

This article may be reprinted free of charge provided 1) that there is clear attribution to the Orthomolecular Medicine News Service, and 2) that both the OMNS free subscription link http://orthomolecular.org/subscribe.html and also the OMNS archive link http://orthomolecular.org/subscribe.html archive link http://orthomolecular.org/subscribe.html archive

FOR IMMEDIATE RELEASE Orthomolecular Medicine News Service, August 16, 2022

Bone Health and Osteoporosis: An Orthomolecular Perspective

Editorial by Richard Z. Cheng, MD, PhD and Thomas E. Levy, MD, JD

OMNS (Aug. 16, 2022) Osteoporosis, like most other disease, is caused by many factors including deficiencies of essential nutrients such as vitamin D. But the central dogma has been promoting just prescription drugs and calcium supplements. This strategy sounds simple and straightforward, but unfortunately not only does it not work, it may even be harmful. There is a rich body of data in the literature showing that lifestyle, nutrition, toxins, and hormonal balance have an impact on bone health and osteoporosis. A brief summary of this research is presented here. For optimal results, the practical management of osteoporosis and other chronic diseases should incorporate this knowledge.

A recent issue of *New England Journal of Medicine* published an article claiming that vitamin D supplementation does not improve osteoporosis. [1] *Forbes* magazine immediately jumped the gun: Stop Taking Vitamin D Already! [2]

Vitamin D is more than just a vitamin; it is more like a hormone with pleiotropic effects on the body, including immune-boosting effects that fight against Covid-19. Giving advice to stop taking vitamin D based on just one negative study is not only unscientific, it's against common sense. (We will not discuss the study design issues, as Dr. William Grant will presently offer his critique of NEJM article's poor study design).

Because vitamin D is involved in many aspects of health, maintaining an adequate level is critically important. Yet many individuals are deficient, which has likely increased the rates of infection and death from Covid-19. There have been many clinical studies on vitamin D3 and Covid-19 in the last two years, including a special collection of Micronutrients for Viral Infections - Reference Bibliography by International Society for Orthomolecular Medicine, [3] and several such papers on Orthomolecular Medicine News Service including a recent review by Dr. Grant. [4] Have the author and editor of the *Forbes* article not been updated on the vitamin D research -- or is there something else?

Prescription drugs and calcium supplements have no significant benefits for treating osteoporosis.

Earlier this year, a meta-analysis published on *JAMA* found that bisphosphonates, a major class of prescription osteoporosis drugs offer very few benefits to osteoporotic patients. [5] Another meta-analysis on *JAMA* showed calcium supplements do not offer significant help to osteoporosis. [6]

Calcium supplements increase the risk of cardiovascular diseases and cancer.

To make matters worse, calcium supplements not only do not improve your health, but may actually increase your risks of cardiovascular diseases and cancer, as reported on a recent study. [7]

Many studies in the literature have demonstrated the risks of calcium supplements, as summarized by Thomas Levy. $[\underline{8},\underline{9}]$

Prescription drugs and calcium supplements are not helpful and may even be harmful. So, are osteoporosis patients doomed?

Not at all. There is a rich body of evidence in the medical literature showing that osteoporosis is a multifactorial disease -- and that a healthy lifestyle, reversing a toxin overload (by detoxification), optimal nutrition, and hormonal balance are effective in improving not only osteoporosis but overall health. [8]

Highlights of some of the relevant research:

- Vitamin C and Osteoporosis:
 - Increased oxidative stress (= inflammatory response) in the bone is accompanied by an increase in C-reactive protein (CRP). The level of CRP can accurately predict fracture risk in older women with osteoporosis. [10]
 - Increases in other inflammatory markers are also closely associated with increased fracture risk. [11]
 - High-dose vitamin C can significantly reduce CRP and many other markers of inflammation. [12]
 - Vitamin C stimulates the development of osteoblasts. [13,14]
 - Vitamin C is necessary for the synthesis of progenin (class III), which is required for the growth of osteoblasts. [15]
 - Dietary vitamin C, which is negligible compared to the level provided by vitamin C supplementation, does not reduce fracture risk. [16]
 - Elderly osteoporosis patients with a history of fractures had significantly lower levels of vitamin C than those without a history of fractures. [17]
 - Supplementation with vitamin C, but not calcium, significantly increased bone mineral density in all bones. [18]
 - In ovariectomized mice, vitamin C prevents bone loss. [19]
 - Vitamin C significantly accelerates fracture healing. [20]
 - An adequate vitamin C level significantly improves the strength of healed fractures.
 [21]
- Magnesium deficiency and osteoporosis:
 - Magnesium is a natural calcium antagonist. [22,23]
 - Magnesium dissolves calcium deposits in soft tissues. [24]
 - Magnesium deficiency leads to a detrimental increase in intracellular calcium. [25]
 - Magnesium increases bone density and reduces fractures. [26]
 - An adequate intake of magnesium reduces all-cause mortality. [27,28]
 - Usual supplemental doses have no toxic side effects.
- Vitamin K deficiency and osteoporosis:
 - Vitamin K inhibits ectopic calcification by activating proteases such as osteocalcin and matrix Gla proteins. [29]
 - Vitamin K helps dissolve deposited calcium in organs and arteries. [30]
 - Neutralizes warfarin (warfarin can cause ectopic calcification). [31]
 - Reduced fracture risk. [32]
 - Improves bone quality. [33]

- Adequate intake of vitamin K reduces cardiac and all-cause mortality. [34]
- At any dose tried, there was no apparent toxicity. [35]
- Vitamin D deficiency and osteoporosis
 - An adequate level of vitamin D ensures that the body gets enough calcium from the diet.
 - The role of vitamin D goes far beyond the metabolism of bone and calcium.
 - Vitamin D regulates about 2000 genes. [36]
 - A deficiency of vitamin D leads to osteoporosis. [37]
 - Too much vitamin D exacerbates osteoporosis. [38]
 - During bone growth and development, vitamin D plays an important role in bone density. [<u>39</u>]
 - Therapeutic doses of vitamin D reduced all-cause mortality. [40,41]
- Estrogens and Osteoporosis:
 - Estrogen reduces coronary calcium deposition. [42]
 - The higher the E2, the lower the CAC score. [43]
 - Estrogen inhibits a calcification-promoting protease. [44]
 - Estrogen deficiency leads to an increase in cytokines that promote inflammation.
 [45]
 - Reduction of fracture risk in patients with osteoporosis. [46]
 - Estrogen deficiency increases all-cause mortality. [47]
 - Estrogen deficiency promotes metabolic syndrome. [48]
- Androgens and Osteoporosis:
 - Testosterone deficiency is a well-established fracture risk factor. [49]
 - Testosterone has a calcium channel blocking function. [50]
 - Prostate cancer patients often have low testosterone levels. [51]
 - Testosterone levels are often inversely proportional to coronary calcium index. [51]
 - Testosterone deficiency increases all-cause mortality. [52,53]
- Thyroid hormones and Osteoporosis:
 - Thyroid hormones have a significant effect on the metabolism of cells throughout the body. [54]
 - The roles of early skeletal development and high bone mass (Peak Bone Mass) are essential. [55]
 - Both high and low thyroid function increase fracture risk. [56]
 - TSH has a direct (non-thyroid-related) bone-protecting function. [57,58]
 - Both too high and too low thyroxine independently increased all-cause mortality. This includes subclinical hypothyroidism and subclinical hyperthyroidism. [59,60]
 - Thyroid hormones status should be a part of routine medical examination, and should be checked regularly (at least annually), especially in the elderly population. Effective therapy is available.
- Essential Fatty Acids (EFA) and Osteoporosis:
 - Some EFAs have calcium channel blocking capabilities. [61,62]
 - Numerous EFAs have been shown to protect bone mineral density. [63,64]
 - Blood EFA levels are inversely related to all-cause mortality. [65]
 - Not toxic, but may cause gastrointestinal discomfort in large quantities.
- Calcium supplements are not only unhelpful, they are harmful: chronic hypercalcemia is common in adults, and calcium supplements promote coronary calcium.

- A recent study showed that calcium supplementation has no effect on osteoporosis.
 [6]
- One-third of Americans over the age of 45 have CT-detected arterial calcification.
 [66]
- Coronary heart disease is associated with osteoporosis. [67]
- Aortic calcification is associated with osteoporosis. [68]
- Calcium supplements promote coronary calcium deposition.
- A recent 10-year large study of 5448 subjects in the United States found that calcium supplementation was 22% more likely to be positive for CAC (coronary calcium index) than those who did not. CAC has been generally recognized as a reliable predictor of atherosclerotic plaque burden, coronary heart disease, and allcause mortality. [69-71]
- A recent meta-analysis again showed that calcium supplements increase the risk of cardiovascular disease. [7]
- Significant calcifications outside the bones: indicating calcium excess
 - Ectopic calcifications are very common in cancer.
 - Using the latest MRI, 22 of 23 prostate patients were found to have prostate calcification. [72]
 - Excessive intracellular calcium is associated with cancer:
 - The relationship between intracellular calcium and cancer is well established. Higher intracellular calcium level increases cancer cell growth and metastasis. [73-75]
 - Conversely, a drop in intracellular calcium reduces cancer cell metastasis. [76]
 - Women with the highest scores on a bone density test had an increased risk of breast cancer. [77]
 - Calcifications are usually seen on mammography in patients with breast cancer.
 [78]
- Calcium and calcium channel blockers (CCBs), also known as calcium ion antagonists, have the effect of reducing intracellular calcium ion level.
 - Evidence that increased intracellular calcium leads to increased intracellular oxidative stress (toxicity):
 - CCBs can prevent methylmercury-induced nerve damage in rats; [79]
 - The use of CCBs is inversely related to the occurrence of prostate cancer; [80]
 - CCBs reduce intracytoplasmic iron accumulation and further increase the increase in intracellular oxidative stress. The accumulation and increase of intracellular iron are also important factors in the carcinogenesis of cells. [81]

To put these altogether, we recommend an integrated management of osteoporosis that includes at least the following:

- 1. Healthy lifestyle
 - a. Sufficient exercise, outdoor activities, relaxation, and sleep.
 - b. Nutrition rich anti-inflammatory healthy diets to include low carbohydrates, sufficient proteins and healthy fats; minimize processed foods and synthetic food additives, agricultural chemicals, antibiotics and hormones, and other environmental pollutants.
- Nutrition: In addition to adequate doses of vitamin C,D,E,K2, and magnesium supplements, macro- and micro-nutrients play a significant roles in the prevention and reversal of bone health and osteoporosis, as reviewed in [82]. Broad spectrum optimal vitamins and micronutrients, esp. vitamin C, D, K2, and magnesium, as these nutrients require each other for optimal effects, as described in [83].
- 3. Toxins and detox. Environmental toxins are a major category of detrimental root causes to our health.

4. Hormonal balance. Monitoring the status of the thyroid, adrenal and sex hormones and balance if indicated, is another under-recognized area in medicine today.

References:

1. LeBoff M, Chou SH, Ratliff KA, et al. (2022) Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. NEJM <u>https://pubmed.ncbi.nlm.nih.gov/35939577</u>

2. Salzberg S (2022) Stop Taking Vitamin D Already! Forbes <u>https://www.forbes.com/sites/stevensalzberg/2022/08/01/stop-taking-vitamin-d-already</u>

3. Micronutrients for Viral Infections - Reference Bibliography. ISOM <u>https://isom.ca/micronutrients-viral-infections</u>

4. Grant WB. (2021) Vitamin D's Role in Reducing Risk of SARS-CoV-2 and COVID-19 Incidence, Severity, and Death. Nutrients 14:183. <u>https://pubmed.ncbi.nlm.nih.gov/35011058</u>

5. Deardorff WJ, Cenzer I, Nguyen B, Lee SJ (2022) Time to Benefit of Bisphosphonate Therapy for the Prevention of Fractures Among Postmenopausal Women With Osteoporosis: A Metaanalysis of Randomized Clinical Trials. JAMA Intern Med. 182:33-41. <u>https://pubmed.ncbi.nlm.nih.gov/34807231</u>

6. Zhao J-G, Zeng X-T, Wang J Liu L (2017) Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA 318:2466-2482. <u>https://pubmed.ncbi.nlm.nih.gov/29279934</u>

7. Park, J-M, et al. (2022) Calcium Supplementation, Risk of Cardiovascular Diseases, and Mortality: A Real-World Study of the Korean National Health Insurance Service Data. Nutrients 14:2538. <u>https://pubmed.ncbi.nlm.nih.gov/35745268</u>

8. Levy T. (2013) Death By Calcium. MedFox Pub. ISBN-13: 978-0615889603 https://www.medfoxpub.com/medicalnews/product/S-DBC/Death-by-Calcium/D

9. Levy T, 成长. 隐形杀手---补钙剂(中文版): 补钙无助于骨质疏松, 反而促进血管硬化, 心脏病(中文版)。 (Kindle Publisher, 2017).

10. Nakamura K, Saito T, Kobayashi R, et al. (2011) C-reactive protein predicts incident fracture in community-dwelling elderly Japanese women: the Muramatsu study. Osteoporos Int. 22:2145-2150. <u>https://pubmed.ncbi.nlm.nih.gov/20936400</u>

11. Lacativa PGS, Farias MLF (2010) de. Osteoporosis and inflammation. Arq Bras Endocrinol Metabol. 54:123-132. <u>https://pubmed.ncbi.nlm.nih.gov/20485900</u>

12. Mikirova N, Casciari J, Rogers A, Taylor P (2012) Effect of high-dose intravenous vitamin C on inflammation in cancer patients. J Transl Med. 10:189. <u>https://pubmed.ncbi.nlm.nih.gov/22963460</u>

13. Carinci F, Pezzetti F, Spina AM, et al. (2005) Effect of Vitamin C on pre-osteoblast gene expression. Arch Oral Biol. 50:481-496. <u>https://pubmed.ncbi.nlm.nih.gov/15777530</u>

14. Choi K-M, Seo Y-K, Yoon H-H, et al. (2008) Effect of ascorbic acid on bone marrow-derived mesenchymal stem cell proliferation and differentiation. J Biosci Bioeng 105:586-594. <u>https://pubmed.ncbi.nlm.nih.gov/18640597</u>

15. Maehata Y, Takamizawa S, Ozawa S, et al. (2007) Type III collagen is essential for growth acceleration of human osteoblastic cells by ascorbic acid 2-phosphate, a long-acting vitamin C derivative. Matrix Biol 26:371-381. <u>https://pubmed.ncbi.nlm.nih.gov/17306970</u>

16. Sahni S, Hannan MT, Gagnon D, et al. (2009) Protective effect of total and supplemental vitamin C intake on the risk of hip fracture--a 17-year follow-up from the Framingham Osteoporosis Study. Osteoporos Int. 20:1853-1861. <u>https://pubmed.ncbi.nlm.nih.gov/19347239</u>

17. Martínez-Ramírez MJ, Pérez SP, Delgado-Martínez AD, et al. (2007) Vitamin C, vitamin B12, folate and the risk of osteoporotic fractures. A case-control study. Int J Vitam Nutr Res. 77:359-368. <u>https://pubmed.ncbi.nlm.nih.gov/18622945</u>

18. Morton DJ, Barrett-Connor EL, Schneider DL (2001) Vitamin C supplement use and bone mineral density in postmenopausal women. J Bone Miner Res. 16:135-140. <u>https://pubmed.ncbi.nlm.nih.gov/11149477</u>

19. Zhu L-L, Cao J, Sun M, et al. (2012) Vitamin C prevents hypogonadal bone loss. PLoS One 7:e47058. <u>https://pubmed.ncbi.nlm.nih.gov/23056580</u>

20. Yilmaz C, Erdemli E, Selek H, et al. (2001) The contribution of vitamin C to healing of experimental fractures. Arch Orthop Trauma Surg. 121:426-428. https://pubmed.ncbi.nlm.nih.gov/11510911

21. Alcantara-Martos T, Delgado-Martinez AD, Vega MV, et al. (2007) Effect of vitamin C on fracture healing in elderly Osteogenic Disorder Shionogi rats. J Bone Joint Surg Br. 89:402-407. https://pubmed.ncbi.nlm.nih.gov/17356161

22. Fawcett WJ, Haxby EJ, Male DA (1999) Magnesium: physiology and pharmacology. Br J Anaesth. 83:302-320. <u>https://pubmed.ncbi.nlm.nih.gov/10618948</u>

23. Anghileri LJ (2009) Magnesium, calcium and cancer. Magnes Res. 22:247-255. https://pubmed.ncbi.nlm.nih.gov/20228002

24. Steidl L, Ditmar R (1990) Soft tissue calcification treated with local and oral magnesium therapy. Magnes Res. 3:113-119. <u>https://pubmed.ncbi.nlm.nih.gov/2133625</u>

25. Fox C, Ramsoomair D, Carter C (2001) Magnesium: its proven and potential clinical significance. South Med J. 94:1195-1201. <u>https://pubmed.ncbi.nlm.nih.gov/11811859</u>

26. Ryder KM, Shorr RI, Bush AJ, et al. (2005) Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects. J Am Geriatr Soc. 53:1875-1880. <u>https://pubmed.ncbi.nlm.nih.gov/16274367</u>

27. Woods KL, Fletcher S (1994) Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). Lancet 343:816-819. <u>https://pubmed.ncbi.nlm.nih.gov/7908076</u>

28. Shechter M, Hod H, Rabinowitz B, Boyko V, Chouraqui P (2003) Long-term outcome of intravenous magnesium therapy in thrombolysis-ineligible acute myocardial infarction patients. Cardiology 99:205-210. <u>https://pubmed.ncbi.nlm.nih.gov/12845247</u>

29. Theuwissen E, Smit E, Vermeer C (2012) The role of vitamin K in soft-tissue calcification. Adv Nutr. 3:166-173. <u>https://pubmed.ncbi.nlm.nih.gov/22516724</u>

30. Schurgers LJ, Spronk HMH, Soute BAM, et al. (2007) Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood 109:2823-2831. https://pubmed.ncbi.nlm.nih.gov/17138823

31. Price PA, Faus SA, Williamson MK (1998) Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. Arterioscler Thromb Vasc Biol. 18:1400-1407. https://pubmed.ncbi.nlm.nih.gov/9743228

32. Shiraki M, Shiraki Y, Aoki C, Miura M (2000) Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. J Bone Miner Res. 15:515-

33. Saito M (2009) [Effect of vitamin K on bone material properties]. Clin Calcium 19:1797-1804. https://pubmed.ncbi.nlm.nih.gov/19949271

34. Geleijnse JM, Vermeer D, Grobbeeet DE, et al. (2004) Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr. 134:3100-3105. <u>https://pubmed.ncbi.nlm.nih.gov/15514282</u>

35. Pucaj K, Rasmussen H, Møller M, Preston T (2011) Safety and toxicological evaluation of a synthetic vitamin K2, menaquinone-7. Toxicol Mech Methods 21:520-532. <u>https://pubmed.ncbi.nlm.nih.gov/21781006</u>

36. Wacker M, Holick MF (2013) Vitamin D - effects on skeletal and extraskeletal health and the need for supplementation. Nutrients 5:111-148. <u>https://pubmed.ncbi.nlm.nih.gov/23306192</u>

37. Bolland MJ, Bacon CJ, Horne AM, et al. (2010) Vitamin D insufficiency and health outcomes over 5 y in older women. Am J Clin Nutr. 91:82-89. <u>https://pubmed.ncbi.nlm.nih.gov/19906799</u>

38. Masterjohn C (2007) Vitamin D toxicity redefined: vitamin K and the molecular mechanism. Med Hypotheses 68:1026-1034. <u>https://pubmed.ncbi.nlm.nih.gov/17145139</u>

39. Pekkinen M, Viljakainen H, Saarnio E, Lamberg-Allardt C, Mäkitie, O. (2012) Vitamin D is a major determinant of bone mineral density at school age. PLoS One 7:e40090. <u>https://pubmed.ncbi.nlm.nih.gov/22768331</u>

40. Semba RD, Houston DK, Bandinelli S, et al. (2010) Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. Eur J Clin Nutr. 64:203-209. <u>https://pubmed.ncbi.nlm.nih.gov/19953106</u>

41. Schöttker B, Haug U, Schomburg L, et al. (2013) Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. Am J Clin Nutr. 97:782-793. <u>https://pubmed.ncbi.nlm.nih.gov/23446902</u>

42. Weinberg N, Young A, Hunter CJ, et al. (2012) Physical activity, hormone replacement therapy, and the presence of coronary calcium in midlife women. Women Health 52:423-436. https://pubmed.ncbi.nlm.nih.gov/22747181

43. Jeon G-H, Kim SH, Yun S-C, et al. (2010) Association between serum estradiol level and coronary artery calcification in postmenopausal women. Menopause 17:902-907. <u>https://pubmed.ncbi.nlm.nih.gov/20512078</u>

44. Osako MK, Nakagami H, Koibuchi N, et al. (2010) Estrogen inhibits vascular calcification via vascular RANKL system: common mechanism of osteoporosis and vascular calcification. Circ Res. 107:466-475. <u>https://pubmed.ncbi.nlm.nih.gov/20595654</u>

45. Das UN (2002) Nitric oxide as the mediator of the antiosteoporotic actions of estrogen, statins, and essential fatty acids. Exp Biol Med. (Maywood) 227:88-93. https://pubmed.ncbi.nlm.nih.gov/11815671

46. de Villiers TJ, Stevenson JC (2012) The WHI: the effect of hormone replacement therapy on fracture prevention. Climacteric. 15:263-266. <u>https://pubmed.ncbi.nlm.nih.gov/22612613</u>

47. de Padua Mansur A, et al. (2012) Long-term prospective study of the influence of estrone levels on events in postmenopausal women with or at high risk for coronary artery disease. Scientific World Journal 2012, 363595. <u>https://pubmed.ncbi.nlm.nih.gov/22701354</u>

48. Mauvais-Jarvis F, Clegg DJ, Hevener AL (2013) The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev. 34:309-338. https://pubmed.ncbi.nlm.nih.gov/23460719 49. Torremadé-Barreda J, et al. (2013) [Testosterone-deficiency as a risk factor for hip fracture in eldery men]. Actas Urol Esp. 37:142-146. <u>https://pubmed.ncbi.nlm.nih.gov/23246104</u>

50. Oloyo AK, Sofola OA, Nair RR, et al. (2011) Testosterone relaxes abdominal aorta in male Sprague-Dawley rats by opening potassium (K(+)) channel and blockade of calcium (Ca(2+)) channel. Pathophysiology 18:247-253. <u>https://pubmed.ncbi.nlm.nih.gov/21439799</u>

51. Mearini L, Zucchi A, Nunzi E, et al. (2013) Low serum testosterone levels are predictive of prostate cancer. World J Urol. 31:247-252. <u>https://pubmed.ncbi.nlm.nih.gov/22068548</u>

52. Fukai S, Akishita M, Yamada S, et al. (2012) Plasma sex hormone levels and mortality in disabled older men and women. Geriatr Gerontol Int. 11:196-203. https://pubmed.ncbi.nlm.nih.gov/21143567

53. Grossmann M, Hoermann R, Gani L, et al. (2012) Low testosterone levels as an independent predictor of mortality in men with chronic liver disease. Clin Endocrinol (Oxf) 77:323-328. <u>https://pubmed.ncbi.nlm.nih.gov/22280063</u>

54. Boelaert K, Franklyn JA (2005) Thyroid hormone in health and disease. J Endocrinol. 187, 1-15. <u>https://pubmed.ncbi.nlm.nih.gov/16214936</u>

55. Williams GR (2009) Actions of thyroid hormones in bone. Endokrynol Pol. 60:380-388. https://pubmed.ncbi.nlm.nih.gov/19885809

56. Wojcicka A, Bassett JHD, Williams GR (2013) Mechanisms of action of thyroid hormones in the skeleton. Biochim Biophys Acta 1830:3979-3986. <u>https://pubmed.ncbi.nlm.nih.gov/22634735</u>

57. Sun L, Zhu L-L, Lu P, et al. (2013) Genetic confirmation for a central role for TNFα in the direct action of thyroid stimulating hormone on the skeleton. Proc Natl Acad Sci. USA 110:9891-9896. <u>https://pubmed.ncbi.nlm.nih.gov/23716650</u>

58. Ma R, Morshed S, Latif R, et al. (2011) The influence of thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibodies on osteoclastogenesis. Thyroid 21:897-906. https://pubmed.ncbi.nlm.nih.gov/21745106

59. Tseng F-Y, Lin W-Y, Lin C-C, et al. (2012) Subclinical hypothyroidism is associated with increased risk for all-cause and cardiovascular mortality in adults. J Am Coll Cardiol. 60:730-737. https://pubmed.ncbi.nlm.nih.gov/22726629

60. Ceresini G, Ceda GP, Lauretani F, et al. (2013) Thyroid status and 6-year mortality in elderly people living in a mildly iodine-deficient area: the aging in the Chianti Area Study. J Am Geriatr Soc. 61:868-874. <u>https://pubmed.ncbi.nlm.nih.gov/23647402</u>

61. Ye S, Tan L, Ma J, et al. (2010) Polyunsaturated docosahexaenoic acid suppresses oxidative stress induced endothelial cell calcium influx by altering lipid composition in membrane caveolar rafts. Prostaglandins Leukot Essent Fatty Acids 83:37-43. https://pubmed.ncbi.nlm.nih.gov/20206488

62. Pages N, Maurois P, Delplanque B, et al. (2011) Brain protection by rapeseed oil in magnesium-deficient mice. Prostaglandins Leukot Essent Fatty Acids 85:53-60. https://pubmed.ncbi.nlm.nih.gov/21664114

63. Farina EK, Kiel DP, Roubenoff R, et al. (2012) Plasma phosphatidylcholine concentrations of polyunsaturated fatty acids are differentially associated with hip bone mineral density and hip fracture in older adults: the Framingham Osteoporosis Study. J Bone Miner Res. 27:1222-1230. https://pubmed.ncbi.nlm.nih.gov/22392875

64. Moon H-J, Kim T-H, Byun D-W, Park Y (2012) Positive correlation between erythrocyte levels of n-3 polyunsaturated fatty acids and bone mass in postmenopausal Korean women with osteoporosis. Ann Nutr Metab. 60:146-153. <u>https://pubmed.ncbi.nlm.nih.gov/22507833</u>

65. Pottala JV, Garg S, Cohen BE, et al. (2010) Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul study. Circ Cardiovasc Qual Outcomes 3:406-412. <u>https://pubmed.ncbi.nlm.nih.gov/20551373</u>

66. Guzman RJ (2007) Clinical, cellular, and molecular aspects of arterial calcification. J Vasc Surg. 45(Suppl A):A57-63. <u>https://pubmed.ncbi.nlm.nih.gov/17544025</u>

67. von der Recke P, Hansen MA, Hassager C (1999) The association between low bone mass at the menopause and cardiovascular mortality. Am. J. Med. 106:273-278. <u>https://pubmed.ncbi.nlm.nih.gov/10190374</u>

68. Bagger YZ, Tankó LB, Alexandersen P, et al. (2006) Radiographic measure of aorta calcification is a site-specific predictor of bone loss and fracture risk at the hip. J. Intern. Med. 259:598-605. <u>https://pubmed.ncbi.nlm.nih.gov/16704561</u>

69. Anderson JJB, Kruszka B, Delaney JAC, et al. (2016) Calcium Intake From Diet and Supplements and the Risk of Coronary Artery Calcification and its Progression Among Older Adults: 10-Year Follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc. 5:e003815. <u>https://pubmed.ncbi.nlm.nih.gov/27729333</u>

70. Jacobs PC, Gondrie MJA, van der Graaf Y, et al. (2012) Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. AJR Am J Roentgenol. 198:505-511. <u>https://pubmed.ncbi.nlm.nih.gov/22357989</u>

71. Kiramijyan S, Ahmadi N, Isma'eel H, et al. (2013) Impact of coronary artery calcium progression and statin therapy on clinical outcome in subjects with and without diabetes mellitus. Am J Cardiol. 111:356-361. <u>https://pubmed.ncbi.nlm.nih.gov/23206921</u>

72. Bai Y, Wang M-Y, Han Y-H, et al. (2013) Susceptibility weighted imaging: a new tool in the diagnosis of prostate cancer and detection of prostatic calcification. PLoS One 8:e53237. https://pubmed.ncbi.nlm.nih.gov/23308170

73. Gudermann T, Roelle S (2006) Calcium-dependent growth regulation of small cell lung cancer cells by neuropeptides. Endocr Relat Cancer 13:1069-1084. <u>https://pubmed.ncbi.nlm.nih.gov/17158754</u>

74. Kaufmann R, Hollenberg MD (2012) Proteinase-activated receptors (PARs) and calcium signaling in cancer. Adv Exp Med Biol. 740:979-1000. <u>https://pubmed.ncbi.nlm.nih.gov/22453980</u>

75. Ryu S, McDonnell K, Choi H, et al. (2013) Suppression of miRNA-708 by polycomb group promotes metastases by calcium-induced cell migration. Cancer Cell 23:63-76. <u>https://pubmed.ncbi.nlm.nih.gov/23328481</u>

76. Lin Q, Balasubramanian K, Fan D, et al. (2010) Reactive astrocytes protect melanoma cells from chemotherapy by sequestering intracellular calcium through gap junction communication channels. Neoplasia 12:748-754. <u>https://pubmed.ncbi.nlm.nih.gov/20824051</u>

77. Zhang Y, Kiel DP, Kreger BE, et al. (1997) Bone mass and the risk of breast cancer among postmenopausal women. N Engl J Med. 336:611-617. <u>https://pubmed.ncbi.nlm.nih.gov/9032046</u>

78. Holmberg L, Wong YNS, Tabár L, et al. (2013) Mammography casting-type calcification and risk of local recurrence in DCIS: analyses from a randomised study. Br J Cancer 108:812-819. https://pubmed.ncbi.nlm.nih.gov/23370209

79. Sakamoto M, Ikegami N, Nakano A (1996) Protective effects of Ca2+ channel blockers against methyl mercury toxicity. Pharmacol Toxicol. 78:193-199. <u>https://pubmed.ncbi.nlm.nih.gov/8882354</u>

80. Poch MA, Mehedint D, Green DJ, et al. (2013) The association between calcium channel blocker use and prostate cancer outcome. Prostate. 73:865-872. https://pubmed.ncbi.nlm.nih.gov/23280547 81. Chattipakorn N, Kumfu S, Fucharoen S, Chattipakorn S (2011) Calcium channels and iron uptake into the heart. World J Cardiol. 3:215-218. <u>https://pubmed.ncbi.nlm.nih.gov/21860702</u>

82. Martiniakova M, Babikova M, Mondockova V, et al. (2022) The Role of Macronutrients, Micronutrients and Flavonoid Polyphenols in the Prevention and Treatment of Osteoporosis. Nutrients 14:523. <u>https://pubmed.ncbi.nlm.nih.gov/35276879</u>

83. Cheng RZ (2022) A Hallmark of Covid-19: Cytokine Storm/Oxidative Stress and its Integrative Mechanism. <u>http://orthomolecular.org/resources/omns/v18n03.shtml</u>

Nutritional Medicine is Orthomolecular Medicine

Orthomolecular medicine uses safe, effective nutritional therapy to fight illness. For more information: <u>http://www.orthomolecular.org</u>

Find a Doctor

To locate an orthomolecular physician near you: http://orthomolecular.org/resources/omns/v06n09.shtml

The peer-reviewed Orthomolecular Medicine News Service is a non-profit and non-commercial informational resource.

Editorial Review Board:

Albert G. B. Amoa, MB.Ch.B, Ph.D. (Ghana) Seth Ayettey, M.B., Ch.B., Ph.D. (Ghana) Ilyès Baghli, M.D. (Algeria) Ian Brighthope, MBBS, FACNEM (Australia) Gilbert Henri Crussol, D.M.D. (Spain) Carolyn Dean, M.D., N.D. (USA) Ian Dettman, Ph.D. (Australia) Susan R. Downs, M.D., M.P.H. (USA) Ron Ehrlich, B.D.S. (Australia) Hugo Galindo, M.D. (Colombia) Martin P. Gallagher, M.D., D.C. (USA) Michael J. Gonzalez, N.M.D., D.Sc., Ph.D. (Puerto Rico) William B. Grant, Ph.D. (USA) Claus Hancke, MD, FACAM (Denmark) Tonya S. Heyman, M.D. (USA) Patrick Holford, BSc (United Kingdom) Suzanne Humphries, M.D. (USA) Ron Hunninghake, M.D. (USA) Bo H. Jonsson, M.D., Ph.D. (Sweden) Dwight Kalita, Ph.D. (USA) Felix I. D. Konotey-Ahulu, MD, FRCP, DTMH (Ghana) Jeffrey J. Kotulski, D.O. (USA) Peter H. Lauda, M.D. (Austria) Alan Lien, Ph.D. (Taiwan) Homer Lim, M.D. (Philippines) Stuart Lindsey, Pharm.D. (USA) Pedro Gonzalez Lombana, MD, MsC, PhD (Colombia) Victor A. Marcial-Vega, M.D. (Puerto Rico) Juan Manuel Martinez, M.D. (Colombia) Mignonne Mary, M.D. (USA) Jun Matsuyama, M.D., Ph.D. (Japan)

Joseph Mercola, D.O. (USA) Jorge R. Miranda-Massari, Pharm.D. (Puerto Rico) Karin Munsterhjelm-Ahumada, M.D. (Finland) Tahar Naili, M.D. (Algeria) W. Todd Penberthy, Ph.D. (USA) Zhiyong Peng, M.D. (China) Isabella Akyinbah Quakyi, Ph.D. (Ghana) Selvam Rengasamy, MBBS, FRCOG (Malaysia) Jeffrey A. Ruterbusch, D.O. (USA) Gert É. Schuitemaker, Ph.D. (Netherlands) Han Ping Shi, M.D., Ph.D. (China) T.E. Gabriel Stewart, M.B.B.CH. (Ireland) Thomas L. Taxman, M.D. (USA) Jagan Nathan Vamanan, M.D. (India) Garry Vickar, M.D. (USA) Ken Walker, M.D. (Canada) Anne Zauderer, D.C. (USA)

Andrew W. Saul, Ph.D. (USA), Editor-In-Chief

Associate Editor: Robert G. Smith, Ph.D. (USA) Editor, Japanese Edition: Atsuo Yanagisawa, M.D., Ph.D. (Japan) Editor, Chinese Edition: Richard Cheng, M.D., Ph.D. (USA) Editor, French Edition: Vladimir Arianoff, M.D. (Belgium) Editor, Norwegian Edition: Dag Viljen Poleszynski, Ph.D. (Norway) Editor, Arabic Edition: Moustafa Kamel, R.Ph, P.G.C.M (Egypt) Editor, Korean Edition: Hyoungjoo Shin, M.D. (South Korea) Editor, Spanish Edition: Sonia Rita Rial, PhD (Argentina) Contributing Editor: Thomas E. Levy, M.D., J.D. (USA) Contributing Editor: Damien Downing, M.B.B.S., M.R.S.B. (United Kingdom) Assistant Editor: Helen Saul Case, M.S. (USA) Technology Editor: Michael S. Stewart, B.Sc.C.S. (USA) Associate Technology Editor: Robert C. Kennedy, M.S. (USA) Legal Consultant: Jason M. Saul, JD (USA)

Comments and media contact: <u>drsaul@doctoryourself.com</u> OMNS welcomes but is unable to respond to individual reader emails. Reader comments become the property of OMNS and may or may not be used for publication.

To Subscribe at no charge: http://www.orthomolecular.org/subscribe.html

To Unsubscribe from this list: http://www.orthomolecular.org/unsubscribe.html

Back To Archive

