Nutrition and Osteoporosis 2022:

Behind the Crystal Ball: Why Are Nutrition/Bone Outcomes So Confusing?

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1

I have no conflicts of interest to report related to the content of this talk.

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Outline

- Vitamin K and vitamin D trials and meta-analyses
- What can we learn from these studies?
- Study outcomes re-evaluated
- Medical foods and bone

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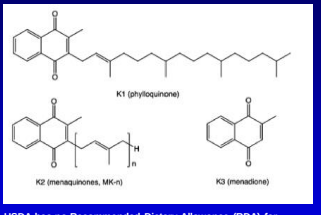
Vitamin K



USDA has no Recommended Dietary Allowance (RDA) for vitamin K
US Institute of Medicine has set Adequate Intake AI at 90 and 120 µg/day for women and men
No known serious side effects from too much vitamin K except related to individuals anticoagulated with vitamin K inhibitors

K1 is in spinach, broccoli, green leaf lettuce is >50% of intake

K2 is in natto, egg yolk, chicken breast and is made by gut bacteria

FDA has banned use of K3 in over the counter supplements because large doses interfere with glutathione and cause oxidative damage to cell membranes

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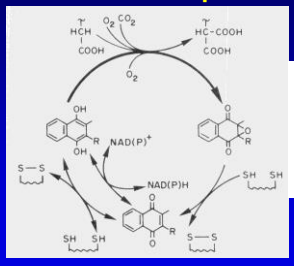
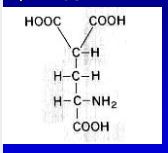
Vitamin K-Dependent Reactions



γ Carboxylglutamic Acid



Coumadin inhibits the regeneration cycle

Modern Nutrition in Health and Disease, 10th edition

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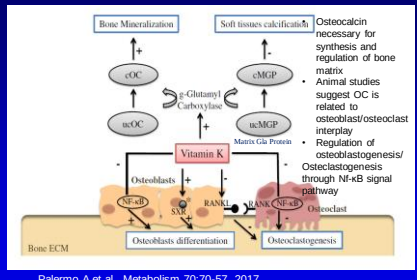
What Does Vitamin K Do in Bone?



- Osteocalcin necessary for synthesis and regulation of bone matrix
- Animal studies suggest OC is related to osteoblast/osteoclast interplay
- Regulation of osteoblastogenesis/ Osteclastogenesis through Nf-κB signal pathway

Palermo A et al. Metabolism 70:70-57, 2017.

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BMD/Fracture and Vitamin K Intake

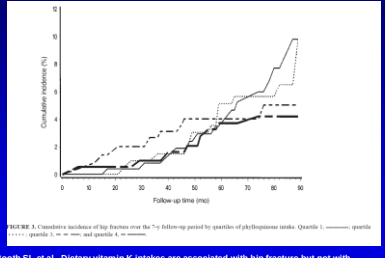

FIGURE 3. Cumulative incidence of hip fracture over the 7-y follow-up period by quartiles of phylloquinone intake. Quartile 1, ——; quartile 2, - - - -; quartile 3, — — —; and quartile 4, ———.

Booth SL et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr 71: 1201-8, 2000.

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Vitamin K and Hip Fracture

TABLE 4
Age-adjusted relative risks (RRs) with 95% CIs for risk of hip fracture by frequency of lettuce consumption

Lettuce servings[1]	Person-years (thousands)	Number of cases	RR (95% CI)
≤ 1/wk	162.5	65	Reference
2–4/wk	219.2	52	0.65 (0.47, 0.90)
5–6/wk	129.8	46	0.73 (0.52, 1.04)
≥ 1/d	190.6	52	0.55 (0.40, 0.78)
P for trend[2]	—	—	0.004

[1] Serving size = 1 cup (≈227 g).
[2] *P* for trend = 0.004; linear trend over categories of lettuce consumption with the median value per category.

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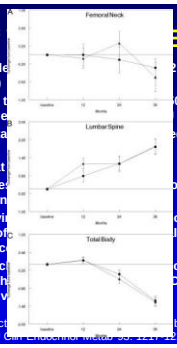
Effect of … Bone Loss

- 3 year, double… … women and men (60-80 years)
- Randomized t… …00 µg/d or no K2, plus 600 mg e… … vitamin D/day
- BMD, and vita… …ed every 6 -12 months
- Intent to treat
- No difference… …of the anatomical sites between…
- Those receivi… …one and a lower percentage of… …lcin than the group not rec…
- Authors conc… …on at a dose available in th… …D when taken with calcium and v…



Booth SL et al. Effect… …bone loss in elderly men and women. J Clin Endocrinol Metab 93: 1217-1223, 2008

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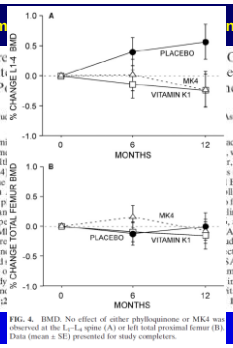
Vitam… …n Trial

Vitamin K Tre… Does Not All… P… Osteocalcin but …etry in Healthy …en

Neil Binkley,[1] Ju… …ast,[1] Dessa Gemar,[1]



ABSTRACT: Low vitami… …acture risk. Additionally, a specific menaquinone, mi… …, whether vitamin K plays a role in the skeletal healt… …r, various K vitamers (e.g., phylloquinone and MK4)… …s study was to evaluate the impact of phylloquinone… …BMD in nonosteoporotic, postmenopausal, North… …lled study, 381 postmenopausal women received p… …for 12 mo. All participants received daily calcium an… …line phosphatase (BSALP) and n-telopeptide of type … …, and 12 mo. Lumbar spine and proximal femur BM… …A at baseline and 6 and 12 mo. At baseline, the thre… …dy endpoints. Compliance with calcium, phylloquin… …ctively. Phylloquinone and MK4 treatment reduced… …SALP or NTX. No effect of phylloquinone or MK4 o… …mur geometric parameters was observed. This study … …in osteoporosis prevention among healthy, postmen… …tamin D supplementation.
J Bone Miner Res 2009;2… 10.1359/JBMR.081254

FIG. 4. BMD. No effect of either phylloquinone or MK4 was observed at the L_1–L_4 spine (A) or left total proximal femur (B). Data (mean ± SE) presented for study completers.

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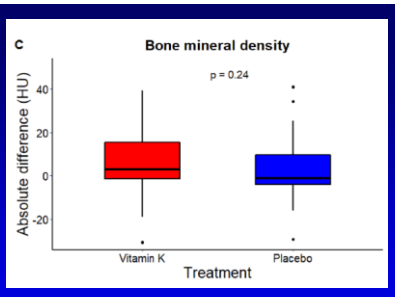

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Effect of vitamin K on bone mineral density and fractures in adults: an updated systematic review and meta-analysis of randomised controlled trials

Check for updates

A. Mott[1] · T. Bradley[2] · K. Wright[3] · E. S. Cockayne[1] · M. J. Shearer[4] · J. Adamson[5] · S. A. Lanham-New[6] · D. J. Torgerson[1]

Received: 7 December 2018 / Accepted: 19 March 2019 / Published online: 10 May 2019
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Abstract

Summary Vitamin K may affect bone mineral density and fracture incidence. Since publication of a previous systematic review the integrity of some of the previous evidence has been questioned and further trials have been published. Therefore an update to the systematic review was required.

Introduction This systematic review was designed to assess the effectiveness of oral vitamin K supplementation for increasing bone mineral density and reducing fractures in adults.

Methods MEDLINE, EMBASE, CENTRAL, CINAHL, clinicaltrials.gov, and WHO-ICTRP were searched for eligible trials. Randomised controlled trials assessing oral vitamin K supplementation that assessed bone mineral density or fractures in adult populations were included. A total of 36 studies were identified. Two independent reviewers extracted data using a piloted extraction form.

Conclusions For post-menopausal or osteoporotic patients, there is no evidence that vitamin K affects bone mineral density or vertebral fractures; it may reduce clinical fractures; however, the evidence is insufficient to confirm this. There are too few trials to draw conclusions for other patient groups.

95%, CI − 0.02 to 1.89) and 2 years (MD 1.63%, 95%CI 0.10 to 3.16) for vitamin K compared to controls; however, removing trials at high risk of bias tended to result in smaller differences that were not statistically significant. At 6 months, it was higher in the hip (MD 0.42%, 95%CI 0.01 to 0.83) and femur (MD 0.29%, 95%CI 0.17 to 0.42). There was no significant difference at other anatomical sites.

Conclusions For post-menopausal or osteoporotic patients, there is no evidence that vitamin K affects bone mineral density or vertebral fractures; it may reduce clinical fractures; however, the evidence is insufficient to confirm this. There are too few trials to draw conclusions for other patient groups.

Mott A et al. Osteoporosis Int 30:1543-1559, 2019

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Vitamin D

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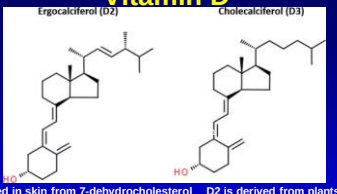
Vitamin D



D3 formed in skin from 7-dehydrocholesterol D2 is derived from plants
Vitamin D is 25-hydroxylated in liver and then 1- hydroxylated in kidney to form active vitamin D.
1,25 OH2 D (calcitriol) formation is upregulated by parathyroid hormone and down regulated by FGF23.
Few dietary sources: Milk is fortified with 400 IU per quart.
RDA: Children and adults aged 6-70 years = 600 IU(15 µg) /d, Adults > 70 years 800IU/d (20 µg)

Researchgate.net
https://www.ncbi.nlm.nih.gov/books/NBK310616

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Vitamin D Reduces Fracture

- Meta-analysis of double-blind, placebo-controlled RCT of vitamin D with/without calcium
- Trials using 700-800 IU of vitamin D (with or without calcium) had a 26% reduction in hip fracture risk and 23% reduction in nonvertebral fracture compared in 400 IU of vitamin per day

Bischoff-Ferrari HA, et al. Fracture prevention with vitamin D supplementation A meta-analysis of randomized controlled trial. JAMA 293: 2257-2264, 2005.

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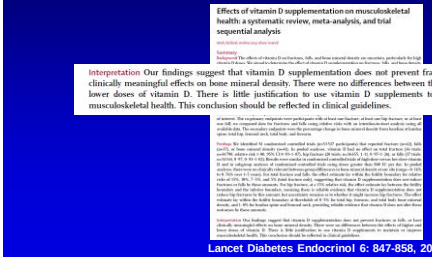
Vitamin D Does Not have Meaningful Bone Effects



Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis

Interpretation Our findings suggest that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. There were no differences between the effects of higher and lower doses of vitamin D. There is little justification to use vitamin D supplements to maintain or improve musculoskeletal health. This conclusion should be reflected in clinical guidelines.

Lancet Diabetes Endocrinol 6: 847-858, 2018.

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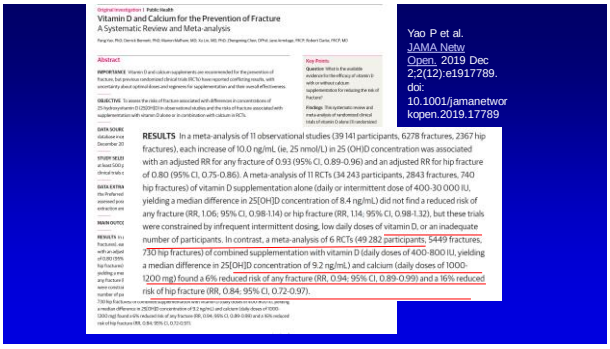

Vitamin D and Calcium for the Prevention of Fracture
A Systematic Review and Meta-analysis

Abstract

RESULTS In a meta-analysis of 11 observational studies (39 141 participants, 6278 fractures, 2367 hip fractures), each increase of 10.0 ng/mL (ie, 25 nmol/L) in 25 (OH)D concentration was associated with an adjusted RR for any fracture of 0.93 (95% CI, 0.89-0.96) and an adjusted RR for hip fracture of 0.80 (95% CI, 0.75-0.86). A meta-analysis of 11 RCTs (34 243 participants, 2843 fractures, 740 hip fractures) of vitamin D supplementation alone (daily or intermittent dose of 400-30 000 IU, yielding a median difference in 25[OH]D concentration of 8.4 ng/mL) did not find a reduced risk of any fracture (RR, 1.06; 95% CI, 0.98-1.14) or hip fracture (RR, 1.14; 95% CI, 0.98-1.32), but these trials were constrained by infrequent intermittent dosing, low daily doses of vitamin D, or an inadequate number of participants. In contrast, a meta-analysis of 6 RCTs (49 282 participants, 5449 fractures, 730 hip fractures) of combined supplementation with vitamin D (daily doses of 400-800 IU, yielding a median difference in 25[OH]D concentration of 9.2 ng/mL) and calcium (daily doses of 1000-1200 mg) found a 6% reduced risk of any fracture (RR, 0.94; 95% CI, 0.89-0.99) and a 16% reduced risk of hip fracture (RR, 0.84; 95% CI, 0.72-0.97).

Yao P et al. JAMA Netw Open. 2019 Dec 2;2(12):e1917789. doi: 10.1001/jamanetworkopen.2019.17789

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Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength
A Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE Among healthy adults, treatment with vitamin D for 3 years at a dose of 4000 IU per day or 10 000 IU per day, compared with 400 IU per day, resulted in statistically significant lower radial BMD; tibial BMD was significantly lower only with the 10 000 IU per day dose. There were no significant differences in bone strength at either the radius or tibia. These findings do not support a benefit of high-dose vitamin D supplementation for bone health; further research would be needed to determine whether it is harmful.

JAMA 322: 736-45, 2019

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The Washington Post

The Big Number: 300,000 break their hips each year. Calcium and vitamin D could cut that number, research says.

The battle lines have been drawn – do nutritional supplements do anything for bone?

Most dietary supplements don't do anything. Why do we spend $35 billion a year on them?

By Tamar Haspel
Columnist, Food
Jan. 27, 2020 at 7:00 a.m. CST

From: Weaver CM et al. Arch Osteoporosis (https://doi.org/10.1007/s11657-019-0589-y) 14: 50, 2019

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Could these confusing and often null and even negative results have been predicted?

WHAT IS GOING ON HERE?

I'd like to suggest some considerations about studying nutrients related to bone health

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The use of evidence-based medicine and reliance upon randomized controlled trials makes sense for drug trials where there is emphasis on size of cohorts, randomization, and blinding and other measures of quality. There is less usefulness for evidence-based medicine and specifically the use of randomized controlled trials to inform decisions about nutritional interventions because of some of the considerations summarized in the next slides:

Heaney RP. Nutrients, endpoints, and the problem of proof. J Nutr 138: 1591-1595, 2008.

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- **Nutrient effects are often related to inadequate intakes and inadequate nutritional status, while drug administration is designed to cure a disease that is not caused by the absence of a drug**.
- This means that drug effects are usually large and generally have a fairly specific outcome and therefore lend them self to evidence-based medicine clinical trials**.**
- **Nutrient effects often affect many tissues and the outcomes are often "within in the 'noise' of biological variability" and therefore nutrient effects are often lost in clinical trials.**

[1]Blumberg, J., et al., *Evidence-based criteria in the nutritional context.* Nutr Rev, 2010. **68**(8): p. 478-84.

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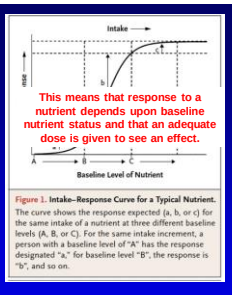
Nutrient effects generally follow a sigmoid curve, while drugs generally have effects in proportion to the dose of the drug. This means that with low nutrient intakes or low nutrient status, there is fairly little biological response. In a drug study, the drug can be tested against a placebo group that doesn't receive the drug. In a nutritional study the placebo group would correctly have zero intake or be deficient, which is difficult and unethical. It also means that the nutritional status of all the groups in a nutritional study should be know prior to starting the study.

"An identical nutrient intake (i.e., prescribed dose) may or may not produce a measureable response (depending on the baseline status)."

"Until we link outcomes to blood levels achieved, and understand what analytic to measure, meta-analyses will not answer the "how much is enough" question".



This means that response to a nutrient depends upon baseline nutrient status and that an adequate dose is given to see an effect.

Figure 1. **Intake–Response Curve for a Typical Nutrient.** The curve shows the response expected (a, b, or c) for the same intake of a nutrient at three different baseline levels (A, B, or C). For the same intake increment, a person with a baseline level of "A" has the response designated "a," for baseline level "B", the response is "b", and so on.

Blumberg, J., et al., *Evidence-based criteria in the nutritional context.* Nutr Rev, 2010. **68**(8): p. 478-84.
Heaney, R.P., *Vitamin D--baseline status and effective dose.* N Engl J Med, 2012. **367**(1): p. 77-8.
Lappe, J.M. and R.P. Heaney, *Why randomized controlled trials of calcium and vitamin D sometimes fail.* Dermatoendocrinol, 2012. **4**(2): p. 95-100.

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RCT Design is Probably Not Suited for Nutrition Studies

- **Nutrition trials are generally designed for well people, drug trials treat a disease**
- **Drug trials generally have a few principal endpoints, nutrients affect many tissues (i.e. vitamins are coenzymes)**
- **Nutrient effects manifest themselves in small differences over long periods of time – therefore a short- term RCT may not see a difference in an outcome such as fracture or BMD**
- **Nutrients work together (i.e. calcium and vitamin D) - as a opposed to drug effects – i.e. could the effect of vitamin K supplementation be difference in a vitamin D insufficient population?**
- **What ever the disease outcome, the unsupplemented group "must develop roughly 13-26 excess incident disease cases or untoward events (i.e. hip fracture)"[1].**
- **Dr Heaney suggests having "global indices" of some sort for nutritional trials.**

[1]Heaney RP. Nutrients, endpoints, and the problem of proof. J Nutr 138: 1591-1595, 2008.

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Nutrient effects are polyvalent with nutrients effecting many tissues and processes while drug effects are often more clear cut and can be studied in isolation, often with single outcomes. An example is that calcium and vitamin D intake are intertwined in bone metabolism, making it difficult to study a single nutrient. Another example is that protein intakes need to be adequate for calcium to have an impact on bone, a relationship that is not controlled for in the calcium/vitamin D bone literature[1,2].

[1]Lappe, J.M. and R.P. Heaney, *Why randomized controlled trials of calcium and vitamin D sometimes fail.* Dermatoendocrinol, 2012. **4**(2): p. 95-100.
[2]Dawson-Hughes, B. and S.S. Harris, *Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women.* Am J Clin Nutr, 2002. **75**(4): p. 773-9.

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Different Tissues May Have Different Response Curves

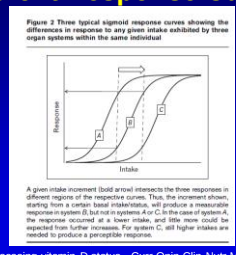

Figure 2 Three typical sigmoid response curves showing the differences in response to any given intake exhibited by three organ systems within the same individual

A given intake increment (bold arrow) intersects the three responses in different regions of the respective curves. Thus, the increment shown, starting from a certain basal intake/status, will produce a measurable response in system B, but not in systems A or C. In the case of system A, the response occurred at a lower intake, and little more could be expected from further increases. For system C, still higher intakes are needed to produce a perceptible response.

Heaney RP Assessing vitamin D status Curr Opin Clin Nutr Metab Care 14: 440-444, 2011

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Nutritional effects may take years or decade to be manifest, while drug studies have relatively short outcomes. This is true of a nutrient like calcium where life time calcium intake is shown to be important and osteoporosis is often discussed as a "pediatric disease with a geriatric outcome". This means that a randomized, controlled trial for a nutrient is often not feasible while a drug trial can be studied in a short time frame[1].

[1]Heaney, R.P., *Long-latency deficiency disease: insights from calcium and vitamin D.* Am J Clin Nutr, 2003. **78**(5): p. 912-9.

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Suggested categorization of deficiency diseases associated with 3 illustrative nutrients[1]

	Index			Nonindex			
Nutrient	Disease	Mechanism	Latency	Disease	Mechanism	Latency	Intake[2]
Calcium	Osteoporosis	Depletion of nutrient reserve	Long	Oxalate urolithiasis	Reduced intestinal binding of oxalic acid	Short	Equal to index
				Colon cancer promotion	Reduced intestinal binding of fatty and bile acids	Long	Equal to index
				"Calcium paradox" diseases[3]	Elevation of intracellular $[Ca^{2+}]$	Long	Uncertain
Vitamin D	Rickets and osteomalacia	Intestinal malabsorption of calcium and phosphorous	Short	Osteoporosis	Same as for index disease	Long	Above index
				Oncogenesis	Reduced control of cell differentiation by 1-α-hydroxylation of 25(OH)D	Long	Above index
Folic acid	Megaloblastic anemia	Impaired DNA synthesis	Short	Neural tube defects	Same as for index disease	Short	Above index
				Oncogenesis	Reduced DNA methylation by methionine	Long	Uncertain
				Connective tissue degenerative disorders[3]	Irreversible degradation of elastic proteins by homocysteine	Long	Uncertain

Vitamin K
Clotting disorders – short latency
If there are alterations in BMD and fracture – long latency – therefore, longer term studies will be necessary

Heaney RP .Nutrients, endpoints, and the problem of proof. J Nutr 138: 1591-1595, 2008.
Heaney RP. Long-latency deficiency disease: insights from calcium and vitamin D. Am J Clin Nutr 78: 912-919, 2003.

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Let's Revisit Some of the Previous Studies

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Lessons Learned Vitamin K

- As would be expected, comparisons to a deficient group show a benefit – an effect of a nutrient on deficiency – but such epidemiological studies do not know baseline nutrient status
- Meta-analysis will not likely shed much light because most studies didn't evaluate baseline vitamin K status – you can't meta-analyze your way out of a mess
- Binkley study did study individuals with low carboxylated osteocalcin – only one year in duration Dr Binkley suggests that relationship with undercarboxylated osteocalcin and bad bone may be from identifying people will a poor diet/ill individuals – so it may be associational not causal
- T2DM study was only 6 months long
- I also wonder about how often individuals have true vitamin K deficiency since it is manufactured by gut flora

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Vitamin D Lessons Learned

- Impossible to study vitamin D in isolation – so many studies have logically evaluated calcium and vitamin D (protein also a factor – it gets complicated fast!)
- Metanalysis won't be useful – Bischoff Ferrari one had a threshold
- Vitamin D dosing may not be adequate
- Don't know baseline status in studies, however many papers have shown how common vitamin D deficiency is an how poor calcium intake is among some individuals

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- "Despite the consensus that more in not better, we have continued to conduct trials (and include them in meta-analyses) without regard to ensuring the presence of two key features: baseline status and dose adequacy."

Heany RP. Vitamin D-Baseline status and effective dose. N Engl J Med 367: 77-78, 2012.

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Metanalysis … Yao et al. al

- Conta… …mple Jach… …lly cal… …oups dif… …ct – th… frac…

"Until we link outcomes to blood levels achieved, and understand what analytic to measure, meta-analyses will not answer the "how much is enough" question".
Dr R P Heaney

…ON

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Burt et al.- Paper Related to High Dose Vitamin D and Bone

- There was a suggestion lower radial BMD with 4000 IU and 10000 IU per day vs 400 IU per day and lower tibial BMD with 10,000 IU per day
- Are we perhaps seeing a threshold effect – i.e. toxicity with increasing doses?
- i.e. Scenario C could include toxicity

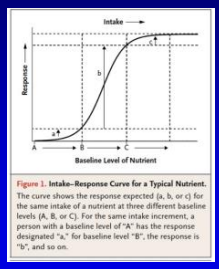

Figure 1. Intake–Response Curve for a Typical Nutrient.
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Burt et al.. JAMA 322: 736-345, 2019.

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- The null outcomes and conflicting results probably occur because of study design and factors we have discussed
- BMD improvement and fracture reduction from a nutrient alone are unlikely
- Rejecting nutrient supplements because of null BMD and fracture studies is tossing out the baby with the bathwater

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Hierarchical structure of dietary patterns, foods, and nutrients for study of food synergy[1]

Food synergy level	Examples of dietary component at each synergy level
Level 5: dietary pattern	"Prudent diet," "Western diet," other combinations of food groups
Level 4: food groups	Whole grain, dairy, fruit, vegetables, meat
Level 3: whole grain	Whole wheat, brown rice, rolled oats
Level 2: whole wheat	Bran, germ, endosperm; extract of fat-soluble portion
Level 1: bran or a single phytochemical	Specific nutrients or phytochemicals

My opinion: Nutrition and bone studies will evolve away from single nutrients to evaluate food patterns

Am J Clin Nutr 2003; 78 (suppl) 508S-13S

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Medical Foods for the Management of Chronic Disease

(One of the challenges of my career has been trying to find more natural approaches to patients who refuse conventional medical treatments)

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Medical Foods

Table 1. Differences Between Medical Foods, Dietary Supplements, and Drugs

Product Class Attribute	Dietary Supplement	Medical Food	Drug
Governing regulation	Dietary Supplements Health & Education Act (DSHEA, 1994)	Orphan Drug Act (amendments, 1988)	Federal Food, Drug and Cosmetic Act (1938 as amended by FDA Modernization Act of 1997)
Intended population	Healthy	Diseased	Diseased
Ingredients	Nutritional	Nutritional, not in ordinary diet	Mostly synthetic, can be nutritional
Product basis	"General expectation" of desired product performance	Dietary need = metabolic imbalance can be restored by special nutrients	Safe & effective for disease & patient population
Safety standard	"General expectation" of safety (ingredients on market prior to DSHEA)	GRAS (generally recognized as safe) as food ingredients = safe for public use	Approved via NDA, ANDA or used as DESI ("grandfathered")
Scientific requirements	None	Recognized science = follows good scientific practices, accepted in clinical practice or peer review	Preclinical & clinical phases I, II, III
Physician supervision	None	Required	Required if prescription drug
Dosing	Oral	Oral or enteral	Any
Distribution	Health food stores, mass market	Hospitals, retail pharmacies	Hospitals, retail pharmacies

Morgan SL, Baggott JE, Nutrition Reviews 64: 495-501, 2006

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Medical Foods

- Codified by C.F.R. sec 101.9 (j) (8), Nutrition labelling of food
- Must justify a distinct dietary need (i.e. for the dietary management of metabolic processes)
- GRAS ingredients
- Enteral/oral administration
- Medically determined dietary needs and based on recognized science
- Given to a diseased population for a chronic condition
- Given under a physician's supervision
- Not approved by FDA, but meets FDA regulations
- Medical foods can't be in the form of conventional foods, make drug claims (cure, prevent, reduce, mitigate) or have too many multiple indications for a product
- There can be FDA inspections of manufacturing, labelling, and distribution

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Examples of Medical Foods

- Ultrase MT® – for exocrine pancreatic insufficiency
- Limbrel™ – for osteoarthritis
- Folgard® – for elevated homocysteine
- BCAD 2 – for MSUD and other errors of branched chain amino acid metabolism (infant formula free of branched chain amino acids)
- Oxepa® – for lung injury patients
- Fosteum™ – for osteopenia and osteoporosis

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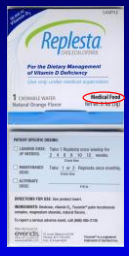
Replesta



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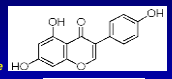
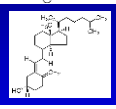
Fosteum®, as an Example of a Medical Food - indicated for the dietary management of the metabolic aspects of osteopenia and osteoporosis

27 mg Genistein Aglycone (>98% purity)
Inhibits Osteoclast and stimulates osteoblast activity- a natural isoflavone phytoestrogen

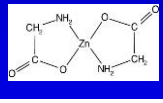


Dose is 1 pill bid orally

200 IU Cholecalciferol (Vitamin D_3)
Essential for Ca^{2+} absorption



20 mg Zinc Chelazome (4 mg elemental zinc)
Co-factor for bone metabolic enzymes and synergizes with genistein



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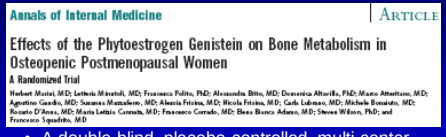
Pivotal Trial: Two Year Trial With Third Year Extension


Annals of Internal Medicine | ARTICLE

Effects of the Phytoestrogen Genistein on Bone Metabolism in Osteopenic Postmenopausal Women

A Randomized Trial

- A double-blind, placebo-controlled, multi-center trial
- 389 Italian postmenopausal, osteopenic and osteoporotic women enrolled in the trial
  - Ages 49-67 and at least 1 yr postmenopausal
  - 304 women completed the 2 year trial
- Third year extension (unpublished)

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Interventions & Design

Endpoints

- BMD and bone markers taken at baseline, 12 and 24 months
- Safety assessments performed every 6 months
- Endometrial thickness assessed at 0, 12, and 24 months

Intervention

- All patients received standard of care for osteopenia:
  - Calcium: 500 mg BID
  - Vitamin D: 400 IU BID
- Treatment group also received 27 mg genistein BID
- Patients counseled to avoid soy-rich foods & supplements

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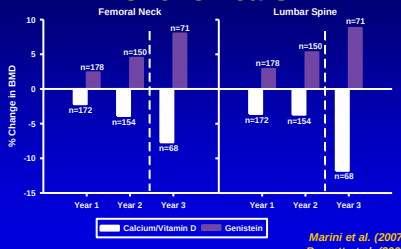
Genistein increases BMD Over 3 Years



Marini et al. (2007)
Burnett et al. (2007)

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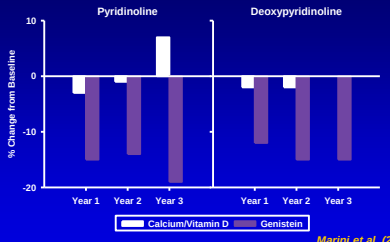
Markers of Bone Resorption



Marini et al. (2007)
Burnett et al. (2007)

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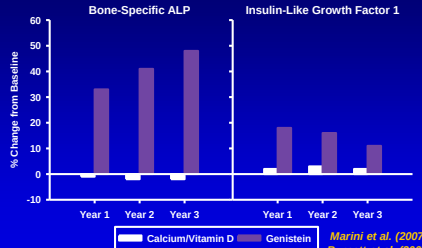
Bone Formation Markers



Marini et al. (2007)
Burnett et al. (2007)

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Author's Conclusions

- **"We found that treatment with genistein, an abundant soy isoflavone, prevents bone loss caused by estrogen deficiency without affecting the uterus in osteopenic postmenopausal women".**
- **Bone resorption markers were lower in genistein group – acknowledged that these may not correlate perfectly with reduction in fracture risk**
- **BSAP increased – speculated that this was related to direct genomic estrogen receptor-medicated effect or nongenomic action in target cells.**
- **Genistein also increased IGF-1 levels- noted that this pattern was similar to rat studies where isoflavones upregulate IGF-1 and transforming growth factor-B and inhibit osteoclastogenesis.**
- **Acknowledged higher GI adverse events**
- **Option for individuals not wanting FDA-approved drugs**

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QUESTIONS?

Summer by Giuseppe Arcimboldo 1563

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