

Vitamin D Supreme and Vitamin D Synergy™

5,000 IU D3 or 2,000 IU D3 with Vitamin K1, K2

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This information is provided as a medical and scientific educational resource for the use of physicians and other licensed health-care practitioners ("Practitioners"). This information is intended for Practitioners to use as a basis for determining whether to recommend these products to their patients. All recommendations regarding protocols, dosing, prescribing, and/or usage instructions should be tailored to the individual needs of the patient considering their medical history and concomitant therapies. This information is not intended for use by consumers.

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 feature two different serving size options of vitamin D, offering support for various clinical needs based on individual factors, such as sun exposure, absorption rates, body sizes, and concurrent supplementation regimens.* Vitamins D and K work synergistically; thus, increasing vitamin D increases the need for vitamin K. Vitamin D increases calcium absorption, while vitamins K1 and K2 support the deposition of calcium into the bone instead of soft tissue, such as the arterial walls and kidneys.* Both of these formulas are designed to help maintain optimal vitamin D status in the body.*

Formula Highlights

- Vitamin D Supreme contains 5,000 IU (125 mcg) of vitamin D3 (cholecalciferol) per serving
- Vitamin D Synergy™ contains 2,000 IU (50 mcg) of vitamin D3 (cholecalciferol) per serving
- Both formulas contain 1,000 mcg of vitamin K1, 1,000 mcg of vitamin K2, and 5 mg GG (as GG-Gold®) per serving to support bone and arterial health*
- Gluten-free, dairy-free, soy-free; non-GMO

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.¹

Inadequate vitamin D status has been shown to decrease bone density and increase fracture risk.² Vitamin D exerts its biological effects through vitamin D receptors (VDRs), which are found throughout the body and help regulate the expression of thousands of genes.^{3,4} Vitamin D is essential for the immune system, modulating both innate and adaptive immune responses through VDR signaling.^{5,6} VDR is the critical transcription factor in differentiating lymphocytes within the bone marrow into monocytes and granulocytes.⁷ Vitamin D can regulate Th1 and Th2 lymphocyte balance and downregulate the expression of inflammatory cytokines, making it an important player in immune health.^{8,9}

The biologically active form of vitamin D, 1,25(OH)D3 (1,25-dihydroxyvitamin D3), significantly modifies the intracellular metabolism of dendritic cells and macrophages, metabolically reprogramming the supportive role in inflammatory responses and autoimmunity by altering the phenotypic expression of cells.¹⁰ In fact, priming 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.¹¹ 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.¹²

Benefits*

- Promotes optimal vitamin D status^{26,27}
- Supports optimal bone health^{32,33,40,41,43-45,48-50}
- Helps maintain healthy immune system balance^{5,6,8,9,29,31}
- Supports cardiovascular health^{1,13,32,33,47}
- Promotes arterial strength and elasticity^{32,33,46,47}
- Helps optimize calcium absorption and utilization^{32,33}
- Helps support normal inflammatory responses^{8-11,42}
- Promotes healthy cognitive health¹⁴⁻¹⁸

Vitamin D Supreme

Supplement Facts

Serving Size 1 capsule		
Amount Per Serving		% Daily Value
Vitamin D (as Cholecalciferol)	125 mcg (5,000 IU)	625%
Vitamin K	2,000 mcg	1,667%
(as Vitamin K1-Phytonadione 1,000 mcg; Vitamin K2-Menaquinone-4 1,000 mcg)		
Trans-Geranylgeraniol (GG-Gold®)	5 mg	*
[from annatto (<i>Bixa orellana</i>)(seed)]		

*Daily Value not established.

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

Vitamin D Synergy™

Supplement Facts

Serving Size 1 capsule		
Amount Per Serving		% Daily Value
Vitamin D (as Cholecalciferol)	50 mcg (2,000 IU)	250%
Vitamin K	2,000 mcg	1,667%
(as Vitamin K1-Phytonadione 1,000 mcg; Vitamin K2-Menaquinone-4 1,000 mcg)		
Trans-Geranylgeraniol (GG-Gold®)	5 mg	*
[from annatto (<i>Bixa orellana</i>)(seed)]		

*Daily Value not established.

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

In addition to its well-known role in bone health and the immune system, vitamin D may also support cardiovascular health.* A systematic review and meta-analysis of clinical and observational trials reported that patients with hypovitaminosis D (defined as 25-hydroxyvitamin D3 [25(OH)D3] levels below 20 ng/mL) exhibited a higher incidence of major adverse cardiovascular events compared to controls (OR: 1.92, $p = 0.003$).¹³ Furthermore, vitamin D plays a role in the brain, influencing brain development in early life and brain function in adults. In fact, vitamin D deficiency is associated with depressed moods and impaired cognition.¹⁴⁻¹⁸

Epidemiological findings indicate that males and females aged two and over consume on average 5 mcg (200 IU) and 3.9 mcg (156 IU), respectively, of vitamin D per day.¹⁹ These findings reveal a substantial gap between average vitamin D intakes and the recommended dietary allowance (RDA) for men and women, which is 15 mcg (600 IU) daily, especially in the setting of inadequate exposure to sunlight.¹⁹ Additionally, some individuals often exhibit clinically low blood levels of 25(OH)D3 despite consuming the RDA, which sets these individuals up for requiring more than the RDA for vitamin D to replete levels.^{20,21}

Inadequate vitamin D status is associated with cardiovascular disease, a compromised immune system, and disrupted immune function from debilitating gastrointestinal diseases.^{12,22-25} Evidence indicates that vitamin D3 (which is produced in human physiology) is far more effective in raising and maintaining serum 25(OH)D3 concentrations, and vitamin D2 (which is produced only in plant physiology) should not be considered an equivalent.^{26,27} These factors highlight the potential clinical utility of vitamin D across various clinical presentations.

While recent guidelines²⁸ recommend against routine vitamin D testing in healthy populations, emerging evidence supports personalized assessment in certain groups, especially during repletion to mitigate under- or over-supplementation.^{1,29} Testing vitamin D status remains critical for monitoring clinical interventions in at-risk individuals, as standardized recommendations may overlook personalized needs based on an individual's baseline status, health, genetics, and goals.^{1,29-31}

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

Vitamin K, like vitamin D, is a fat-soluble vitamin that supports bone and cardiovascular health, along with many other aspects of physiology.^{32,33} For example, vitamin D increases calcium absorption, whereas vitamin K improves calcium deposition in the bones while inhibiting its accumulation in the arterial walls.³² 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.^{32,33}

Vitamin K exists in two main forms: vitamin K1 (VK1), as phyloquinone, which is found in leafy green vegetables, and vitamin K2 (VK2), also known as menaquinones, which are found in certain animal products, fermented foods, and are also produced by gut microbiota.^{34,35} VK2 occurs naturally with various lengths ($n = 1$ to 14) of their side chains, abbreviated as VK2 (MK-n). VK2 (MK-4) is the predominant form in extrahepatic tissues, while VK1 is primarily stored in the liver.³⁶ Animal studies have shown that other forms of VK2 convert into MK-4 in all tissues except the liver, indicating its functional importance in these tissues.³³

For adults 19 years and older, the adequate intake (AI) for VK1 is 120 mcg for men and 90 mcg for women, but these amounts are only sufficient to activate blood-clotting proteins fully.³⁷ No AI has been set for VK2, and no upper level of toxicity has been established by the Institute of Medicine for VK1 or VK2.³⁷ However, extensive evidence has revealed various extra-hepatic roles for VK1 and VK2, which may require much higher intakes of these vitamins.³³ 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.³⁶ 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.³³ Oc and MGPs should be maximally carboxylated for optimal activity, as assessed in many studies investigating the effects of VK1 or VK2 supplementation on improving bone strength and arterial elasticity or reducing the progression of calcium stores in coronary arteries.³³

Vitamin K1 and Geranylgeraniol Metabolic Pathways

VK1 is partially stored in tissues and partially converted to MK-4 with VK3 as an intermediate, which requires the incorporation of geranylgeraniol (GG) from GG pyrophosphate (GGPP; see Figure 1). GGPP is a metabolic intermediate in the mevalonate pathway and may also be supplemented from plant extracts, such as annatto, flaxseed, sunflower oil, olive oil, tomatoes, and select medicinal herbs.^{38,39} While humans endogenously produce GG and GGPP, body levels may decline with age or be suppressed by certain medications such as statins and bisphosphonates that inhibit the mevalonate pathway.³⁹ This inhibition can potentially affect VK1-to-MK-4 conversion and limit tissue deposition of MK-4.

Vitamin K2 Metabolic Pathways

Vitamin K2, as MK-4, is the primary form stored in extrahepatic tissues, accounting for approximately 90% of total vitamin K forms stored, with the rest mainly being VK1. Each extrahepatic tissue preferentially stores VK1 and MK-4 in a ratio that supports its primary functions. For example, 90%/10% is in the heart, 25%/75% is in the arteries, and 23%/77% is in the bone (see Figure 1 for examples).³³

MK-4 has unique genetic and metabolic effects in human physiology, which are believed to be due to its GG component.³⁹ In addition to its role in carboxylation, MK-4 exerts feedback inhibition through molecular mimicry with GGPP, a downstream metabolite in the mevalonate pathway. This may be why MK-4 has distinct effects compared with other VK2s or VK1. In vitro studies with MK-4 have shown that it can increase osteoblast production of Oc and collagen, which may help support bone strength.⁴⁰ In vitro addition of GG to Oc has been shown to inhibit osteoclast formation in pathways similar to, and independent from, those of MK-4. This was mediated by suppression of the receptor activator of nuclear factor kappa B (NF- κ B) ligand (RANKL) expression, and there was no competitive action among GG and MK-4 molecules.^{41,42}

Rationale for 1 mg Serving of VK1 and 1 mg Serving of VK2

Studies have been conducted in several populations to investigate the effects of VK1 outcomes on bone and cardiovascular health, along with their effects on vitamin K status, as reflected by the percentage of undercarboxylated osteocalcin (ucOC).⁴³⁻⁴⁷ Compared to placebo, healthy postmenopausal women who were given a supplement that contained one mg of VK1, along with calcium (Ca), magnesium (Mg), and zinc (Zn) daily for three years, exhibited a 30% decrease in the rate of bone mineral density (BMD) in the femoral neck.⁴³ Additional findings reported that ucOC was significantly reduced to 0.5%, a level considered a detection limit, in the group of healthy post-menopausal women who received VK1.⁴³ These results suggest a repleted vitamin K status in this population, which may support bone quality, strength, and health. Compared to baseline, post-menopausal women given 0.1 mg of VK1 exhibited a 1.3% increase in total body BMD scores.⁴⁵ It is important to note that nutrients work synergistically to support bone health, and the addition of vitamins and minerals, including vitamin D, Ca, and Mg, is often investigated together, as was the case in the included studies.^{43,45} Findings indicate that a daily intake of approximately 1 mg is needed to maximize Oc carboxylation, which is essential for optimal bone health.⁴⁴

Apart from bone health, VK1 has been studied for its role in supporting cardiovascular health. Compared to post-menopausal women who were given a placebo or a combination of Ca, Mg, Zn, and vitamin D, women who were given a supplement that contained 1 mg of VK1 and varying amounts of Ca, Mg, Zn, and vitamin D experienced arterial elasticity preservation.⁴⁶ Additionally, compared to a group that received a multivitamin alone, men and women who received 0.5 mg of VK1 experienced a 6% reduction in arterial calcium score progression.⁴⁷

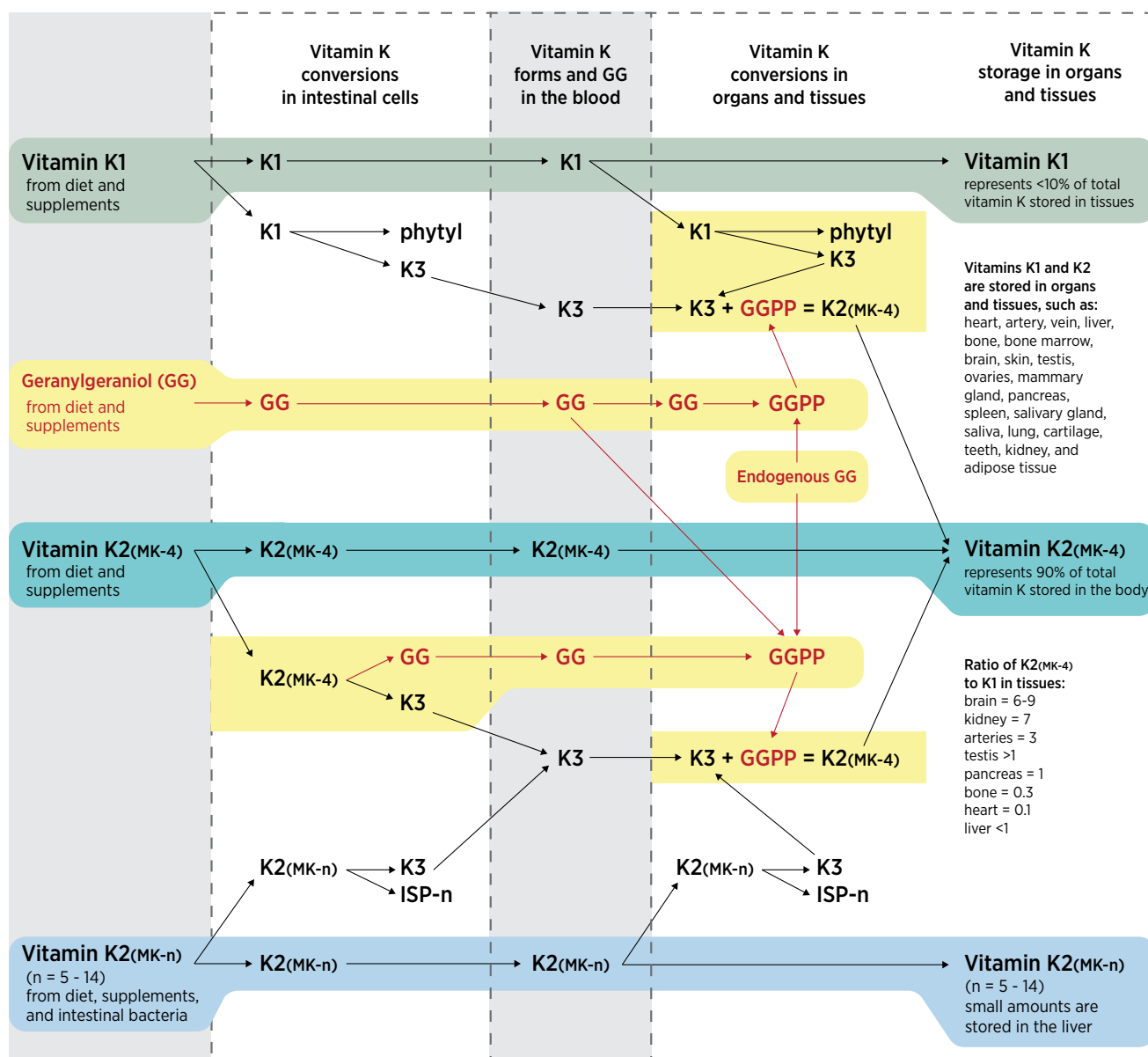
Studies have evaluated the effects of MK-4 on markers associated with bone health.³³ In one study, postmenopausal women given 0.5 mg of MK-4 daily for nine weeks experienced a decrease in ucOC to 8.7% from 16.8%, suggesting improved vitamin K status.⁴⁸ In a separate study, young males who received 0.3 mg and 0.9 mg of MK-4 exhibited reductions in ucOC to 21% and 11.5%, respectively.⁴⁹ Additionally, post-menopausal women who were given 1.5 mg of MK-4 daily for one year maintained forearm BMD compared to the placebo group, who experienced a 2.4% decline over the same period.⁵⁰ The group given MK-4 also demonstrated increased plasma MK-4 concentrations, from 0.1 ng/mL to 0.29 ng/mL, and a decline in ucOC percentage from 43% to 14%, indicating improved bone metabolism.⁵⁰

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

The average intake of VK1 has been reported in the U.S. for men and women aged two and older at 113.8 mcg per day¹⁹ and in Europe at 211.7 mcg per day (9.1 to 991 mcg per day).⁵¹ VK1 intakes in the younger U.S. population (aged between 2 and 19 years) report intakes of 73 mcg per day for men and 71.4 mcg per day for women, intakes that do not meet clotting needs for vitamin K, and moreover, do not meet the whole body recommendations for VK1.³⁷ In European populations, the average VK2 intakes have been estimated at 29.1 mcg per day (0.9 mcg to 128 mcg per day).⁵¹ No survey for VK2 intake is available for the U.S. population. To assess vitamin K status in the body, ucOC and dephosphorylated-uncarboxylated Matrix Gla Protein (dp-ucMGP) are considered validated laboratory markers of whole-body vitamin K status as they reflect vitamin K sufficiency for extra-hepatic tissues.^{52,53} Plasma VK1 and VK2 are not validated markers due to the many variables involved, such as triglyceride and cholesterol levels, and the timing and duration of vitamin K ingestion.³³

The amounts of VK1, VK2, and GG featured in Vitamin D Synergy™ and Vitamin D Supreme are intended to meet the foundational needs for vitamin K in the liver and extra-hepatic tissues, especially for young and healthy adults.* Individuals seeking additional support for vitamin K status — particularly those who are older or who have dietary patterns or lifestyles that may influence bone and cardiovascular health — may benefit from additional VK1 and MK-4, as well as GG.* These ingredients are featured in Designs for Health's Tri-K™, BRF 45™, Osteoben®, OsteoForce™ Supreme, and OsteoForce™ formulas to support nutritional needs associated with healthy aging and nutrient repletion.*

Figure 1: Role of geranylgeraniol in vitamin K conversions and tissue storage.³³



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; MK-n = menaquinone-n

Note: Plasma levels of vitamin K1 or K2 are not validated indicators of vitamin K status, risk of osteoporosis or arterial calcification.

Scientifically validated functional markers of vitamin K status are:³³

1. Undercarboxylated osteocalcin (ucOC) levels and % ucOC of total osteocalcin
2. Dephosphorylated-uncarboxylated Matrix Gla Protein (dp-ucMGP)

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

Warning: Due to the inclusion of vitamin K in these products, use caution when recommending Vitamin D Synergy™ and Vitamin D Supreme for patients who are taking Coumadin, warfarin, or other anticoagulant medications.

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

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

Dosing recommendations are given for typical use based on an average 150-pound healthy adult. Health-care 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.

GG-Gold® is a registered U.S. trademark of American River Nutrition, LLC.

***These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

To contact Designs for Health, please call us at (860) 623-6314, or visit us on the web at www.designsforhealth.com.