Promoting Optimal Health with Food-Grown Vitamins D3, K1 and K2, and Vitamin A from Mixed Carotenoids

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Discussion

There is high consensus today that vitamin D deficiency is pandemic.[1,2] Since it is found only minimally in foods, we derive most of our vitamin D from exposure to sunlight. Food sources include sardines, egg yolks, and mushrooms. Synthesized in the skin from ultraviolet B in sunlight, vitamin D is further metabolized in the liver, kidneys, and other organs and tissues.

Many factors influence our ability to synthesize vitamin D from sun exposure including season, time of day, latitude, cloud cover, smog, sunscreen use, and what percentage of our body is exposed to the sun.[1,2,4] In today's world, where sun exposure is often limited for numerous reasons, the need for vitamin D supplementation has become highlighted, especially with increased knowledge regarding the many roles of vitamin D in promoting health.

Vitamins D, K and A (from mixed carotenoids) are all recognized as pleiotropic compounds, offering a diverse and wide range of biological effects which support allostasis. There is considerable overlap in the influence they exert on the cellular level to modulate and calm inflammatory response and oxidative pathways. Combined together, they exert a powerful synergistic influence.

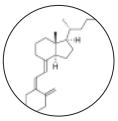
Well-known for their anti-inflammatory influence, both the carotenoid complex and vitamin D play key roles in cellular health and are found to exert protective benefits against multiple chronic and degenerative conditions. Vitamins D and K are both found to modulate pro-inflammatory cytokines. Vitamins K2 and D are found synergistic to modulate bone mineralization and studies find that increased K2 intake significantly increases vitamin D levels. D3 combined with high doses of K2 (about 2mg/kg/day for 12 weeks) shows an additive effect, influencing significant increase in osteocalcin and in lumbar bone mineral density compared to vitamin D3 alone.[5-7]

Nutritional Benefits of Food-Grown Nutrients

Whole foods contain a complex array of vitamins, minerals, phytochemicals, enzymes and other beneficial compounds. These essential nutrients and cofactors influence cellular health, cell-signaling, enzyme system response, and other activities that support physiological homeostasis.

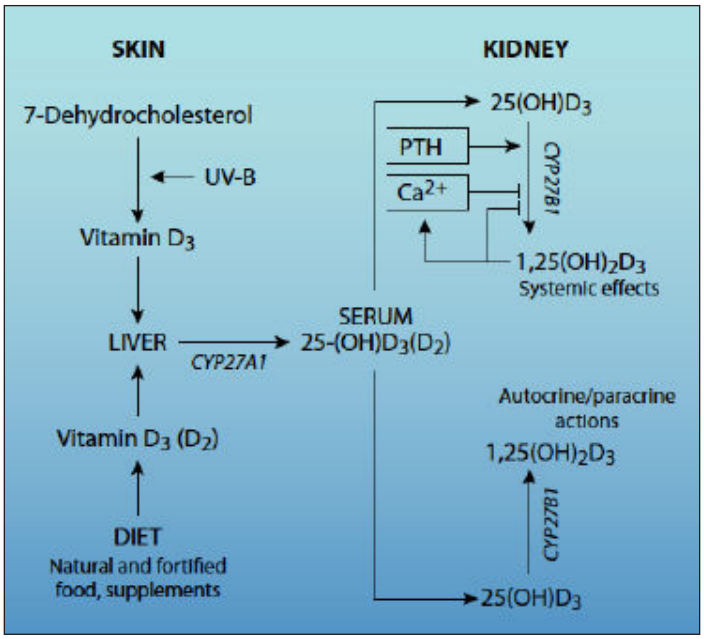
Food-grown nutrients are delivered in the context of a whole food matrix that facilitates their bioavailabilty. This matrix includes naturally-occurring peptide carriers and cofactors that act as chaperones, delivering nutrients to the cells and tissues of the body. Human physiology is designed to obtain nutrients from plants and natural foods. Food-grown nutrients are designed to emulate whole foods while delivering a higher concentration of specific vitamins or minerals.

Vitamin D3, Vitamin K1 and K2, and Vitamin A



Vitamin D3

Research indicates that D3 is substantially more bioavailable and potent for supplemental use in humans.[8] While Vitamin D is most well-known for its role in calcium homeostasis and skeletal health, burgeoning research over the last 15 years finds it exerts a far wider influence with a diverse, complex role in human health. Vitamin D plays a regulatory role in kidney, heart and immune



The Absorption and Metabolic Conversion of Vitamin D (*see reference #6*)

system function and is found to exert anti-inflammatory, anti-apoptotic, and anti-fibrotic influence. It is found to be essential for physiological homeostasis through its regulation and modulation of hormone secretion, cell proliferation, and cell differentiation. The biologically active form of vitamin D binds to cell receptors of the immune, nervous, and cardiovascular systems where it plays a key role in cell cycle regulation. It is found to be protective of the kidneys, partially through its anti-inflammatory influence. It is also found to effect production of renin and insulin.[1,2,9,10]

As an immune system modulator, Vitamin D strongly influences immune function and is well-known for its ability to enhance immune response when at optimal serum and tissue levels.[1,2,8,9,10,12] Vitamin D is found to lower the inflammatory markers CRP (C-reactive protein) and IL-6. Decreased vitamin D levels found in otherwise healthy people is correlated with increased inflammation while supplementing vitamin D is found to decrease inflammatory processes.[2,11,13,14]

Vitamin D Receptors Widespread

Vitamin D Receptors (VDRs) are found in the cells of most tissues where vitamin D is found to exert multiple influences. VDRs are found in the tissues of many organs including the pancreas, small intestine, colon, nervous system, and muscles. They are widely found in multiple areas of the brain and possibly even in some muscle tissues.[10]

Skeletal Health

Widely recognized for its importance to skeletal heath, many studies demonstrate that vitamin D plays a major role in risk reduction for fractures and falls in the elderly.[8,15-17] It is found to benefit neuromuscular tone, strength, and control. VDRs have been identified in striated muscle and a correlation found between decreased muscle tone and lower expression of VDRs. Correlation between muscle strength and vitamin D deficiency is reported as high as 34%.[3]

Vitamin D is found to be of more benefit and more essential than calcium for skeletal health including osteoarthritis. Increased calcium can suppress 1,25-dihyroxyvitamin D3 (the active form of D), causing a deficiency of vitamin D and concurrent risk for osteoporosis and bone fractures.[5,18-23]

The Role of Vitamin D in Overall Health

Research finds that Vitamin D deficiency is linked to autoimmune diseases, infectious diseases, type 2 diabetes, cardiovascular disease, and various cancers while supplementation of vitamin D to sustain optimal serum levels is found to be highly preventive.[1,6,8,9,12]

There is a large, expanding body of research showing that vitamin D deficiency is linked to inflammatory processes and influences many diseases including heart disease, hypertension, obesity, osteoporosis, cancer, depression, and chronic tension-type headaches. It is also implicated in muscle weakness, type-2 adult onset diabetes[24,25], and at higher serum levels is found to be highly protective against cancer.[26-29] Optimum serum levels of vitamin D are found to exert protective benefits and to decrease risk of cardiovascular disease.[11,30]

Alleviates Depression and Enhances Brain Health

Researchers find a distinct correlation between vitamin D intake and depression.[9,31] In the Netherlands, 1282 people aged 65 to 95 years were studied and significant correlation was found between depression, the severity of depression, and decreased serum 25(OH)D levels.[31] Another study of 12,594 participants also found significant correlation with depression and vitamin D deficiency. They further noted that higher levels of vitamin D correlated with significant

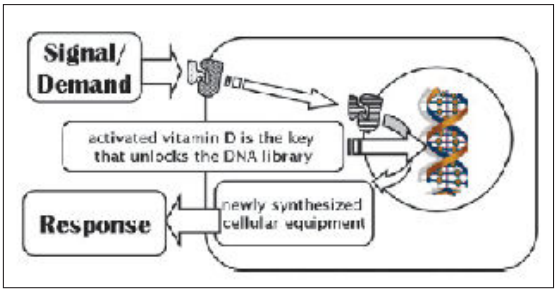
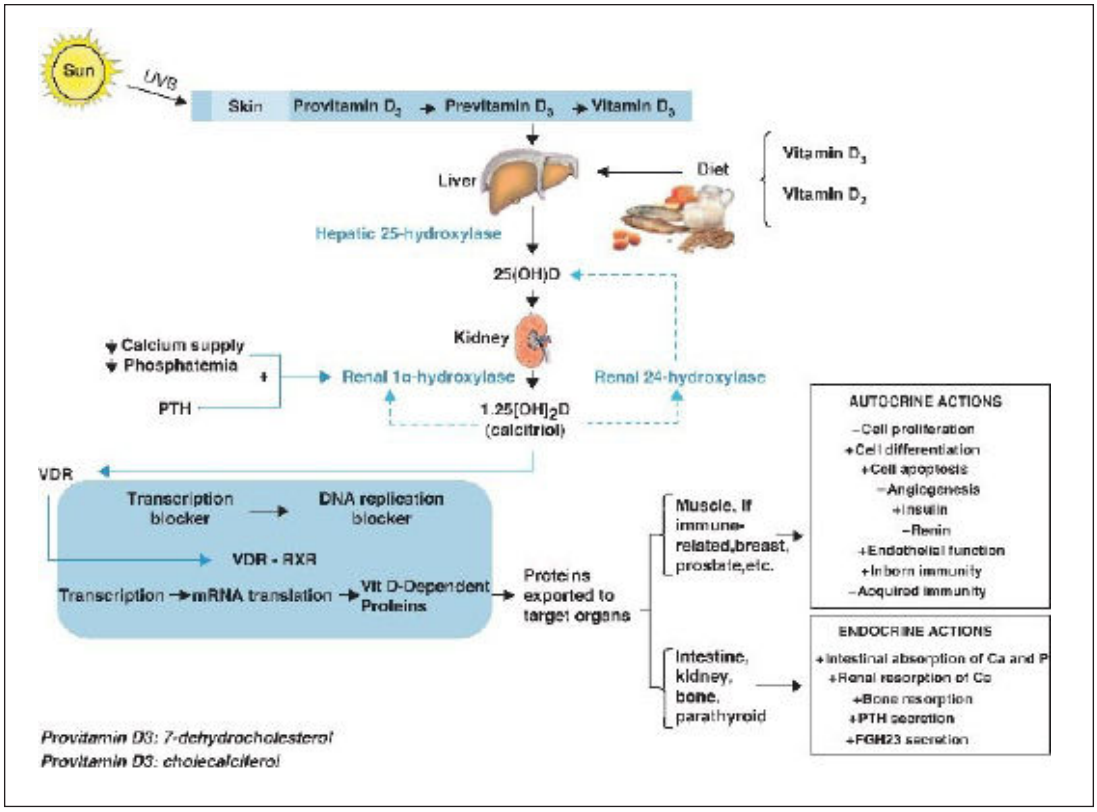


Diagram of the key role calcitrol, synthesized within the cell cornered, plays in cellular responses requiring gene expression. (*see reference #8)*



Mesa-Ramos M, Caeiro-Rey JR, et al. *Review Article: Aspects of interest on vitamin D for the traumatologist and orthopaedic surgeon*. Rev Esp Cir Ortop Traumatol. 2102. 56(2):164-173.

Sunlight exposure
Skin pigmentation
Baseline vitamin D level
Intestinal absorption rates
Type of vitamin D supplement (D3 is 3x more potent than D2)
Age (with age there is a reduced photoconversion of 7-dehydrocholesterol to vitamin D
Genetic variation in vitamin D receptor activity

Variables influencing Vitamin D requirements. (*see reference #17)*

decrease in depression. It is theorized that vitamin D may influence dopamine and norepinephrine. There is a high density of VDRs in the hypothalamus and dopaminergic neurons of the substantia nigra. Researchers have found VDRs in the hippocampus and cerebellum – areas of the brain that are involved with processing information, planning, and with formation of new memories. In addition, vitamin D may influence other factors in the brain including nerve growth factor synthesis and neurotransmitters.[9] Vitamin D is well-known for its anti-inflammatory influence and research reports higher levels of brain inflammation in those with depression.[8]

Modulates Gene Expression and Cellular Response

Calcitrol (1,25(OH)2D) is a substrate for cellular repair and maintenance and exerts endocrine and autocrine functions.[2] Calcitrol, the hormonally active metabolite form of vitamin D, can bind to VDRs to modulate gene transcription.[2,10] Vitamin D is essential for healthy cellular function and influences many cellular processes.[1,2,9] Known to activate over 200 human genes, it acts as a molecular "on-off" switch for multiple cellular responses and plays a key role in gene expression. Vitamin D influences genes that encode proteins involved with modulation of cell cycle activity including apoptosis.[2,5]

Studies show that calcitrol influences gene expression, epigenetic processes and DNA repair.[1,2,9] Studies report that calcitrol acts much like a key that is able to open the DNA genome library, allowing the cells to access blueprints for synthesis of vital proteins. In the autocrine system, calcitrol facilitates signaling systems that connect extracellular signals to genomic responses. Low serum vitamin D is found to impair these processes of cellular response.[5,8]

Healthy Serum Levels of Vitamin D

Some studies indicate that blood levels of 25(OH)D > 80 nmol/L are essential to optimize the multiple-faceted benefits of vitamin D. Most researchers find that the optimal pleiotropic and protective effects of vitamin D occur when serum levels are around 75ng/mL to 80 ng/mL up through 100 ng/mL to 125 ng/mL and are lost when levels fall below 75 ng/mL. This is reported in the literature regarding the influence of vitamin D on cellular signaling, cellular health, depression, anti-inflammatory influence, cardiovascular protection, and other areas of vitamin D's influence.[2,8-10,14,17]

Since serum levels are dependent on a variety of factors, it is advisable to establish a baseline and then recheck for response seasonally. Serum levels are affected by exposure to sunlight, season, aging (which slows assimilation through the skin) and multiple other factors. It is noted that there is seen a decline in the efficiency of vitamin D synthesis with age.[8,17] Historically, it is only fairly recently that people have less exposure to sunlight. In tropical areas, those working outside in the sun on a regular basis are reported to have serum levels of around 120 to 200 nmol/L.[8]

When circulating vitamin D3 levels decrease, there is insufficient substrate for conversion to the active form that plays a significant role in cellular and other functions throughout the body. Suboptimal, lower serum levels of vitamin D are not correlated with disease per se, but rather with increased risk for inflammatory processes and chronic disease to develop. Sufficient vitamin D is also found essential to immune system function and to combat inflammation.[8,14]

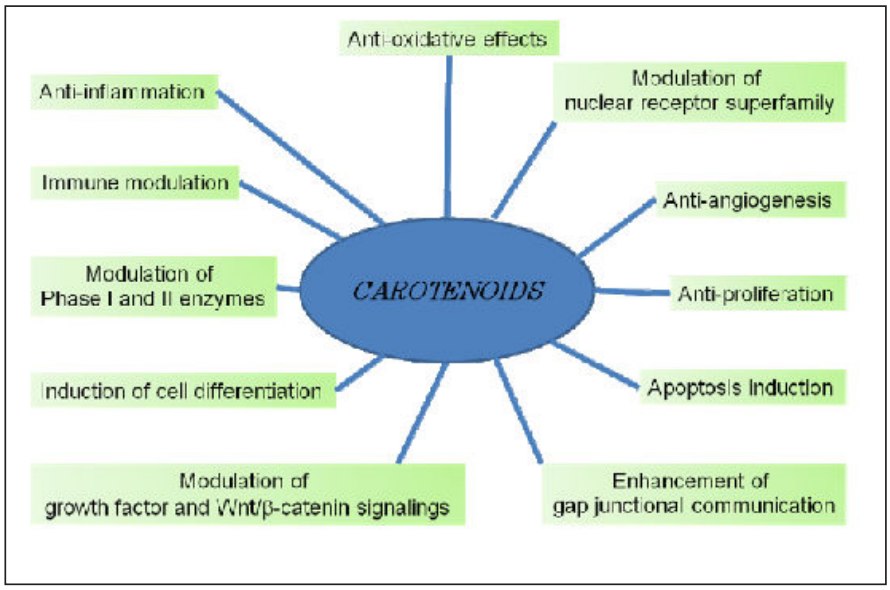
There is a complex relationship between vitamin D and calcium absorption where Vitamin D plays a role in enabling the physiological regulation of absorption. Calcium absorption is found to increase by almost 70% greater efficiency in those whose 25(OH)D concentration was an average of 86 nmol/L than others in the study whose concentrations were at 50 nmol/L.[8]

Vitamin A as Mixed Carotenoids

Vitamin A can be produced as a natural mixed carotenoid complex derived from a reddish vegetable oil concentrate that has been extracted from red palm fruits (*Elaeis guineensis*). Red palm oil was traditionally used and revered by those living on the African continent, including by the ancient Egyptians, as a nutritious food and valuable medicine. Virgin crude palm oil contains high concentrations of naturally-occurring carotenoids and is a rich plant source of carotenes in terms of retinol (vitamin A) equivalents. Carotenoids in oil extracted from red palm fruit consist predominantly of alpha-carotene, beta-carotene, gamma-carotene, and lycopene, along with a small amount of other carotenoids.

Though hundreds of carotenoids have been identified, only around 40 are commonly present in the human diet and around six have been found in human blood and tissues. Studies show that fatty acids enhance the bioavailability and absorption of carotenoids. Carotenoids are considered most effective when used as a complete complex found in their natural state.[32-35]

There are two main types of carotenoids. Those in the carotene group can convert to provitamin A. The other group, including lycopene, cannot convert to provitamin A but offer a wide range of activity. Carotene is one of the most widely-researched compounds as it possesses the highest



(*see reference #34)*

pro-vitamin A activity. Dietary sources of carotene include green leafy vegetables and carrots. Lycopene is primarily found in tomatoes and is also found in watermelon, guava, and pink grapefruit.[33-35] Studies report that diets rich in fruits and vegetables are correlated with greater longevity and with lower morbidity from chronic disease, which is partially attributed to their high carotenoid content.[36]

A large body of research demonstrates the antioxidant, anti-inflammatory, and immune-enhancing effects of carotenoids. They exert a highly protective influence, particularly of the cells and epithelial tissue, from oxidative damage. Carotenoids are known as powerful antioxidants, able to quench free radicals, reduce damage from reactive oxidative species (ROS) and to inhibit lipid peroxidation.[36] There is found to be significant correlation with consumption of carotenoids and decrease of lipid and oxidative biomarkers.[37] Healthy serum levels of the carotenoid complex in general are correlated with decreased risk of chronic disease and an increase in healthy cellular function and overall health and well-being.[36,38-40]

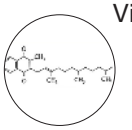
Carotenoid compounds are found to facilitate intercellular communication, to influence the cell cycle, and to induce apoptosis.[36,38,41] Recent studies find that higher serum levels of carotenoids were associated with protection of telomeres from oxidative stress and may play a role in modulating telomere length. Telomere length is a biomarker for aging.[42]

Carotenoids modulate immune system function and are found to inhibit production of inflammatory factors including pro-inflammatory cytokines.[43] B-carotene acts as an immune modulator and antioxidant. In multiple studies, inclusion of carotenoid-rich fruits and vegetables in the diet is found to correlate with reduced cardiovascular disease risk.[44] Carotenoids are being investigated for their protective influence from breast cancer.[45] Alpha- and beta-carotene are pro-vitamin A compounds and can be converted to vitamin A in the body. Vitamin A modulates immune response partially through enhancing production of cytokines and immunogobulins. It also modulates the function of neutrophils and lymphocytes.[46]

While lycopene does not convert to provitamin A, it has many molecular targets. As with all the carotenoids, it exerts strong antioxidant activity. It also is involved with cell regulation including induction of apoptosis, cell cycle arrest, growth factors, and signaling pathways. Lycopene is found protective against chronic disease including cancer, diabetes, atherosclerosis, and some inflammatory diseases.[34,40] Research demonstrates clear evidence that lycopene is protective against some cancer lines, particularly that of prostate cancer. Many studies indicate that increased dietary lycopene correlates with decreased risk of prostate cancer.[47] Research indicates that lycopene plays a role in modulating the hormonal system, immune system, and metabolic pathways.[38] It is related to modulation of insulin-like growth factor (IGF-I).[43]

In a 17-year study of 370 Caucasian men and 576 Caucasian women with an average age of 75 high carotenoid intake was found protective against bone fractures. Specifically, high lycopene intake was correlated with decreased risk of hip fracture and non-vertebral osteoporotic fracture.[48]

Vitamins K1 and K2



Vitamin K, a cofactor for blood clotting, is a fat-soluble vitamin essential for proteins vital to the process of blood clotting. It was designated "K" as the original German research called it the Koagulationsvitamin. Vitamin K is also a cofactor in bone metabolism where it is found to be synergistic with vitamin D.

The main dietary source of vitamin K is K1 (phylloquinone) found in green leafy vegetables where it plays a role in photosynthesis. K1 is also found in other higher plants including algae. The average diet contains 90 to 120 mcg of vitamin K. K2 (menaquinone) occurs in foods in smaller amounts – mostly in butter, eggs, cow liver, cheese, and in fermented products. Fermented soybeans in the form of natto are especially rich in K2. Our bodies convert K1 to K2 and a small amount of K2 is produced from our beneficial large intestinal bacteria.[6,49,50]

Vitamin K is also a cofactor for bone mineralization. Higher levels of vitamin K are found to benefit vitamin K-dependent proteins including the bone protein osteocalcin and is also found to benefit bone mineral density and decreased fracture risk in elderly women.[49] In Japan, K2 is widely used for those with osteoporosis.[49] Vitamin K supplementation is found to help decrease incidence of fractures.[51,52]

Research with animals suggests that high doses of vitamin K2 (100mg/kg/body weight daily) may inhibit arterial calcification and reduce coronary calcification. It is also found to lower total cholesterol and to decrease lipid peroxidation.[49,51,53] K2 is found to benefit cardiovascular health. Overall higher intake of vitamin K is associated with decreased serum levels of the inflammatory marker CRP (C-reactive protein).[6,49,50] Vitamin K is found to exert antioxidant influence.[6] Modern research finds vitamin K beneficial to inhibit unhealthy cell growth in vivo and in vitro[48] and that vitamin K2 can benefit apoptosis.[6,49,50]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

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