

Calcium and Vitamin D: What you Need to Know

Virtual Own the Bone Symposium
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Conflicts of Interest

- None

Outline

- Physiologic role of vitamin D and calcium in bone
- Vitamin D: recommended intake levels, safety questions
- Calcium: recommended intake levels, safety questions

Vitamin D, Calcium, and Bone Health

A patient who is currently taking denosumab (Prolia) to treat her osteoporosis sends you the following message via the EMR:

Hello XXX –

I recently saw my PCP, and he checked my blood tests. My vitamin D level was high (40 ng/ml) and my blood calcium level was normal. He told me to stop my vitamin D and calcium supplements because recent studies show that they don't help. What should I do?

USPSTF 2018:

Vitamin D +/- Calcium and Fractures

JAMA | US Preventive Services Task Force | **EVIDENCE REPORT**

Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults

Evidence Report and Systematic Review for the US Preventive Services Task Force

Leila C. Kahwati, MD, MPH; Rachel Palmieri Weber, PhD; Huiling Pan, BA; Margaret Gourlay, MD, MPH; Erin LeBlanc, MD, MPH; Manny Coker-Schwimmer, MPH; Meera Viswanathan, PhD

CONCLUSIONS AND RELEVANCE Vitamin D supplementation alone or with calcium was not associated with reduced fracture incidence among community-dwelling adults without known vitamin D deficiency, osteoporosis, or prior fracture. Vitamin D with calcium was associated with an increase in the incidence of kidney stones.

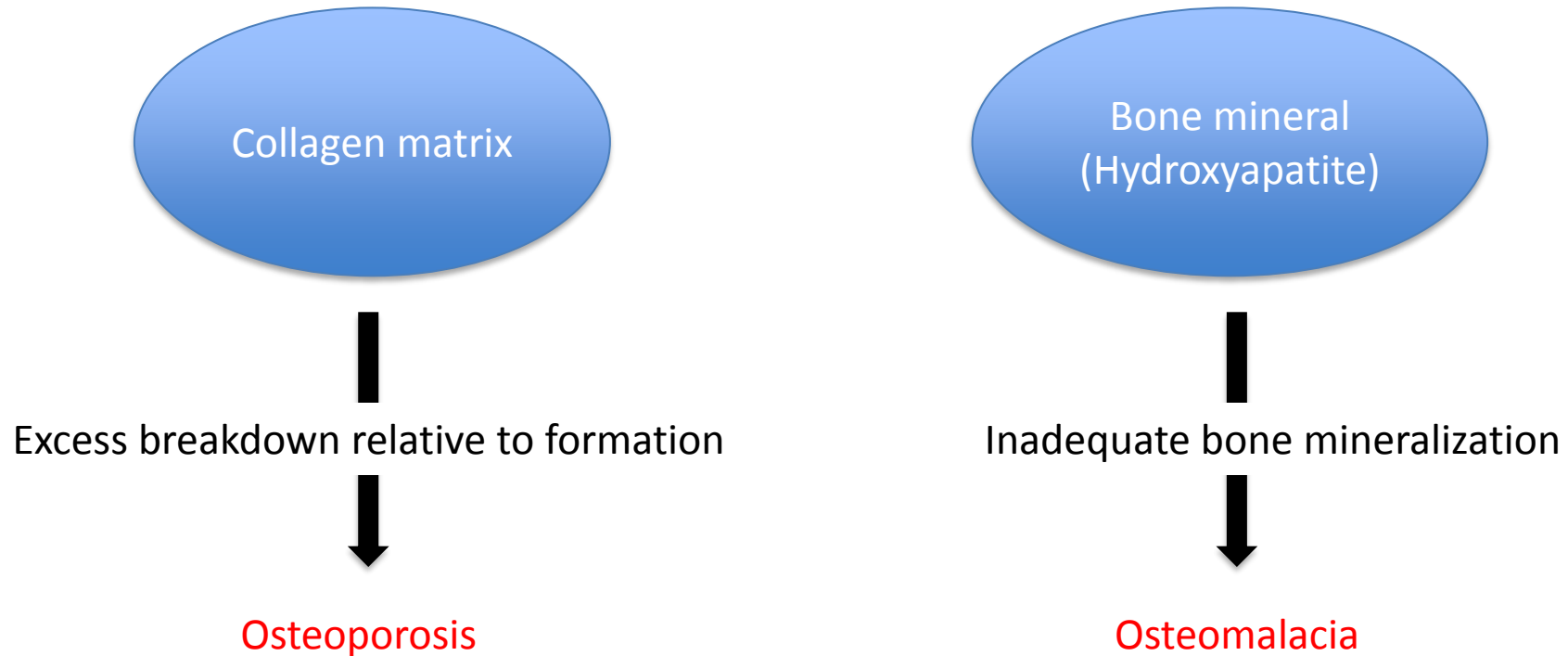
Vitamin D in the Media

***Why Are So Many People
Popping Vitamin D?***

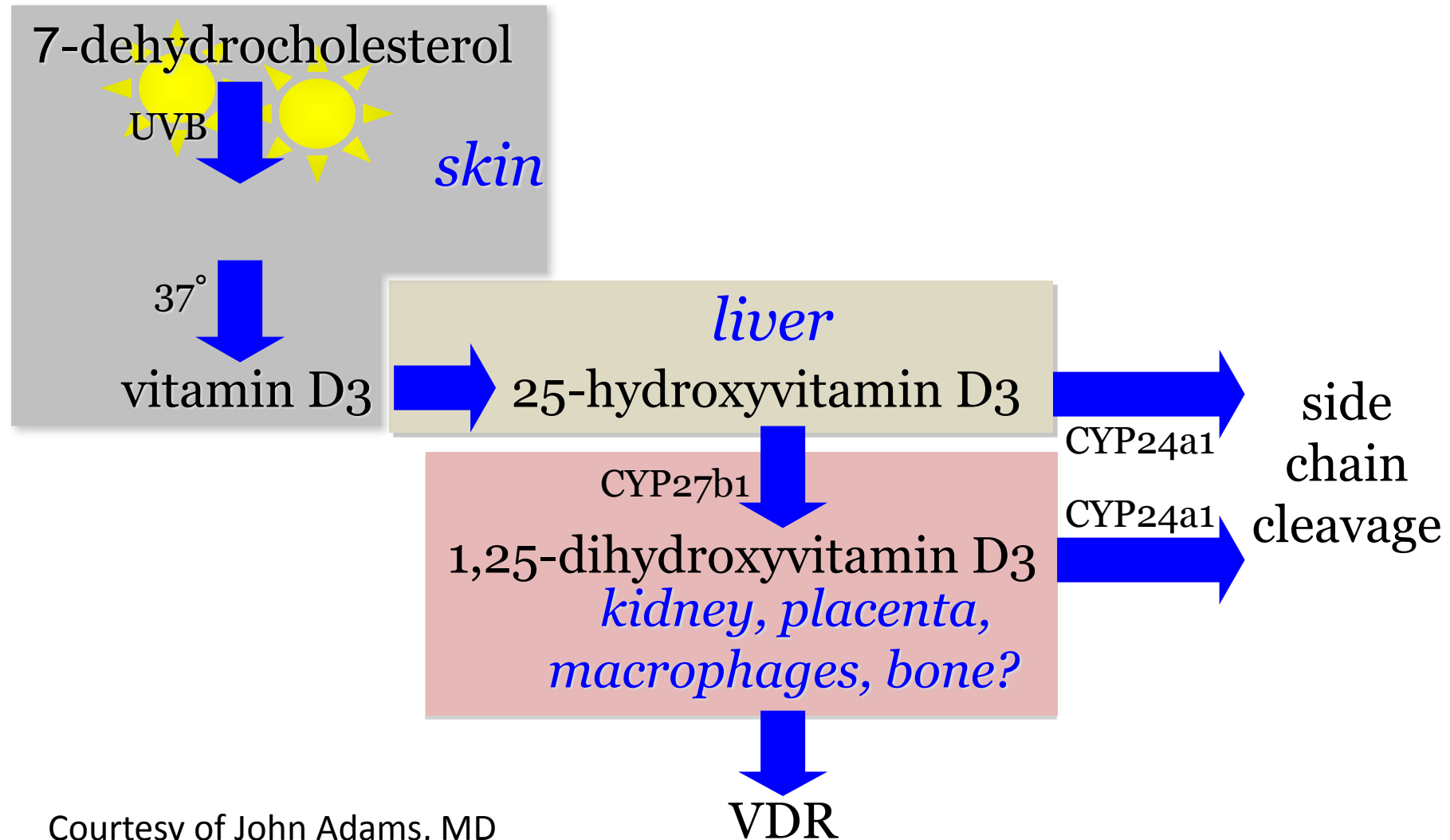


Craig Frazier

What is bone made of?

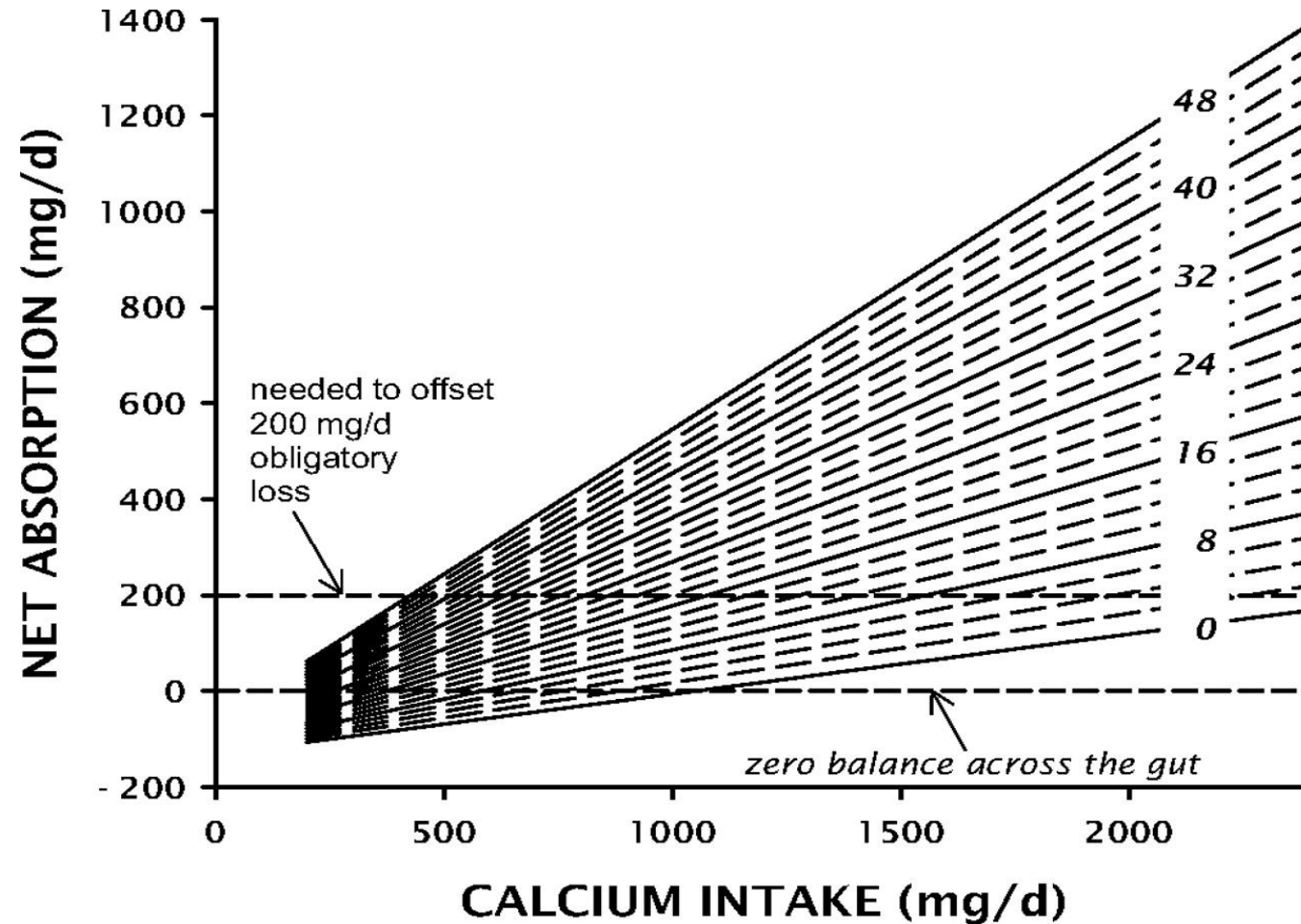


Vitamin D Synthesis and Metabolism



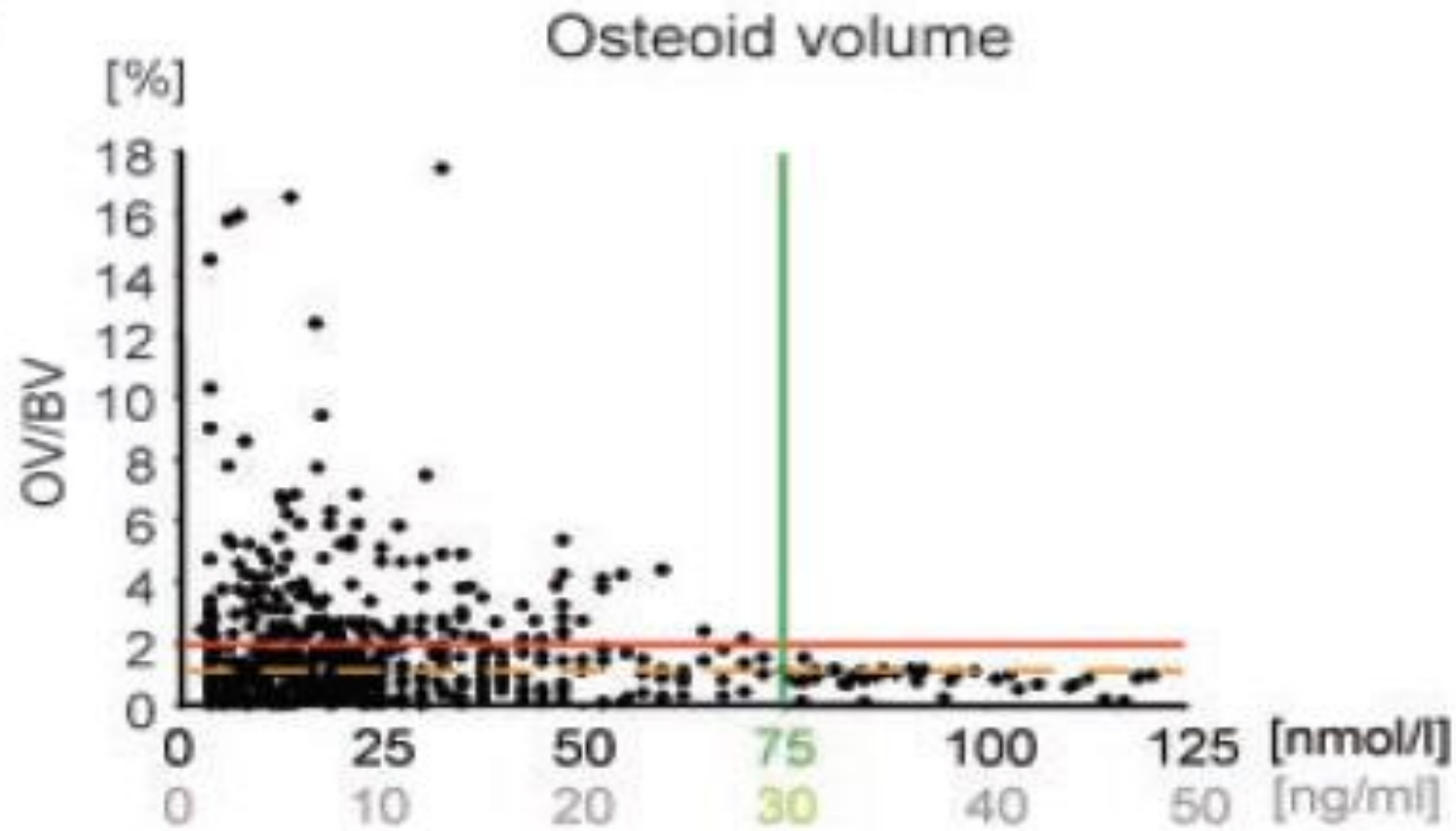
Courtesy of John Adams, MD

Classical Vitamin D Endocrinology



Heaney, R. P. (2008). Vitamin D and calcium interactions: functional outcomes. *The American journal of clinical nutrition*, 88(2), 541S-544S.

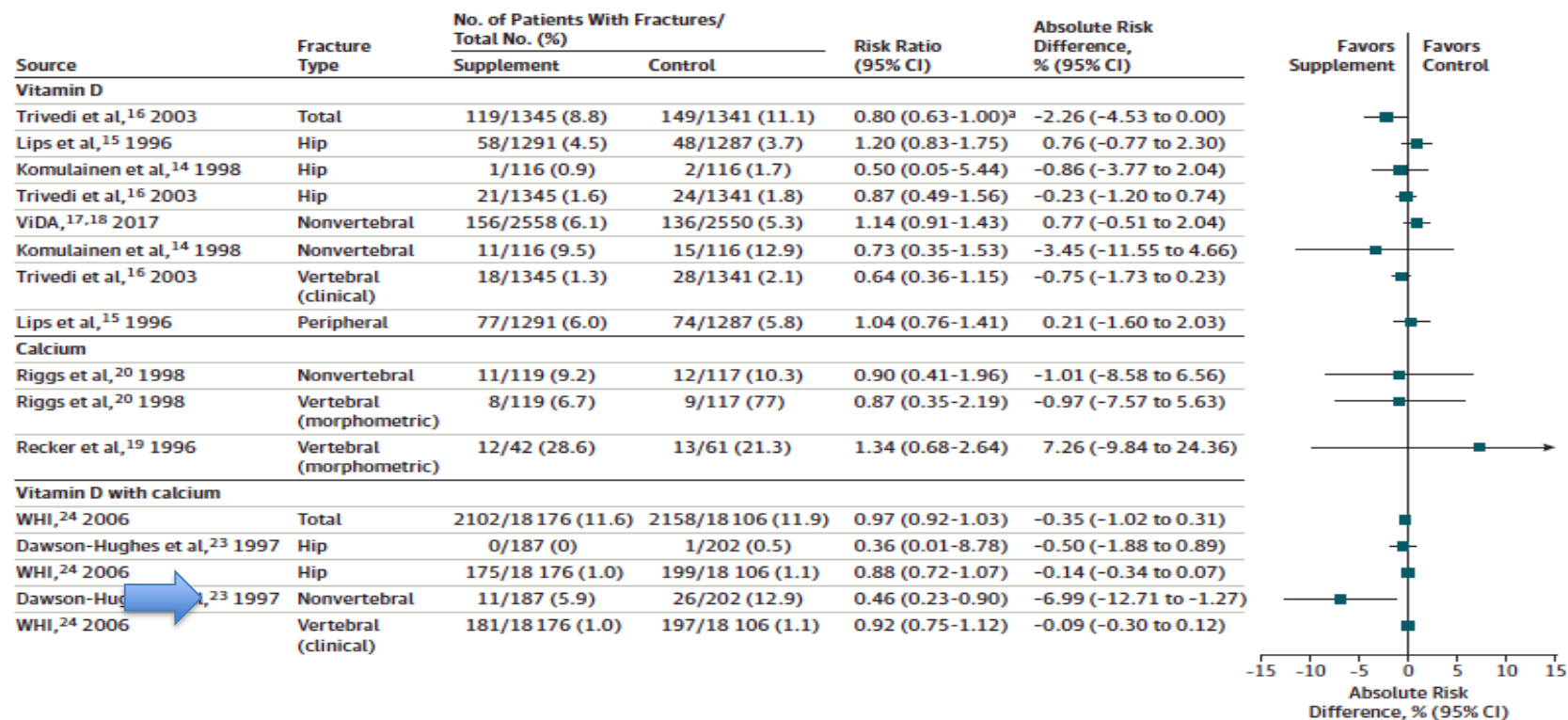
Classical Vitamin D Endocrinology



Priemel, M., von Domarus, C., Klatte, T. O., Kessler, S., Schlie, J., Meier, S., ... & Amling, M. (2010). Bone mineralization defects and vitamin D deficiency: Histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *Journal of Bone and Mineral Research*, 25(2), 305-312.

Who Benefits from Vitamin D and Calcium?

Figure 3. Comparison of Incident Fracture in Randomized Trials Comparing Vitamin D, Calcium, or Both With Placebo or Control



Placebo alone was the comparator for all studies except Komulainen et al,¹⁴ for which calcium was the comparator (See Table 1). ViDA indicates Vitamin D Assessment; WHI, Women's Health Initiative.

^a Calculated based on raw data provided in study; the authors reported an age-adjusted RR of 0.78 (95% CI, 0.61-0.99).

US Preventive Services Task Force. Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling AdultsUS Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(15):1592–1599. doi:10.1001/jama.2018.3185

Who Benefits from Vitamin D and Calcium?

The New England Journal of Medicine

EFFECT OF CALCIUM AND VITAMIN D SUPPLEMENTATION ON BONE DENSITY IN MEN AND WOMEN 65 YEARS OF AGE OR OLDER

BESS DAWSON-HUGHES, M.D., SUSAN S. HARRIS, D.Sc., ELIZABETH A. KRALL, Ph.D., AND GERARD E. DALLAL, Ph.D.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 389 STUDY SUBJECTS.*

CHARACTERISTIC	MEN		WOMEN	
	PLACEBO GROUP (N=90)	CALCIUM-VITAMIN D GROUP (N=86)	PLACEBO GROUP (N=112)	CALCIUM-VITAMIN D GROUP (N=101)
Age (yr)	71±5	70±4	72±5	71±4
Height (cm)	173.8±6.9	174.3±6.2	159.5±6.6	159.2±6.4
Weight (kg)	81.5±12.8	82.4±11.3	68.1±12.4	67.6±12.1
Dietary calcium intake (mg/day)	673±349	748±391	798±366	689±286
Dietary vitamin D intake (IU/day)	197±117	202±104	184±110	174±90
Smoker (%)	4.4	7.0	5.4	5.9
Physical-activity score	127±56 (89)	124±60 (85)	108±54	105±48
Bone mineral density (g/cm ²)				
Femoral neck	0.95±0.12	0.99±0.14	0.81±0.11	0.80±0.11
Spine	1.27±0.20 (89)	1.32±0.21	1.05±0.20 (109)	1.03±0.18 (97)
Total body	1.19±0.09 (89)	1.22±0.09	1.02±0.09	1.02±0.10

*Plus-minus values are means ±SD. When there were missing data, the number of subjects for whom data were available is shown in parentheses.

Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337(10):670-676.

Key Points:

Vitamin D, Calcium, and Bone Health

- The physiologic role of vitamin D and calcium in bone is to promote bone mineralization. Inadequate vitamin D and/or calcium leads to decreased bone mineralization (osteomalacia).
- Vitamin D and calcium are threshold nutrients; once you take enough, taking more is not additionally beneficial.

Vitamin D and Calcium Intake Requirements

An 80-year-old patient is admitted to the hospital with a hip fracture. She is currently not taking any vitamin D or calcium supplementation. Her serum 25(OH)D level is 12 ng/ml and her calcium is 9.7 mg/dl.

Recommended 25(OH)D Targets

	Recommended 25OHD (ng/ml)	Outcome of Interest
Institute of Medicine	20	Skeletal health
Endocrine Society	30	Skeletal health
AACE	30	Skeletal health
National Osteoporosis Foundation	30	Skeletal health
American Geriatrics Society	30	Skeletal health Falls

- Ross, A. C., Manson, J. E., Abrams, S. A., Aloia, J. F., Brannon, P. M., Clinton, S. K., ... & Shapses, S. A. (2011). The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *The Journal of Clinical Endocrinology & Metabolism*, 96(1), 53-58.
- Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., ... & Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, 96(7), 1911-1930.
- J Am Geriatr Soc 62:147–152, 2014.

Recommended Vitamin D Intake

	Vitamin D	Calcium
Institute of Medicine 51-70 years 71+ years	600 IU 800 IU	1000 mg (M); 1200 mg (F) 1200 mg
Endocrine Society 51-70 years 71+ years	1500-2000 IU 1500-2000 IU	N/A
AACE Osteoporosis	1000-2000 IU	1200 mg
National Osteoporosis Foundation 51-70 years 71+ years	800-1000 IU 800-1000 IU	1000 mg (M); 1200 mg (F) 1200 mg
American Geriatrics Society 65+ years	≥1000 IU	N/A

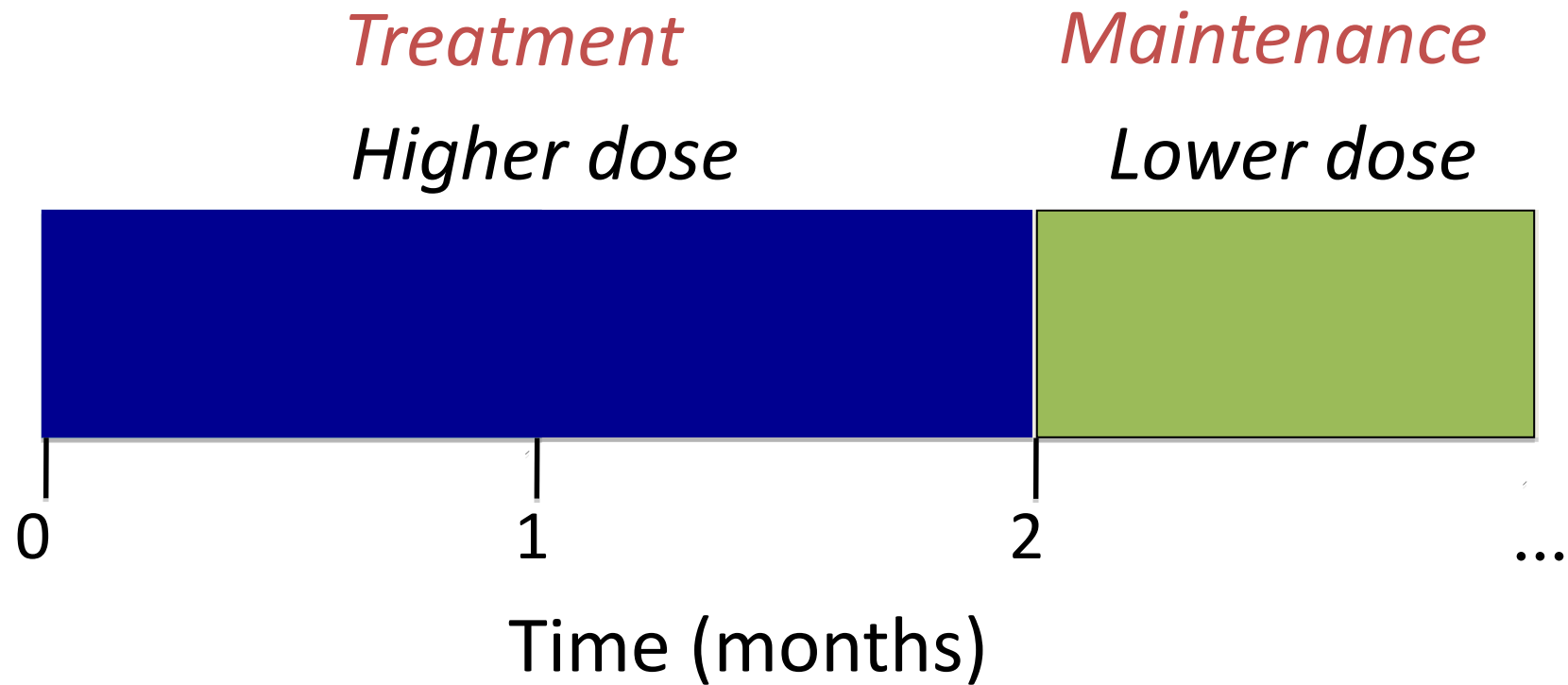
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Vitamin D2 vs. D3

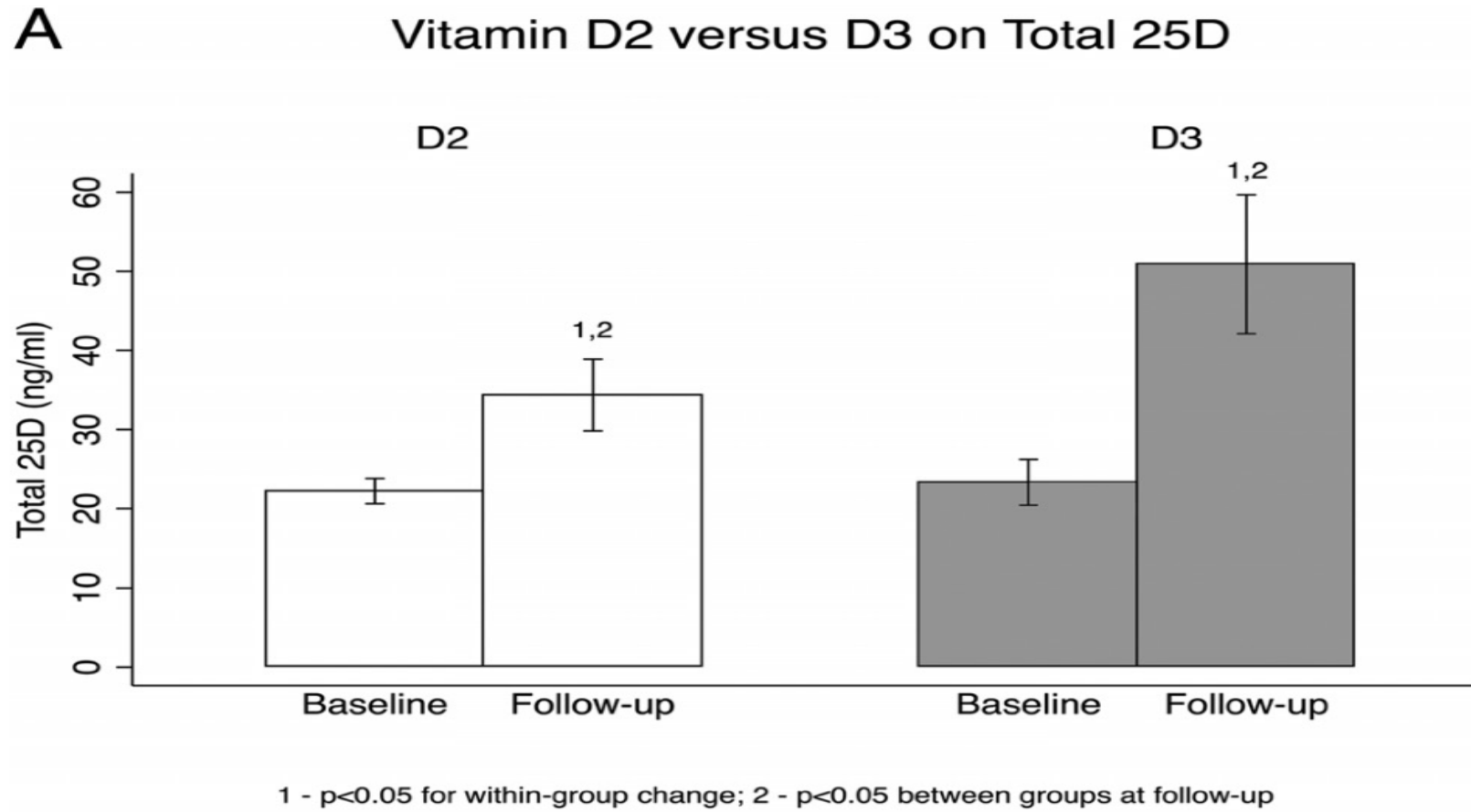
	D2	D3
Source	Plant sources - UV irradiation of ergosterol	Animal sources - UV irradiation of 7-dehydrocholesterol
Molecular weight	399	384
Binding affinity for DBP	Less	More
Half life of 25(OH)D	13.9 \pm 2.6 days	15.1 \pm 3.1 days

Jones, K. S., Assar, S., Harnpanich, D., Bouillon, R., Lambrechts, D., Prentice, A., & Schoenmakers, I. (2014). 25 (OH) D2 half-life is shorter than 25 (OH) D3 half-life and is influenced by DBP concentration and genotype. The Journal of Clinical Endocrinology & Metabolism, 99(9), 3373-3381.

Approach to Vitamin D Replacement



D2 v D3: 50,000 IU weekly x10 weeks



Shieh, A., Chun, R. F., Ma, C., Witzel, S., Meyer, B., Rafison, B., ... & Adams, J.S. (2016). Effects of high-dose vitamin D2 versus vitamin D3 on total and free 25-hydroxyvitamin D and markers of calcium balance. *The Journal of Clinical Endocrinology & Metabolism*, jc-2016.

Bolus Dosing of Vitamin D and Falls

Bolus doses of vitamin D associated with an increased risk of falls in older adults

- 500,000 IU PO annually for 3-5 years
 - 15% greater risk of falls ($p=0.03$)
- 60,000 IU PO monthly for 1 year
 - 40% greater risk of falls ($p=0.04$)

- Sanders, K. M., Stuart, A. L., Williamson, E. J., Simpson, J. A., Kotowicz, M. A., Young, D., & Nicholson, G. C. (2010). Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *Jama*, 303(18), 1815-1822.
- Bischoff-Ferrari, H. A., Dawson-Hughes, B., Orav, E. J., Staehelin, H. B., Meyer, O. W., Theiler, R., ... & Egli, A. (2016). Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. *JAMA internal medicine*, 176(2), 175-183.

Key Points:

Vitamin D Intake Requirements and Safety

- In adults without osteoporosis, a 25(OH)D level of ≥ 20 ng/ml is likely sufficient
 - 800 IU/day
- In adults with osteoporosis (especially if being treated with an anti-resorptive), a 25(OH)D level of ≥ 30 ng/ml is likely necessary (goal 30-50 ng/ml)
 - If 25(OH)D < 20 ng/ml: 4000 IU/day or 50,000 IU/week for 8-10 weeks, followed by 1000-2000 IU/day

Recommended Calcium Intake

	Vitamin D	Calcium
Institute of Medicine 51-70 years 71+ years	600 IU 800 IU	1000 mg (M); 1200 mg (F) 1200 mg
Endocrine Society 51-70 years 71+ years	1500-2000 IU 1500-2000 IU	N/A
AACE Osteoporosis	1000-2000 IU	1200 mg
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Dietary Sources of Calcium

Dietary source	Serving size	Calcium content (mg)
<u>Produce</u>		
Broccoli	8 oz	65
Bok choy		160
Kale (frozen)		180
Collard greens (frozen)		360
<u>Seafood</u>		
Sardines, canned with bones	3 oz	325
Salmon, canned with bones		180
<u>Dairy</u>		
Milk	8 oz	300
Yogurt	6 oz	260
Yogurt (Greek)	6 oz	200
Ice cream	8 oz	85
Cheese	1 oz	100-200

Choice of Calcium Supplements

	Calcium Carbonate	Calcium Citrate
Elemental calcium	40%	21%
Pill needed	Fewer	More
Cost	Less	More
Require gastric acid	Yes	No
GI side effects	More	Less

For optimal absorption, calcium supplementation should not exceed 500 to 600 mg per dose. If more than 600 mg of calcium supplementation is needed, the dose should be divided.

Safety of Calcium Supplementation

- Nephrolithiasis
 - High intake levels associated with kidney stones
- Cardiovascular disease
 - Inconsistent data
 - Verification of cardiovascular events an issue

Calcium and Cardiovascular Disease

Annals of Internal Medicine

CLINICAL GUIDELINE

Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology

Stephen L. Kopecky, MD; Douglas C. Bauer, MD; Martha Gulati, MD; Jeri W. Nieves, PhD; Andrea J. Singer, MD; Peter P. Toth, MD, PhD; James A. Underberg, MD; Taylor C. Wallace, PhD; and Connie M. Weaver, PhD

Description: Calcium is the dominant mineral present in bone and a shortfall nutrient in the American diet. Supplements have been recommended for persons who do not consume adequate calcium from their diet as a standard strategy for the prevention of osteoporosis and related fractures. Whether calcium with or without vitamin D supplementation is beneficial or detrimental to vascular health is not known.

Methods: The National Osteoporosis Foundation and American Society for Preventive Cardiology convened an expert panel to evaluate the effects of dietary and supplemental calcium on cardiovascular disease based on the existing peer-reviewed scientific literature. The panel considered the findings of the accompanying updated evidence report provided by an independent evidence review team at Tufts University.

Recommendation: The National Osteoporosis Foundation and American Society for Preventive Cardiology adopt the position that there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time. In light of the evidence available to date, calcium intake from food and supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000 to 2500 mg/d) should be considered safe from a cardiovascular standpoint.

Ann Intern Med. 2016;165:867-868. doi:10.7326/M16-1743 www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 25 October 2016.

Kopecky, S. L., Bauer, D. C., Gulati, M., Nieves, J. W., Singer, A. J., Toth, P. P., ... & Weaver, C. M. (2016). Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults: a clinical guideline from the National Osteoporosis Foundation and the American Society for Preventive Cardiology. *Annals of internal medicine*, 165(12), 867-868.

Key Points:

Calcium Intake Requirements and Safety

- 1,000 to 1,200 mg/day of calcium between diet and supplement is enough
 - AACE and NOF recommend getting as much calcium through dietary sources as possible
 - Taking more than 2,000 mg/day of calcium is not necessary and not recommended

Acknowledgements

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John Adams, MD