

- Medications
- Diet
- Exercise
- Environmental modifications
- Targeted nutrients
  - Calcium
  - Vitamin D
  - Vitamin K
  - Strontium
Exercise and Environment

- **Goal:** Reduce falls and fall-related injuries
- **Exercise:**
  - Improve balance
  - Improve strength
  - You don’t have to go to a gym!
  - Walks, park further away, isometric exercises, Stork Exercise, yoga, Tai Chi.
- **Environment:**
  - Fix loose stairs
  - Make sure pathways in home are well-light and free from obstacles
  - Get rid of throw rugs
  - Add aides to help get in and out of showers and bathtubs
Coffee and Osteoporosis Risk

- Is coffee good or bad?
- Coffee can increase calcium excretion in the urine
- However, this does not occur if people consume the dietary reference intakes (DRIs) or more of calcium per day


Coffee and Osteoporosis (cont’d)

- Norway study of 40,000 men and women evaluated diet and coffee consumption and the risk of fractures.
- Ages 47 to 68 years
- Only women eating diet high in non-dairy animal protein and low in calcium was the risk for fractures increased
- Risk increased: 9 or more cups of coffee/day combined with low calcium intake.
- Conclusion: in moderation and combined with a healthy diet and adequate calcium, coffee does not appear to increase one’s risk for osteoporosis.

Diet: Ca, K, Mag, Vit K, Vit D

- Osteoporosis risk increased by low intakes of:
  - Calcium
  - Potassium
  - Magnesium
  - Vitamin K
- ...and by low concentrations of vitamin D


Diet: Copper and Zinc

- **Zinc**
  - People with low BMD have lower zinc concentrations in their bones
  - Found in hydroxyapatite crystals in bone
  - Involved in stimulating osteoblastic activity while suppressing osteoclastic activity

- **Copper**
  - required for bone formation
  - cofactor for the lysyl-oxidase enzyme, which forms collagen and elastin cross-links from the essential amino acid lysine


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Mediterranean Diet Reduces Fracture Risk

- Case-control study of 290 middle-aged women (45-65 years) with and without an osteoporosis diagnosis.
- Average age: 56.78 years and BMI 24.8
- “Women with higher MD adherence had lower risk of bone fracture (as measured using FRAX), corroborating current scientific evidence showing an inverse relationship between bone fracture risk and the MD.”
- Protective factors: legumes and wine were observed to be protective factors, whereas butter and meat were risk factors. Fish and olive oil were also protective factors.
- This study confirms previous studies regarding the bone-health benefits of the Mediterranean diet.

Meta-analysis: higher adherence to the MD is associated with a 21% decreased hip fracture risk and a higher BMD in the lumbar spine, whole body, and trochanter.

Higher MD adherence also tends to be associated with healthier lifestyles (greater physical activity and fewer toxic habits).

Other studies reported 6% fewer hip fractures related to high adherence to the MD [33-35] and that higher MDI scores were positively and dose-dependently associated with BMD.

The Rotterdam study [36] also highlighted that diets similar to the MD may be associated with lower fracture risk.


Mediterranean Diet

Reduces risk for:

- Heart disease
- Obesity
- Diabetes
- Osteoporosis
- Fractures
- Cancer
- Death from cancer
- All-cause mortality
- Alzheimer’s disease
- Reverses non-alcoholic fatty liver disease (NAFLD)

For more info and citations, see my blog Food Matters at https://nbihealth.com/food-matters/

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Help Clients Make the Switch

- A program I created in my clinical practice.
- Focus: Plants and Protein
  - 30 grams total dietary fiber per day
  - Calculate individual protein requirements based on body weight: 0.8-1.2 mg protein per kilogram body weight per day.
- Transition over 4-6 weeks
- Teach people how to eat to promote their health for life
- For step by step instructions on how to transition, and client handouts, see my blog, Dr. Neustadt’s 3-Steps to Eating Healthy for Life at [https://nbihealth.com/dr-neustadts-3-steps-to-eating-healthy-for-life/](https://nbihealth.com/dr-neustadts-3-steps-to-eating-healthy-for-life/)
**Vitamin K**

- **Two natural forms:**
  - Vitamin K1 (phylloquinone)
  - Vitamin K2 (menaquinone)
    - has two major forms, MK4 and MK7
    - is more active than K1 at promoting bone formation.


Vitamin K (cont’d)

- Vitamin K1 and MK4 inhibit osteoclast formation and induces osteoblast formation in vitro.
- MK4 increases vitamin D3-induced bone mineralization by osteoblasts in vitro
- MK4 used in Japan as osteoporosis tx since 1995.
- MK4 prevents and reverses arterial calcification.
- MK7 derived from natto; longer half-life than MK4


Vitamin K2 (Menaquinones)

- Contain side chains of various lengths.
- Designated as MK-n, where n is the number of isoprenoid residues, all which are unsaturated.
- Long-chain menaquinones (MK7 through MK10) are exclusively synthesized by bacteria.
- MK4 can be synthesized in testis, pancreas, and arterial walls.
  - Accumulation of vitamin K in these tissues is almost exclusively as MK4


Vitamin K

- K1: preferentially used by the liver.
- K2 is 15 times more powerful antioxidant than K1
- K2: the predominant form and preferentially used by extrahepatic tissues, such as brain, vasculature, breast, kidneys and bone.
- In the brain, K2 contributes to production of myelin and sphingolipids and protects agains oxidative damage.

Vitamin K: Safety

- No Tolerable Upper Intake Limit set (safe at all doses)
- Human coagulation studies using up to 135 mg/day MK4 showed no significant increase in pathologic coagulation risk.
- Even MK4 doses in rats as high as 250 mg/kg body weight did not alter the tendency for blood-clot formation to occur.
- Caution with MK7, derived from natto (soy) in patients with celiac and gluten intolerance, due to elevated risk of soy allergy in these patients.
Vit K: Safety Citations


K1 vs K2 for Fx Prevention
What’s the Evidence?

- Vitamin K1 (phyloquinone):
  - No clinical trials to show it decreases fractures;
  - Epidemiological data show phylloquinone consumption may decrease fx risk.

- Vitamin K2 (menaquinones; MK-n)
  - MK4:
    - Multiple clinical trials show it decreases fractures at a dose of 45 mg/day (https://nbihealth.com/bone-support)
    - Studies show it decreases uOC and can improve bone density.
    - Also has anti-cancer activity shown in basic research and up to Phase II clinical trials (https://nbihealth.com/cancer-support/)
  - MK7:
    - No clinical trials to show it decreases fractures;
    - Studies show it decreases uOC and improve bone density.
    - No anticancer activity.
Vitamin K1

- Study design: observational
- N = 888 (335 men, 553 women; avg age: 75.2 yrs).
- Duration: 7 yrs.
- Data source: Framingham Heart Study (1988-1995)
- Evaluated phylloquinone (K1) consumption
- 65% reduction in fx risk in highest quartile of vitamin K1 intake (254 mcg/d) vs. lowest quartile (56 mcg/d)
Vitamin K1 (cont’d)

- Limitations:
  - Evaluated just phylloquinone intake.
  - Excluded:
    - Home-bound participants
    - People consuming < 600 or > 4,000 kcal per day.
    - People who left >12 food items blank on FFQ.
  - People who had complete data (BMD tests and FFQ) were significantly younger and more physically active.

Eat Your Greens

- Phylloquinone content in:
  - Green leafy vegetables: 1000-8000 mcg/kg
  - Other vegetables and fruit: 10-500 mcg/kg
  - Dairy: 3-70 mcg/kg (dependent on fat content)
  - Grains: 0.5-70 mcg/kg

- BUT: because of large variations in absorbability, vitamin K content of foods alone is insufficient to determine whether someone intake is adequate

- Vitamin K intake decreases with age.
- Vitamin K intake inversely associated with osteoporosis.

Dietary Sources of Vitamin K

<table>
<thead>
<tr>
<th>Food source</th>
<th>Vitamin K&lt;sub&gt;1&lt;/sub&gt; content (µg/100 g)</th>
<th>Vitamin K&lt;sub&gt;2&lt;/sub&gt; content (µg/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>0.5–5</td>
<td>1–30</td>
</tr>
<tr>
<td>Fish</td>
<td>0.1–1</td>
<td>0.2–4</td>
</tr>
<tr>
<td>Fruit</td>
<td>0.1–3</td>
<td>—</td>
</tr>
<tr>
<td>Green vegetables</td>
<td>100–700</td>
<td>—</td>
</tr>
<tr>
<td>Grains</td>
<td>0.5–3</td>
<td>—</td>
</tr>
<tr>
<td>Natto</td>
<td>20–40</td>
<td>900–1200</td>
</tr>
<tr>
<td>Cheese</td>
<td>0.5–10</td>
<td>40–90</td>
</tr>
<tr>
<td>Other milk products</td>
<td>0.5–15</td>
<td>0.2–50</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.5–2.5</td>
<td>10–25</td>
</tr>
<tr>
<td>Margarine and plant oils</td>
<td>50–200</td>
<td>—</td>
</tr>
</tbody>
</table>
MK4 for Preventing Bone Loss
Clinical Trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>Leuprolide (a GnRH agonist)</td>
</tr>
<tr>
<td>Cirrhosis of the liver</td>
<td>Menopause (estrogen deficiency)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Disuse from stroke</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Immobilization (eg, extended illness,</td>
<td>Testosterone deficiency (eg, aging,</td>
</tr>
<tr>
<td>hospitalization)</td>
<td>prostate CA tx)</td>
</tr>
</tbody>
</table>

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Ushiroyma T, Ikeda A, Ueki M. Effect of continuous combined therapy with vitamin K(2) and vitamin D(3) on bone mineral density and coagulofibrinolysis function in postmenopausal women. *Maturitas* 2002;41:211-221.
MK4 and Fractures
Clinical Trial 1

- Design: Randomized, controlled, open-label study.
- N = 241 osteoporotic women (avg. age ≈ 67 yrs.)
- Control group (N = 121): 150 mg elemental calcium/day
- MK4 group (N = 120): 150 mg Ca/d plus 45 mg/d MK4
- Duration: 24 months
- Outcomes:
  - BMD
  - Fractures

Clinical Trial 1 (cont’d)

Vertebral fx incidence:

- Shiraki M, ShControl: 30 fx (30.3%)
- MK4: 13 fx (10.9%)
- Statistically significant difference: p = 0.0273

<table>
<thead>
<tr>
<th>Group</th>
<th>No</th>
<th>Vertebral</th>
<th>Forearm</th>
<th>Femoral neck</th>
<th>Other site</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>64</td>
<td>30</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>MK4</td>
<td>77</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>91</td>
</tr>
</tbody>
</table>

MK4 and Fractures
Clinical Trial 2

Design: multicenter, randomized, double-blinded, double-dummy, noninferiority, positive drug-controlled clinical trial

N = 213 women with postmenopausal osteoporosis

Groups:
- (1) MK4 (45 mg/day)
- (2) vitamin D (as alfalcacidol) 0.5 micrograms/day

Duration: 12 months

Outcomes:
- BMD
- Fractures
- Serum osteocalcin (OC) and undercarboxylated osteocalcin (ucOC)

Clinical Trial 2 (cont’d)

- Fractures:
  - MK4 group: 50% fewer fractures in the MK4 group compared to the vitamin D group (P>0.05). Two fractures in MK4 group versus four fractures in vitamin D group.

- BMD:
  - MK4 group: increased from baseline by 1.2% and 2.7% at the lumbar spine and trochanter, respectively (P<0.001);
  - Vitamin D group: 2.2% and 1.8%, respectively (P<0.001).
  - No difference was observed between groups.
  - There were no changes in femoral neck BMD in both groups.

- Osteocalcin: OC and ucOC improved significantly more on the MK4 group than in the vitamin D group.
Strontium ranelate (SR)

- The form which all clinical trials have used.
- Not available in the U.S.
- Sold in Europe as the medication, Protelos® (Les Laboratoires Servier, Neuilly-Sur-Seine, France)
- 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-3-thiophenacetic acid distrontium salt
- *In vitro*: decreases osteoclast activity and increases osteoblast activity

SR Clinical Trial 1

- **Study:** SR for the tx of osteoporosis (STRATOS)
- **Design:** randomized, multicenter, double-blind, placebo-controlled, dose-response trial
- **Duration:** 2 years
- **Volunteers:** 353 non-obese, post-menopausal, osteoporotic women between 45 and 78 years of age

SR Clinical Trial 1 (cont’d)

- Groups:
  - Placebo
  - SR 0.5 g/d
  - SR 1.0 g/d
  - SR 2.0 g/d.

- Everyone also received: calcium (500 mg/d) and vitamin D (vitamin D3, 800 IU/d)

SR Clinical Trial 1 (cont’d)

- **Endpoints:**
  - **Primary:** LBMD
  - **Secondary:**
    - femoral neck BMD (FN-BMD)
    - incidence of new vertebral deformities
    - biochemical markers of bone metabolism

SR Clinical Trial 1 (cont’d)

- Results after 2 yrs:
  - SR 0.5 g/d: 29% decrease in fx risk compared to placebo.
  - SR 2.0 g/d: 23% decrease in fx risk compared to placebo.
  - SR 2.0 g/d resulted in greater increases in BMD, about 3% per year.

SR Clinical Trial 2

- Design: randomized, double-blind
- Duration: 3 years
- Intervention: 2 g SR/d or placebo, plus all volunteers received ≤ 1000 mg calcium/d and 400-800 IU Vitamin D (form not specified) per day
- N = 1442 postmenopausal, osteoporotic women (mean age ≈ 69 yrs)

SR Clinical Trial 2 (cont’d)

- Results after 3 years:
  - SR group:
    - LBMD increased 12.7%
    - FN-BMD increased 7.2%
    - Hip BMD increased 8.6% (*P* < .001 for all three sites)
    - 41% lower risk of a new vertebral fracture compared to placebo (*P* < .001).
    - The researchers concluded that to prevent 1 patient from suffering a vertebral fracture, 9 patients would need to be treated for 3 years with SR.

SR Safety

- Strontium has an atomic mass greater than calcium and attenuates the X-rays from a DEXA scan to a greater extent than calcium.

- Unless radiologist corrects for this, the DEXA scan will not provide an accurate measure of BMD.

- Safety profile “compares favorably with the other currently marketed antiosteoporosis medications.”


Dr. Neustadt’s Bone Health Nutritional Rx

- **Diet:**
  - Whole foods, minimal processed foods, lean proteins.
  - See step-by-step guide to transitioning into eat this way in the blog, Dr. Neustadt’s 3-Steps for Eating Health for Life ([https://nbihealth.com/dr-neustadts-3-steps-to-eating-healthy-for-life/](https://nbihealth.com/dr-neustadts-3-steps-to-eating-healthy-for-life/))

- **Exercise:**

- **Dietary supplements** ([https://shop.nbihealth.com](https://shop.nbihealth.com))
  - NBI Osteo-K or Osteo-K Minis
  - NBI Supreme Multivitamin

- **Tests** ([https://shop.nbihealth.com/products/lab-tests](https://shop.nbihealth.com/products/lab-tests)):
  - Serum ferritin for iron status: The Most Important Lab Test Women aren’t Getting ([https://nbihealth.com/the-most-important-lab-test-women-arent-getting/](https://nbihealth.com/the-most-important-lab-test-women-arent-getting/))
NBI Bone Health Products

Formulated by physicians from Harvard, Cornell, MIT and Bastyr

Per day:

• 45 mg MK4

• 1000 or 400 mg calcium (as calcium citrate)

• 2000 IU (50 mcg) vitamin D3

Coupon code: IFNA10 for 10% off all dietary supplements. One-time use.