

Integrative Medicine Literature Update 2019

MONA
M. Chris Link, MD

Overview

Vitamins – do they work, apparently not...?

Vitamin D – deep dive

Osteoporosis – linked to the microbiome

Sauna

Metabolism/Diabetes – microbiome, fasting, low carb/low insulin

Coffee – is it cancer causing, is it healthy?



Vitamins – Headline

**“Most popular vitamin and mineral
supplements provide no health
benefit, study finds”**

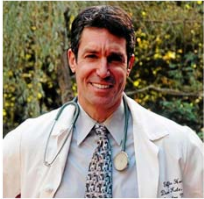
They looked at heart disease and stroke outcomes, ONLY.



Supplemental Vitamins and Minerals for CVD Prevention and Treatment

Folate decreased stroke. (Multiple studies)
B-complex decreased stroke.
Niacin may increase all cause mortality, (glycemic effect)
Anti-oxidants may increase all cause mortality, (Beta-carotene, vitamin E.)
Optimally, eat a diet high in plants that will contain many of these vitamins and minerals!
Vitamin D, Calcium, vitamin C had no benefit in CVD.

In the author's own words, **"...MVM supplement use was inversely related to the incidence of CHD when all studies were considered."**



"Let's conclude. If you want to reduce your risk of cardiovascular disease, eat well, be active, avoid toxins, and...so on. Use lifestyle as medicine, in other words. Don't rely on a MVM for this purpose, obviously. But if you have other reasons for taking a MVM, this study, like all before it, leave room for potential benefit, while pretty reliably ruling out any meaningful harm. "

David Katz, MD, MPH
Professor of Public Health Yale

"Well, duh"

<https://www.linkedin.com/pulse/multivitamins-wont-help-you-well-duh-david/>

REDUCE-IT Trial



September 24th 2018

REDUCE-IT™, a global study of **8,179 statin-treated adults** with elevated CV risk. 4.9 years average follow up. Primary endpoint demonstrating an approximately **25% relative risk reduction, a high statistical significance, in major adverse CV events** with use of **Omega3/EPA 4 grams/day** as compared to placebo.



March 2018

Erythrocyte long-chain omega-3 fatty acid levels are inversely associated with mortality and with incident cardiovascular disease: The Framingham Heart Study - 2500 patients followed for 7.3 years

Omega 3 levels and cholesterol were measured



Those with the highest levels of omega three had the 34% decreased risk of dying from any cause, and 39% lower risk of CVD event

When total cholesterol was compared with the Omega-3 Index in the same models, the latter was significantly related with these outcomes, but the former was not.



May 2018

AHA SCIENCE ADVISORY

Seafood Long-Chain n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease: A Science Advisory From the American Heart Association

We conclude that 1 to 2 seafood meals per week be included to reduce the risk of congestive heart failure, coronary heart disease, ischemic stroke, and sudden cardiac death, especially when seafood replaces the intake of less healthy foods.



THE LANCET

955 patients

November, 2017

Vitamin D supplementation to prevent asthma exacerbation's:
systematic review and meta-analysis of individual participant data

Conclusion

Vitamin D supplementation reduced the rate of asthma exacerbations requiring systemic corticosteroids



January 2018

Preventive effects of vitamin D on Seasonal Influenza in Infants:
A multicenter, randomized, open, controlled clinical trial

400 infants randomized into low-dose (400IU) and high-dose vitamin D, (1200IU), groups

Decreased Influenza cases: 78 low-dose vitamin D, 43 high dose vitamin D.

Influenza was less severe in the high-dose vitamin D

Never no adverse effects and the high-dose vitamin D

AAFP recommends 400IU



June, 2018

Breast cancer risk markedly lower with serum 25-hydroxy vitamin D concentration greater than 60 versus less than 20 ng/milliliter: Pooled analysis of two randomized trials and the perspective cohort

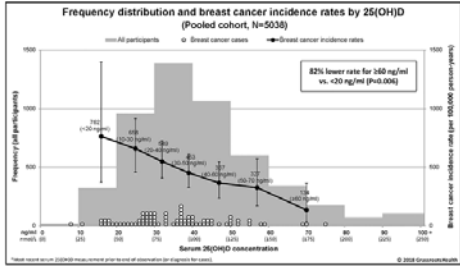
5038 patients, 4 years, 77 developed breast cancer

Conclusions

Higher 25-hydroxy vitamin D concentrations were associated with the dose response decrease in breast cancer risk with concentrations greater than 60ng/ml being most protected.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199265>

Fig 1. Frequency distribution and breast cancer incidence rates by 25(OH)D concentration, pooled cohort (N = 5036).

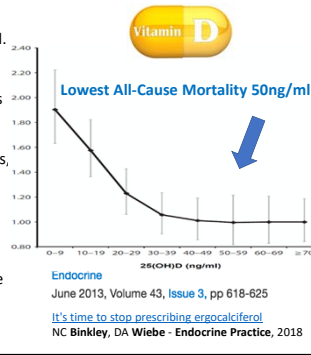


McDonnell SL, Baggerly CA, French CB, Baggerly LL, Garland CF, et al. (2018) Breast cancer risk markedly lower with serum 25-hydroxyvitamin D concentrations 260 vs 81-20 ng/ml (150 vs 50 nmol/L): Pooled analysis of two randomized trials and a prospective cohort. PLOS ONE 13(6): e0199265. <https://doi.org/10.1371/journal.pone.0199265>
<https://pubmed.ncbi.nlm.nih.gov/30199265/>



Vitamin D

- Test – **treat to target**, 40 - 60ng/ml, +/- 5 ng/ml.
- 2000 – 5000 IU daily typical
- D3 generally thought to be better. “D2, Past it’s usefulness...” Binkley
- Bolus dosing increases risk of fractures and falls, 100,000IU or greater. Not recommended.
- Replacement dose 5000 – 10,000 for 8 to 12 weeks.
- Safety – remarkable **rare toxicity**, LAB Medicine 2018, 130,000 levels, 16 years, 4 with symptomatic toxicity.




Vitamins – Headline


“Most popular vitamin and mineral supplements provide no health benefit, study finds”


In Fact ... B-Vitamins, Vitamin D, Omega 3's Conclusively Beneficial


Not a well informed statement!

Osteoporosis

 **PLOS** Greater Intake of Fruit and Vegetables Is Associated with Greater Bone Mineral Density and Lower Osteoporosis Risk in Middle-Aged and Elderly Adults – Cross sectional, 3000 Adults.
January, 2017
Greater intake of **Fruits and Vegetables** was independently associated with a **higher BMD** and a lower presence of osteoporosis in middle-aged and elderly...

 **nutrients** Adherence to a Mediterranean Diet and Bone Mineral Density in Spanish Premenopausal Women – 442 Post Menopausal Women, DEXA
March 2019
We conclude that the **adherence to the Mediterranean Diet** was positively associated with **better bone mass** in Spanish premenopausal women.

 **OSTEOPOROSIS INTERNATIONAL** Mediterranean diet and hip fracture incidence among older adults: the CHANCES project - 140,000 women/men followed 10 years.
July 2018
In this large sample of older adults from Europe and the USA, increased **adherence to Mediterranean Diet** was associated with a **7% lower hip fracture** incidence.

 **CLINICAL NUTRITION** Extra virgin olive oil consumption reduces the risk of osteoporotic fractures in the PREDIMED trial 870 participants, 9 years of f/u, 114 osteoporotic fractures
2016
2 Groups, 1.) Mediterranean diet; 2.) Mediterranean diet plus additional extra virgin olive
51% fewer fractures at highest Olive Oil intake, highest tertile, 4 additional Tbsp of olive oil daily.

Nutrition

Current Osteoporosis Reports August, 2015

Dietary Approaches for Bone Health: Lessons from the Framingham Osteoporosis Study
Evidence indicates that **diet** at the level of vitamins, minerals, food groups and dietary patterns play an **important role in skeletal health**.

Higher fruit and vegetable intake associated with **higher BMD** in young adults and **decreased bone loss over time**.

Greater Protein intake benefits **BMD** and **protects against fracture**.

How Much Calcium ?

35% of US adults take calcium supplements.

Taking too much?

Probably a sweet spot around 1000 mg of calcium intake daily.

Food is optimal – wide margin of safety.

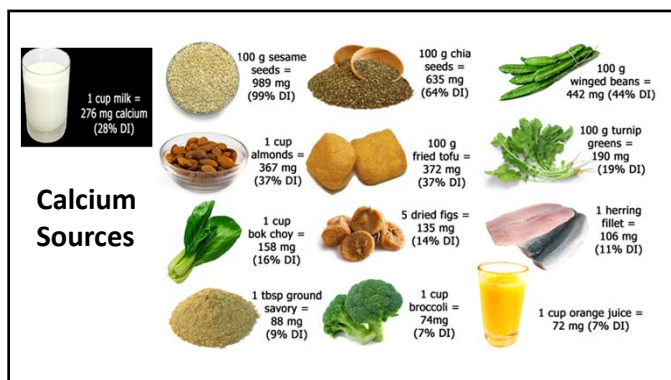
Food limits the acute rise in serum calcium and provides other health benefits.

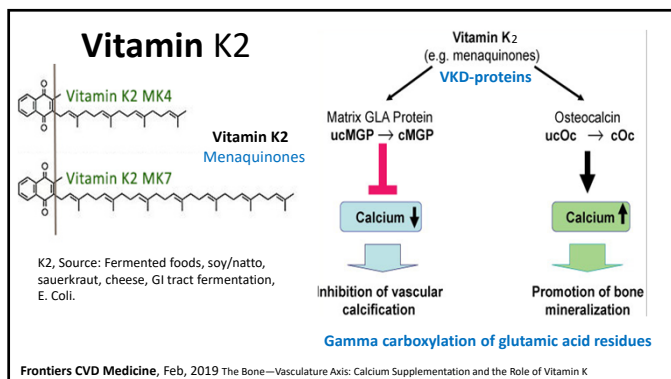
Excess calcium may promote vascular calcification and nephrolithiasis.

Excess calcium promotes and worsens constipation in elderly.

Supplementation – Calcium citrate 150 – 200mg 1 or 2 daily.

Frontiers CVD Medicine, Feb, 2019 The Bone—Vasculature Axis: Calcium Supplementation and the Role of Vitamin K





Frontiers CVD Medicine, Feb, 2019 The Bone—Vasculature Axis: Calcium Supplementation and the Role of Vitamin K

JBMR

Poor Vitamin K Status Is Associated With Low Bone Mineral Density & Increased Fracture Risk in CKD
November 2018

frontiers
in Cardiovascular Medicine

February 2019

The Bone-Vascular Axis: calcium supplementation in the role of vitamin K

Western diet low in Vitamin K

Calcium Paradox, Low BMD, Inc. Vascular Calcium, Osteoporosis, CKD

Calcium/Vitamin D improves BMD but Inc. Vascular Calcium

Conclusion "Clinical studies demonstrate that increased intake of vitamin K could be a promising complementary nutrient in supporting both bone health and protecting vascular calcification."

Vitamin K2

OSTEOPOROSIS
INTERNATIONAL

Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women
2013

Vitamin K2 – MK7, 180ug daily, 244 patients, 3 years f/u

Improved vitamin K status based on ratio carboxylated/uncarboxylated Osteocalcin

Increased BMD spine and femoral neck

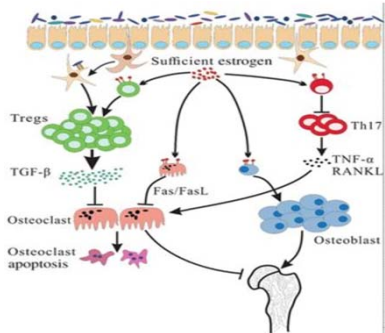
180 mcg daily

Nexus – Estrogen, GI Barrier, Inflammation, Probiotics, Calcium, & Bone Health

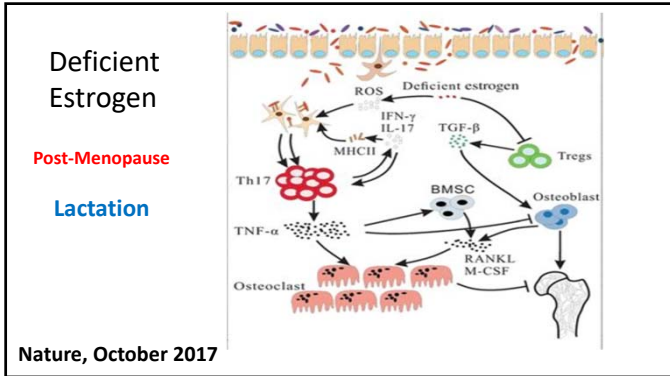
- **Estrogen Deficiency**, post menopausal and during lactation, leads to **compromised GI barrier** function and **decreased BMD**.
- In lactation **physiologic** provides necessary calcium for breast milk, in menopause it leads to osteoporosis. (Roberto Pacifici, MD, Paul J. Kostenuik, PhD. Santa Fe Bone Symposium, 2018)
- **Compromised GI barrier** initiates an inflammatory immune cascade, increased Th17 cells in the gut. These translocate to the bone increasing **osteoclastogenic** TNF, IL-17, RANKL, decreased BMD.
- **Probiotics** act to restore GI barrier and normalize host inflammatory immune response BMD.

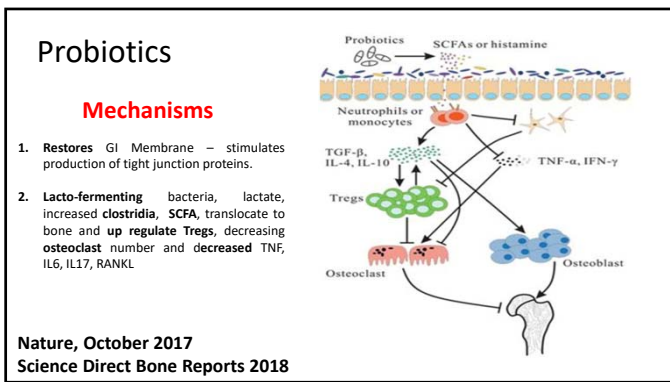
Journal of Clinical Densitometry, Vol. 22, January through March 2019
Proceedings of the 2018 Santa Fe Bone Symposium: Advances in the Management of Osteoporosis

Sufficient
Estrogen



Nature, October 2017





Nutritional Support of Bone Health - Probiotics

Mouse Studies

JBMR 2012, Gut Microbiome regulation Bone in Mice – Sterile/ Notobiotic mice had **30% increased BMD**.

Ovaryectomized, Sterile/Notobiotic mice have little decrease in BMD (Multiple studies)

Human Studies

JIM Journal of Internal Medicine Founded in 1843 June 2018

L. Reuteri (10 Billion CFU) Reduced Bone Loss in Older Women, 12 months, Tibia BMD.

JBMR Jan. 2019, L. Reuteri Prevents Post Antibiotic Bone Loss By Reducing Dysbiosis And Barrier Dysfunction.

Dosing – Multispecies, Lactobacillus and Bifidobacter, **10 – 450 Billion CFU**

Estrogen Replacement Therapy: Risk Benefit Analysis

WHI – 33% decrease in hip fracture, **no** increase in all cause mortality or breast cancer mortality.

POSITION STATEMENT The 2017 hormone therapy position statement of The **North American Menopause Society**

Book: **Estrogen Matters**, Avrum Bluming, MD, 2018

Exercise for Bone Health

- “Exercise should be used as a **first line therapy for bone health**” Lora Giangregario, PhD. Effects ... musculoskeletal load, physiology, balance, tissue mass.
- **Walking** is terrific exercise but “**not sufficient**” to impact BMD. (Inc. lumbar BMD only)
- **Progressive resistance training needed** – optimally twice weekly, **5 – 10 reps, approaching 85% of one rep max.** Improves BMD, balance, functional strength. (LiftMor trial JBMR, 2018, Watson)
- This type exercise **increases type 2 myofibers** responsible for strength and responsiveness.
- **Balance challenging** exercises – these shift center of gravity and narrow base of support. Many examples Tai Chi is one example.

Complimentary Therapies For Bone Health

Bone - ECHO, April 30th, 2019

- Exercise** Strength and Balance
- Nutrition** Nutrient dense colorful
- Estrogen** Judicious replacement

Protein 30 gm per meal, at least twice daily.

Vitamin D test, optimize, level 40 – 60 ng/ml

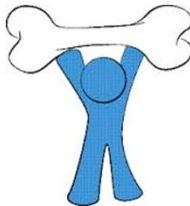
Calcium 1000mg dietary sources optimal

Vitamin K2 180 mcg daily

Probiotics 10 – 450 billion CFU, multispecies - Lactobacillus, Bifidobacter

Olive Oil 3 – 4 TBSP daily

Silica 10mg daily



Sauna

Neurology®

May 2018

Sauna bathing reduces the risk of stroke in Finnish men and women: A prospective cohort study
Finnish study. 5.5 million people, (1 million saunas in Finland!)

Sauna 4 times weekly or greater were **61% less likely to have a stroke.**

Saunas improve the following conditions: Pain, Fibromyalgia, CHF, LDL cholesterol, Hyperglycemia

Conclusions This long-term follow-up study shows that middle-aged to elderly men and women who take frequent sauna baths have a **substantially reduced risk of new-onset stroke.**



August 2018

Cardiovascular and Other Health Benefits of Sauna Bathing: A Review of the Evidence

Emerging evidence suggests that beyond its use for pleasure, sauna bathing may be linked to several health benefits, which include reduction in the risk of vascular diseases such as high blood pressure, cardiovascular disease, and neurocognitive diseases; nonvascular conditions such as pulmonary diseases; mortality; as well as amelioration of conditions such as arthritis, headache, and flu.

CONCLUSION Sauna bathing, an activity used for the purposes of pleasure, wellness, and relaxation, is linked to a **remarkable array of health benefits.** It is a **safe activity** and can even be used in people with stable CVD, provided it is used sensibly for an appropriate period of time.

Fasting/Metabolism

Diabetes Therapy

April 2018

Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study

349 Adults with Type 2 Diabetes - Low Carb dietary intervention

Weight decline 13.8 kg

Insulin therapy reduced or eliminated in 94%

Sulfonylureas entirely eliminated

HbA1c decreased 7.6 to 6.3

HDL increased 18%

Triglycerides decreased 24%



<https://www.youtube.com/watch?v=da1wiyg5tQ>

PEDIATRICS

June, 2018

Management of type 1 diabetes with a very low carbohydrate diet: Ludwig, Boston Children's Hospital

Facebook community: **TypeOneGrit (Law of Small Numbers)**

138 patients data and medical records confirmed

VLCD, **36 grams of carbohydrates** daily

Average hemoglobin A1C 5.7, some below 5

Very low insulin requirements. Few adverse reactions

CONCLUSIONS: Exceptional glycemic control of T1DM with low rates of adverse events was reported by a community of children and adults who consume a VLCD.

Cell Metabolism

August 2, 2018

Remission of Human Type 2 Diabetes Requires Decrease in Liver and Pancreas Fat Content but Is Dependent upon Capacity for β Cell Recovery

The **Diabetes Remission Clinical Trial** reported return and persistence of non-diabetic blood glucose control in 46% of people with type 2 diabetes of up to 6 years duration.

This study demonstrates that **β cell ability to recover long-term function** persists after diagnosis **changing the previous paradigm of irreversible loss of β cell function in type 2 diabetes.**

<https://www.sciencedirect.com/science/article/pii/S1550413118304467>

Eat Late.... to Gain Weight!

Daytime

Digestion Optimal

Insulin Sensitivity Highest

Energy Utilization Highest

Food Choices Healthier

7 A.M.



7 P.M.

Nighttime

Digestion Wanes

Insulin Sensitivity Lowest

Fat Storage Increases

Poor Food Choices Common

Eat When the Sun is Out

Obesity

High caloric intake at breakfast vs. dinner influences weight loss of overweight and obese women.

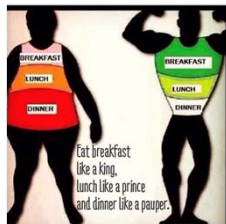
Old Adage....

Two Groups (Randomized women with prediabetes)

1. Breakfast 200, Lunch 500, Dinner 700 calories
2. Breakfast 700, Lunch 500, Dinner 200 calories

Group 2.

- Greater weight loss
- Smaller waist circumference
- Lower glucose and insulin
- Lower triglyceride numbers
- **Less hungry while losing weight!**
- **Increased fertility** in women with PCOS



Daniela Jakubowicz, Oren Froy, July 2013

Time Restricted Eating

Fast overnight 13 or more hours

Fast 3 hours before bed

No specific calorie intake

Metabolism

Lowers cholesterol

Water, Tea, Black Coffee ok!

Lowers blood sugar/Insulin

Enhances fat burning

Improves Fatty Liver Disease

Lowers Inflammation

Leads to healthy nutritional ketosis

Benefits seen with only 5 of 7 days weekly



First Meal



Last Meal

JAMA Oncology

Prolonged Nightly Fasting and Breast Cancer

Prognosis

JAMA Oncol. 2016;2(8):1049-1055. doi:10.1001/jamaoncol.2016.0164.

Catherine R. Marinac, BA^{1,2,3}; Sandahl H. Nelson, MS^{1,2}; Caitlin L. Breen, BS, BA¹; Sheri J. Hartman, PhD^{1,2};
Loki Natarajan, PhD^{1,2}; John P. Pierce, PhD^{1,2}; Shirley W. Flatt, MS¹; Dorothy D. Sears, PhD^{1,2,4}; Ruth
E. Patterson, PhD^{1,2}

2400 Women, 7 years of F/U

April 2016

Fasting for 13 hours over night, 5 days weekly

36% Decreased in Recurrence of Breast Cancer

22% Decreased Risk of Death From Any Cause

And...

Lower cholesterol, A1C, CRP, Less GERD, & Better Sleep

In Meal Timing

Food Order Has a Significant Impact on Postprandial Glucose and Insulin Levels

The mean post-meal glucose levels were decreased at 30, 60, and 120 min, respectively, and the **incremental area under the curve was 73% lower** when **vegetables and protein were consumed first**, before carbohydrate, compared with the reverse food order.

Coffee

Coffee \neq Caffeine



Coffee is a very complex beverage. It is high in polyphenols, **100's**, and minerals like magnesium.

Caffeine has stimulant effects, antioxidant, decrease neurodegeneration, depression, mitochondria, anti-inflammatory effects.

Chlorogenic acid, strongest anti-oxidant in coffee, bitter/aromatic, improves BP and glucose metabolism.

Improves health with decreased CVD and decreased all cause mortality with **caffeinated as well as decaffeinated coffee.**

Frank Hu, M.D., Harvard, Chairman of Public Health

Coffee Decreases All-Cause Mortality



Harvard, Nurses health study, Health professionals follow-up study 300,000 men and women, followed for 20-30 years

Strong inverse association between Coffee consumption, dose-dependent, in cardiovascular disease, neurological disease, and suicide.

Similar benefits found with **caffeinated** or **decaffeinated** coffee consumption.

Frank Hu, M.D., Harvard, Chairman of Public Health

Coffee and Health Promotion



Coffee consumption is associated with multiple beneficial health outcomes:

- Type II diabetes
- Oral cancers
- Cirrhosis, chronic liver disease, Liver cancer
- Kidney stones
- Leukemia
- Gout
- Post MI mortality

Frank Hu, M.D., Harvard, Chairman of Public Health

Coffee Neuroprotective Effects



Parkinson's disease 25% decrease risk

Alzheimer's disease 20% decrease risk

Suicide, 3 cups/day, 45% decrease risk

Depression to 3 cups/day, 15% decreased risk

Mechanism may be due to the **anti-inflammatory/polyphenols** and **caffeine** benefits on neurotransmitters like dopamine

Frank Hu, M.D., Harvard, chairman of public health



Long-Term Coffee Consumption and Risk of Cardiovascular Disease

Meta-analysis come **1.3 million participants**
15% decrease cardiovascular mortality, 3 to 5 cups/day

Conclusion Moderate coffee consumption was inversely significantly associated with CVD risk, with the lowest CVD risk at **3 to 5 cups per day**, and heavy coffee consumption was not associated with elevated CVD risk

**Integrative Medicine
Literature Update**

2019

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Questions ?
