Vitamin D Supreme and Vitamin D Synergy™

With Vitamin K1 and K2

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Vitamin D Supreme and Vitamin D Synergy™ provide clinically useful servings of vitamin D3 and vitamin K as both K1 and K2 (as MK-4), along with geranylgeraniol (GG) to promote optimal bone and arterial health, and to maintain immune system balance.* These synergistic formulas offer two different dosing options of vitamin D, depending on the clinical need. With a higher targeted serving, Vitamin D Supreme may be ideal when more aggressive nutrient repletion is required and for individuals who do not get adequate sunlight exposure or dietary sources of vitamins D and K.* Vitamin D Synergy™ may be ideal for those looking to maintain optimal vitamin D status in the body.* Vitamins D and K work synergistically; thus, increasing vitamin D increases the need for vitamin K.* Both formulas provide 1,000 mcg of vitamin K1 (as phytonadione), 1,000 mcg of vitamin K2 (as MK-4), and 5 mg of GG (as GG-Gold®) for more comprehensive bone and arterial support.*

Highlights

- **Vitamin D Supreme** contains 5,000 IU (125 mcg) of vitamin D3 (cholecalciferol) per serving when higher servings are required for vitamin D deficiency or insufficiency*
- **Vitamin D Synergy™** contains 2,000 IU (50 mcg) of vitamin D3 as a dosage option for maintaining optimal vitamin D status*
- Both formulas contain 1,000 mcg of vitamin K1 (as phytonadione), 1,000 mcg of vitamin K2 (as MK-4), and 5 mg GG (as GG-Gold®) per serving to support bone and arterial health*
- Gluten-free, dairy-free, soy-free, or non-GMO

Vitamin D

Vitamin D is a fat-soluble vitamin that is well-known to support bone health through the regulation of calcium-phosphorus homeostasis and its role in bone turnover. Low vitamin D levels have been shown to decrease bone density and increase fracture risk.[1] Vitamin D receptors (VDRs) are found throughout the body and have been shown to influence the expression of thousands of genes.[2,3] Vitamin D is essential for the immune system as it modulates the response of the innate and adaptive immune system by VDRs. VDR is the critical transcription factor in differentiating lymphocytes within the bone marrow into monocytes and granulocytes.[4] Vitamin D can regulate Th1 and Th2 lymphocyte balance and downregulate the expression of inflammatory cytokines overall. Vitamin 1,25(OH)D3 has been shown to heavily influence and shift the intracellular metabolism of dendritic cells and macrophages, metabolically reprogramming their role in inflammation and autoimmunity by altering the phenotypic expression of the cells.[5] In fact, research showed that priming of naive CD4+ T cells with vitamin D-treated tolerogenic dendritic cells induced the T-regulatory cells that support a healthy inflammatory response and impact autoimmune processes.[6] Low concentrations of vitamin D are associated with disrupted immune function in gastrointestinal diseases.[7,8] VDR regulates the innate immune response in the gut, plays a critical role in regulating endothelial tight junction protein expression, and regulates the intestinal microbiota by controlling microflora composition.[7]

In addition to its well-known support of bone health and the immune system, vitamin D may also support cardiovascular health. A systematic review and meta-analysis of randomized controlled trials showed that vitamin D supplementation, which included D3 and D2, was not statistically significant in lowering mortality.

Benefits*

- Supports cardiovascular health
- Supports optimal bone health
- Promotes arterial strength and elasticity
- Helps maintain healthy immune system balance and inflammatory response
- Helps optimize calcium absorption and utilization

Vitamin D Supreme

Supplement Facts

Serving Size 1 capsule

Amount Per Serving		% Daily Value
Vitamin D (as Cholecalciferol)	125 mcg (5000 IU)	625%
Vitamin K (as Vitamin K1-Phytonadione 1,000 mcg; Vitamin K2-Menaquinone-4 1,000 mcg	2,000 mcg	1,667%
Trans-Geranylgeraniol (GG-Gold®)	5 mg	*

*Daily Value not established.

Other Ingredients: Cellulose (capsule), microcrystalline cellulose, L-leucine.

Vitamin D Synergy™

Supplement Facts

Serving Size 1 capsule

Amount Per Serving		% Daily Value
Vitamin D (as Cholecalciferol)	50 mcg (2000 IU)	250%
Vitamin K (as Vitamin K1-Phytonadione 1000 mcg; Vitamin K2-Menaquinone-4 1000 mcg)	2000 mcg	1667%
Trans-Geranylgeraniol (GG-Gold®)	5 mg	*

*Daily Value not established.

Other Ingredients: Microcrystalline cellulose, cellulose (capsule), L-leucine.

Yet, when D3 was studied as a subgroup, all-cause mortality was significantly lower than in trials with D2.[9] Vitamin D also plays a role in the brain, influencing brain development in early life and brain function in adults, and vitamin D deficiency can be associated with depressed moods and impaired cognition.[10-14]

Epidemiological findings indicate that almost 30% of the U.S. adult population is deficient in this vitamin with another 40% who are insufficient.[15] Vitamin D deficiency has been shown to play a role in autoimmune diseases, heart disease, and certain types of cancer.[9,16,17] Evidence indicates that vitamin D3 is far more effective in raising and maintaining serum 25(OH)D concentration, and vitamin D2 should not be considered an equivalent.[18,19] These factors highlight the potential clinical utility and value of supplementation with vitamin D across a variety of clinical presentations.

Vitamin K Forms, Adequate Intake for Clotting Versus for Extra-hepatic Roles

Vitamin K is a fat-soluble vitamin like vitamin D, and complements the support of bone and cardiovascular health, along with many other aspects of physiology.[20,21] For example, vitamin D increases calcium absorption, whereas vitamin K improves calcium deposition in the bones while inhibiting its accumulation in the arterial walls. This explains the results from studies that have found the combined supplementation of vitamins D and K to be more effective than that of either vitamin alone.[20,21]

Vitamin K exists in two main forms: vitamin K1 (VK1), as phylloquinone, which is found in leafy green vegetables, and vitamins K2 (VK2s), also known as menaquinones, which are found in certain animal products, fermented foods, and are also produced by gut microbiota. VK2 occurs naturally with various lengths (n = 1 to 14) of their side chains, abbreviated here as VK2 (MK-n). VK2 (MK-4) represents 90% of the total vitamin K stored in the human body. Animal studies have shown that other forms of VK2s convert into VK2 (MK-4) in all tissues, except the liver.[21]

For adults 19 years and older, the adequate intake (AI) for VK1 was set at 120 mcg for men and 90 mcg for women, but this level is only sufficient to fully activate blood-clotting proteins.[22] No AI has been set for VK2s and no upper level of toxicity has been established by the Institute of Medicine for VK1 or VK2s.[22] However, extensive evidence has revealed a variety of extra-hepatic roles for VK1 and VK2, which may require much higher intake levels of these vitamins.[21] The most researched roles involve control of calcium transport between tissues. VK1 and VK2 are transported in part to the liver to support the production of coagulation factors and to extra-hepatic tissues where they have various roles. These include: (a) carboxylation of gamma-carboxyglutamate proteins (GLA) on osteocalcin (Oc), which is involved in calcium deposition in bone and teeth; (b) carboxylation of matrix gamma-carboxyglutamate proteins (MGPs), which is involved in preventing calcium deposition in the vascular wall, heart valves, lungs, and kidneys.[21,23] Oc and mgPs should be maximally carboxylated for optimal activity, as assessed in many studies investigating the effects of VK1 or VK2s supplementation on improving bone density and arterial elasticity or reducing progression of calcium scores in coronary arteries.[21]

Vitamin K1 and Geranylgeraniol Metabolic Pathways

VK1 is partially deposited in tissues as phylloquinone and is partially converted to VK2 (MK-4) by conversion to VK3 and the addition of geranylgeraniol (GG) (see Figure 1) from GG pyrophosphate (GGPP). GGPP is a metabolic intermediate in the mevalonate pathway and may also be supplemented from plant extracts; annatto, flaxseed, sunflower oil, olive oil, tomatoes, and select medicinal herbs.[24,25] Thus, GG is a precursor to endogenously synthesized VK2 (MK-4) from VK3. VK3 is derived from ingested VK1 or any VK2s ingested as such or derived from gut fermentation of VK1.

GG and GGPP are synthesized endogenously in humans, but this may not always be adequate to support the body's needs, especially during aging. GGPP plays a pivotal role in protein synthesis, CoQ10 production, and VK2 (MK-4) conversion from VK3, further emphasizing its biological importance.[25] Medications with inhibitory actions on the mevalonate pathway (such as statins or bisphosphonates) were found to inhibit GG synthesis in various tissues, such as kidney, vascular smooth muscle, and white blood cells.[25] GG deficiency likely impairs VK1 to VK2 (MK-4) conversion, which results in less VK2 (MK-4) tissue deposition. Supplementation with GG may mitigate some of these detrimental effects.[25] The 5 mg serving of GG in these formulas supports the partial conversion of VK1 to VK2 (MK-4) before tissue deposition. This may especially benefit older individuals or those taking statins or bisphosphonates.[25]

Vitamin K2 (MK-4) Metabolic Pathways

Ninety percent of the vitamin K that is stored in the body is represented by VK2 (MK-4), with the rest mostly being VK1. However, each extrahepatic tissue seems to store a preferential ratio of VK1/VK2 (MK-4), such as: 90% VK1 and 10% VK2 (MK-4) in the heart, 25% VK1 and 75% VK2 (MK-4) in the arteries, and 23% VK1 and 77% VK2 (MK-4) in the bone.[21] See Figure 1 for examples of tissue ratios for VK1/VK2 (MK-4).

VK2 (MK-4) has unique genetic and metabolic effects in human physiology, which are believed to be due to its GG component.[25] In addition to its role in carboxylation, VK2 (MK-4) exerts feedback inhibition through molecular mimicry with GGPP, a downstream metabolite on the mevalonate pathway. This may be why VK2 (MK-4) has distinct effects compared with other VK2s or VK1. In vitro studies with VK2 (MK-4) have shown that it can increase osteoblast production of osteocalcin and collagen type 2.

Additionally, VK2 (MK-4) has been shown to reduce osteoblast apoptosis, demonstrating its unique ability to support bone strength.[21] In vitro addition of GG to osteoclasts has been shown to inhibit their formation in pathways similar and independent from those of VK2 (MK-4). This was mediated by suppression of the receptor activator of nuclear factor kappa B (NF-κB) ligand (RANKL) expression, and there was no competitive action among GG and VK2 (MK-4) molecules.[26]

Rationale for 1 mg Serving of VK1 and 1 mg Serving of VK2 (MK-4)

The serving of 1 mg of VK1 in these formulas is substantiated by the results of the following interventions: A serving of 1 mg of VK1 lowered the percentage of uncarboxylated osteocalcin (ucOC) to <5% in three studies reported here.[27-29] A serving of 0.1 mg of VK1 achieved a 1.3% increase in bone density for menopausal women when supplemented along with vitamin D, calcium (Ca), and magnesium (Mg).[29] A dose of 1 mg of VK1 preserved arterial elasticity when supplemented with additional Ca, mg, zinc, and vitamin D.[30] A serving of 0.5 mg of VK1 caused a 6% reduction in arterial calcium score progression in one study[31] and an 80% reduction in dephosphorylated, uncarboxylated matrix Gla protein (dp-ucMGP) in another study (from 485 to 97 pmol/L).[31]

Evolutionary intakes have been estimated at approximately 1 mg of VK1 per day, which further substantiates recommending this serving to meet foundational needs.[32]

The serving of 1 mg of VK2 (MK-4) was set in these formulas based on the following considerations:

- Provides a pre-formed source of VK2 (MK-4) for tissue deposition due to VK2 (MK-4) being the preferred form, representing 90% of total VK stored in the body.
- Provides an additional source of GG and is made available to various tissues that require it to partially convert VK1 to VK2 (MK-4). VK2 (MK-4) is cleaved to VK3 and GG during gut absorption and possibly other tissues.
- Studies have evaluated the effects of supplementing with VK2 (MK-4) in the range of 0.3 mg to 45 mg.[21] Doses in the range of 0.3 mg to 1.5 mg showed the following benefits:
    - » Post-menopausal women who supplemented with 0.5 mg of VK2 (MK-4) for 9 weeks observed a reduction of the percentage of ucOC to 8.7%.33 Another study found that 0.3 mg and 0.9 mg of VK2 (MK-4) administered to young males reduced the percentage of ucOC to 21% and 11.5%, respectively.[34] With 0.9 mg of VK2 (MK-4) used in the latter study, plasma ucOC was reduced to 2.9 ng/mL. This UcOC level falls below the threshold of 4.5 ng/mL, which was established in another study to correlate with significantly reduced bone fracture risk.[35]
    - » Menopausal women who supplemented with 1.5 mg of VK2 (MK-4) for 1 year observed no decline in forearm bone mineral density (BMD) compared to the placebo group who experienced −2.4% decline in BMD. Final percentage of ucOC for the treatment group was 14% while plasma VK2 (MK-4) increased from 0.1 ng/mL to 0.29 ng/mL.[36]

VK2 (as MK-4) is the preferred clinical source of VK2 in dietary supplementation due to its unique structure, metabolic pathways, predominance in the body, and effects on bone and arterial health. However, since VK2 (MK-4) cannot convert to VK1, it makes sense for it to be supplemented along with a foundational serving of 1 mg of VK1 due to its own unique tissue deposition patterns and its study results on lowering the percentage of ucOC and uc-dpMGP while supporting bone and arterial health.

Vitamin K Intakes and Markers of Whole-Body Vitamin K Status

The average intake of VK1 has been estimated in the U.S. at 92.2 mcg per day (30 mcg to 222 mcg per day),[37] and in Europe at 211.7 mcg per day (9.1 to 991 mcg per day).[38] Average VK2 intakes have been estimated in a modern European population at 29.1 mcg per day (0.9 mcg to 128 mcg per day).[38] No survey for VK2 intake is available for the U.S. population. This implies that a significant proportion of the general population in the U.S. does not meet clotting needs for vitamin K, and moreover, does not meet the whole body needs for VK1 and VK2. Study subjects who did not supplement with vitamin K were found to have elevated baseline values of the percentage of ucOc (range, 42% to 65.5%) in American, European and Canadian studies.[21] Similarly, baseline values of dp-ucMGP were found to be elevated (range, 319 pmol/L to 789 pmol/L).[21] The ucOc and dp-ucMGP are considered validated laboratory markers of whole body vitamin K status as they reflect vitamin K sufficiency for extra-hepatic tissues. Plasma VK1 and/or VK2 are not relevant markers due to the many variables involved, such as triglyceride and cholesterol levels and the timing and duration of vitamin K ingestion.[21]

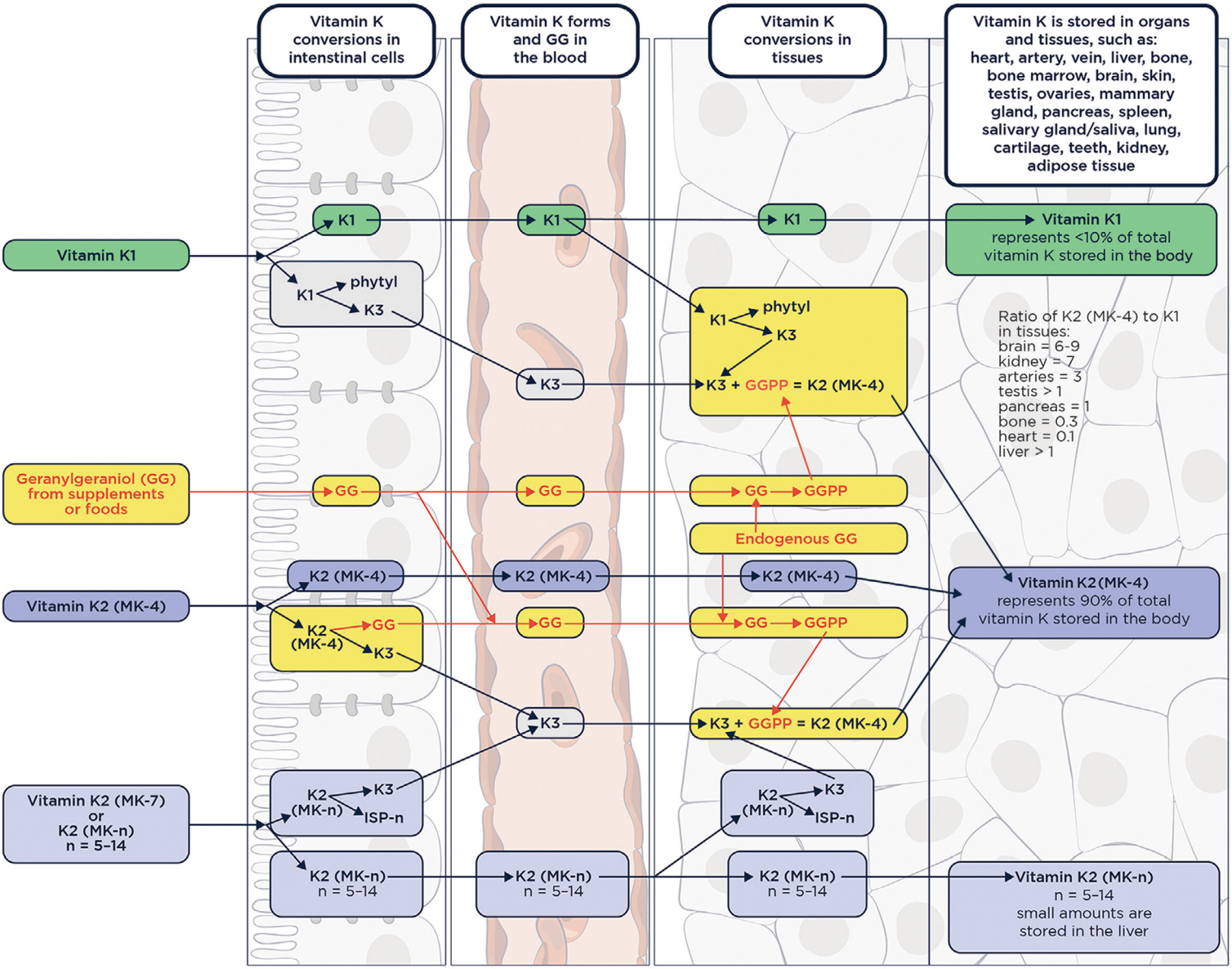
The amounts of VK1, VK2, and GG that are contained in Vitamin D Synergy™ and Vitamin D Supreme™ are intended to meet foundational needs for vitamin K in the liver and extra-hepatic tissues, especially for young and healthy adults.

For intensive interventions in older individuals, those with osteoporosis, arterial stiffness, high arterial calcium scores, and for those using statins or bisphosphonates, additional supplementation with vitamins K1 and K2 (MK-4), along with GG may be warranted, as offered by the Designs for Health Tri-K™ product formula.

Recommended Use: Take 1 capsule per day with a meal or as directed by your health-care practitioner.

Warning: Consult your health-care practitioner before using this product if you are taking Coumadin, warfarin, or other anticoagulant medications.

Figure 1. Vitamin K forms and the role of geranylgeraniol in their conversions and tissue storage.[21]



GG = geranylgeraniol; GGPP = geranylgeraniol pyrophosphate (activated geranylgeraniol); ISP-n = isoprenoid ligand of menaquinone-n; K1 = vitamin K1; K2(MK-n) = vitamin K2 forms with various isoprenoid ligands; K2 (MK-4) = vitamin K2 (MK-4) or menaquinone-4; K3 = vitamin K3; MK-n = menaquinone-n

For a list of references cited in this document, please visit:

https://www.designsforhealth.com/api/library-assets/literature-reference---vitamin-d-tech-sheet-references

Dosing recommendations are given for typical use based on an average 150 pound healthy adult. Healthcare practitioners are encouraged to use clinical judgement with case-specific dosing based on intended goals, subject body weight, medical history, and concomitant medication and supplement usage.

Vitamin D Supreme and Vitamin D Synergy™

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References

1. Sassi F, Tamone C, D'Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. *Nutrients*. 2018;10(11):1656. doi:10.3390/nu10111656.

2. Tuoresmäki P, Väisänen S, Neme A, Heikkinen S, Carlberg C. Patterns of genome-wide VDR locations. *PLoS One*. 2014;9(4):e96105. doi:10.1371/journal.pone.0096105.

3. Zhang Y, Wu S, Sun J. Vitamin D, vitamin D receptor and tissue barriers. *Tissue Barriers*. 2013;1(1):e23118. doi:10.4161/tisb.23118.

4. Carlberg C. Nutrigenomics of vitamin D. *Nutrients*. 2019;11(3):676. doi:10.3390/nu11030676.

5. Vanherwegen AS, Gysemans C, Mathieu C. Vitamin D endocrinology on the cross-road between immunity and metabolism. *Mol Cell Endocrinol*. 2017;453:52-67. doi:10.1016/j.mce.2017.04.018.

6. Vanherwegen AS, Eelen G, Ferreira GB, et al. Vitamin D controls the capacity of human dendritic cells to induce functional regulatory T cells by regulation of glucose metabolism. *J Steroid Biochem Mol Biol*. 2019;187:134-145. doi:10.1016/j.jsbmb.2018.11.011.

7. Giustina A, Adler RA, Binkley N, et al. Consensus statement from 2nd International Conference on Controversies in Vitamin D. *Rev Endocr Metab Disord*. 2020;21(1):89-116. doi:10.1007/s11154-019-09532-w.

8. Gubatan J, Chou ND, Nielsen OH, Moss AC. Systematic review with meta-analysis: association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2019;50(11-12):1146-1158. doi:10.1111/apt.15506.

9. Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis [published correction appears in *BMJ*. 2020;366:370]. *BMJ*. 2019;366:l4673. doi:10.1136/bmj.l4673.

10. Kesby JP, Eyles DW, Burne TH, McGrath JJ. The effects of vitamin D on brain development and adult brain function. *Mol Cell Endocrinol*. 2011;347(1-2):121-7. doi:10.1016/j.mce.2011.05.014.

11. Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front Neuroendocrinol*. 2013;34(1):47-64. doi:10.1016/j.yfrne.2012.07.001.

12. Groves NJ, McGrath JJ, Burne TH. Vitamin D as a neurosteroid affecting the developing and adult brain. *Annu Rev Nutr*. 2014;34:117-41. doi:10.1146/annurev-nutr-071813-105557.

13. Annweiler C, Dursun E, Féron F, et al. 'Vitamin D and cognition in older adults': updated international recommendations. *J Intern Med*. 2015;277(1):45-57. doi:10.1111/joim.12279.

14. Schlögl M, Holick MF. Vitamin D and neurocognitive function. *Clin Interv Aging*. 2014;9:559-568. doi:10.2147/CIA.S51785.

15. Liu X, Baylin A, Levy PD. Vitamin D deficiency and insufficiency among US adults: prevalence, predictors and clinical implications. *Br J Nutr*. 2018;119(8):928-936. doi:10.1017/S0007114518000491.

16. Yamamoto E, Jorgensen TN. Immunological effects of vitamin D and their relations to autoimmunity. *J Autoimmun*. 2019;100:7-16. doi:10.1016/j.jaut.2019.03.002.

17. Trehan N, Afonso L, Levine DL, Levy PD. Vitamin D deficiency, supplementation, and cardiovascular health. *Crit Pathw Cardiol*. 2017;16(3):109-118. doi:10.1097/hpc.0000000000000122.

18. Logan VF, Gray AR, Peddie MC, Harper MJ, Houghton LA. Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25- hydroxyvitamin D status over the winter months. *Br J Nutr*. 2013;109(6):1082-8. doi:10.1017/S0007114512002851.

19. Martineau AR, Thummel KE, Wang Z, et al. Differential effects on oral boluses of vitamin D vs vitamin D3 on vitamin D metabolism: a randomized controlled trial. *J Clin Endocrinol Metab*. 2019;104(12):5831-5839. doi:10.1210/jc.2019-00207.

20.van Ballegooijen AJ, Pilz S, Tomaschitz A, Grübler MR, Verheyen N. The synergistic interplay between vitamins D and K for bone and cardiovascular health: a narrative review. *Int J Endocrinol*. 2017;2017:7454376. doi:10.1155/2017/7454376.

21. Pizzorno JE, Murray MT. *Textbook of Natural Medicine,* 5th ed. St. Louis, MO: Elsevier; 2020. https://www.elsevier.com/books/textbook-of-natural-medicine/pizzorno/978-0-323-43044-9.

22. Institute of Medicine, Food and Nutrition Board. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. National Academy Press. Washington, DC, 2001. https://www.ncbi.nlm.nih.gov/books/NBK222310/?term=dietary%20reference%20intakes%202001.

23. Janssen R, Visser MPJ, Dofferhoff ASM, Vermeer C, Janssens W, Walk J. Vitamin K metabolism as the potential missing link between lung damage and thromboembolism in Coronavirus disease 2019 [published online ahead of print, October 7, 2020]. *Br J Nutr*. 2020;Oct 7:1-8. doi:10.1017/S0007114520003979.

24. Shidoji Y, Ogawa H. Natural occurrence of cancer-preventive geranylgeranoic acid in medicinal herbs. *J Lipid Res*. 2004;45(6):1092-103. doi:10.1194/jlr.M300502-JLR200.

25. Paul C, Brady D, Tan B. Geranylgeraniol (GG) boosts endogenous synthesis of coenzyme Q10 (CoQ10) and cell essential metabolites, overcoming CoQ10 supplementation limitations. *Townsend Letter*. July 5, 2022. https://www.townsendletter.com/article/453-geranylgeraniol-coq10-cell-essential-metabolites/.

26. Hiruma Y, Nakahama K, Fujita H, Morita I. Vitamin K2 and geranylgeraniol, its side chain component, inhibited osteoclast formation in a different manner. *Biochem Biophys Res Commun*. 2004;314(1):24-30. doi:10.1016/j.bbrc.2003.12.051.

27. Braam LA, Knapen MH, Geusens P, et al. Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcif Tissue Int*. 2003;73(1):21-26. doi:10.1007/s00223-002-2084-4.

28. Binkley NC, Krueger DC, Kawahara TN, et al. A high phylloquinone intake is required to achieve maximal osteocalcin gamma-carboxylation. *Am J Clin Nutr*. 2002;76(5):1055-1060.

29. Kanellakis S, Moschonis G, Tenta R, et al. Changes in parameters of bone metabolism in postmenopausal women following a 12-month intervention period using dairy products enriched with calcium, vitamin D, and phylloquinone (vitamin K1) or menaquinone-7 (vitamin K2): the Postmenopausal Health Study II. *Calcif Tissue Int*. 2012;90(4):251-262. doi.org/10.1007/s00223-012-9571-z.

30. Braam LA, Hoeks AP, Brouns F, Hamulyák K, Gerichhausen MJ, Vermeer C. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. *Thromb Haemost*. 2004;91(2):373-80. doi:10.1160/TH03-07-0423.

31. Shea MK, O'Donnell CJ, Hoffmann U, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. *Am J Clin Nutr*. 2009;89(6):1799-1807. doi:10.3945/ajcn.2008.27338.

32. Cordain L. The nutritional characteristics of a contemporary diet based upon paleolithic food groups. *J Am Nutraceuitcal Assoc*. 2002;5(3):14-24. https://thepaleodiet.com/wp-content/uploads/2015/08/The-Nutritional-Characteristics-of-aContemporary-Diet-Based-Upon-Paleolithic-Food-Groups-The-Paleo-Diet.pdf.

33. K Giri T, Newton D, Chaudhary O, et al. Maximal dose-response of vitamin-K2 (menaquinone-4) on undercarboxylated osteocalcin in women with osteoporosis. *Int J Vitam Nutr Res*. 2020;90(1-2):42-48. doi:10.1024/0300-9831/a000554.

34. Nakamura E, Aoki M, Watanabe F, Kamimura A. Low-dose menaquinone-4 improves γ-carboxylation of osteocalcin in young males: a non-placebo-controlled dose-response study. *Nutr J*. 2014;13:85. doi:10.1186/1475-2891-13-85.

35. Shiraki M, Aoki C, Yamazaki N, Ito Y, Tsugawa N, Suhara Y, Okano T. Clinical assessment of undercarboxylated osteocalcin measurement in serum using an electrochemiluminescence immunoassay: establishment of cut-off values to determine vitamin K insufficiency in bone and to predict fracture leading to clinical use of vitamin K2. *Jpn J Med Pharm Sci*. 2007;57:537-546.

36. Koitaya N, Sekiguchi M, Tousen Y, et al. Low-dose vitamin K2 (MK-4) supplementation for 12 months improves bone metabolism and prevents forearm bone loss in postmenopausal Japanese women. *J Bone Miner Metab*. 2014;32(2):142-150. doi:10.1007/s00774-013-0472-7.

37. National Health and Nutrition Examination Survey 2001-2002. National Health and Nutrition Examination Survey. National Center for Health Statistics. Centers for Disease Control and Prevention. https://wwwn.cdc.gov/nchs/nhanes/Search/DataPage.aspx?Component=Examination&CycleBeginYear=2001.

38. Gast GC, de Roos NM, Sluijs I, et al. A high menaquinone intake reduces the incidence of coronary heart disease. *Nutr Metab Cardiovasc Dis*. 2009;19(7):504-510. doi:10.1016/j.numecd.2008.10.004.