Vitamins

Vitamin D and Prevention of Human Disease

Vitamin D₂ (ergocalciferol) is naturally synthesized from ergosterol by invertebrates, fungi, and plants in response to ultraviolet B irradiation, while vitamin D₃ synthesis (cholecalciferol) is uniquely initiated in the skin of vertebrates. During sun exposure, ultraviolet B photons are absorbed by 7-dehydrocholesterol, which is found within the plasma membranes of epidermal and dermal skin layers. This reaction yields an unstable derivative of 7-dehydrocholesterol, named precholecalcitrol, which rapidly rearranges to vitamin D₃. Vitamin D binding protein (DBP) is a carrier protein responsible for drawing vitamin D₃ from the plasma membrane into the dermal capillaries within the extracellular space. Vitamin D₃ may be commercially synthesized from cholesterol extracted from the lanolin of sheep wool. The extracted cholesterol is converted to 7-dehydrocholesterol and then treated with UV light to produce vitamin D₂. Both vitamin D₂ and D₃ are commercially used in fortified foods and supplements.

Both forms of vitamin D undergo two hydroxylations to form the active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)₂D), termed calcitriol (1,25(OH)₂D₃) when specifically referring to the synthesis from vitamin D₃. The first hydroxylation occurs in the liver where D-25-hydroxylase, encoded by CYP2R1 (cytochrome P450, family 2, subfamily R, polypeptide) converts vitamin D₂ into 25-hydroxyvitamin D₂ (calcidiol or 25(OH)D₂). With the assistance of DBP, 25-hydroxyvitamin D₂ circulates into a renal tubule, where a second hydroxylation by 25-hydroxylase, encoded by CYP27B₁, yields 1,25-dihydroxyvitamin D₂ (1,25(OH)₂D₂). This reaction is inhibited by free calcium, inorganic phosphate, and the end product (1,25(OH)₂D₂) and stimulated by parathyroid hormone (PTH), a regulator of 25-hydroxyvitamin D-1 α-hydroxylase. Figures 1 and 2 show the synthesis pathway of 1,25-dihydroxyvitamin D₂ and 1,25-dihydroxyvitamin D₃.

1,25(OH)₂D is responsible for the intestinal transport of calcium, renal calcium absorption, bone formation and maintenance, insulin secretion, and blood pressure regulation. To initiate these biological processes, 1,25(OH)₂D binds with its high-affinity vitamin D receptor (VDR), a ligand-activated transcription factor, which complexes with retinoid X receptor (RXR) to form a heterodimer, resulting in vitamin D response element recognition and gene transcription related to these biological processes.

In the intestine, binding of the heterodimer complex regulates the transcription of the calcium binding protein, calbindin, which assists in the transfer of calcium across the cell membrane and into the bloodstream. The 1,25(OH)₂D assisted regulation of calbindin expression appears to control the intracellular calcium flux within insulin-secreting islet cells. 1,25(OH)₂D is also critical for osteoblastic bone formation and osteoclastic maintenance. In the osteoblast, the heterodimer induces the expression of receptor activator NF-κB ligand (RANKL). The binding of RANKL to the RANK receptor unleashes a signaling cascade resulting in differentiation and osteoclast growth. In the parathyroid glands, 1,25(OH)₂D is involved in the suppression of PTH gene transcription, the regulation of VDR concentration, and parathyroid response to calcium. The correlation between vitamin D deficiency and high blood pressure may be attributed to the role of 1,25(OH)₂D as a negative endocrine regulator of the renin-angiotensin system. An experimental study showed that VDR knock-out mice experienced high levels of renin expression and angiotensin production resulting in hypertension.

In addition to the involvement of VDR in these biological processes, VDR is required for the β-catenin (cadherin associated protein) assisted induction of hair follicle formation in adult epidermis. Palmer et al., demonstrated in transgenic mice constructed.
with a 4-hydroxy-Tamoxifen (4OHT) inducible form of stabilized β-catenin under the control of the keratin 14 promoter (K14ΔNβ-
cateninER) that a vitamin D analog inhibits β-catenin-induced hair follicle tumor formation. Figure 3, A-C compares the tail of vitamin D analog (EB1089) treated and non-treated mice and stained tail sections of wild type and K14ΔNβ-cateninER transgenic mice. Palmer et al., also reported in the absence of VDR, β-catenin induces human tumors characterized as infiltrative basal cell carcinomas. Figure 3, D and E, shows stained human skin sections of trichofolliculoma and basal cell carcinoma labeled with β-catenin and VDR. The experimental study concluded that VDR is a transcriptional effector of the Wnt pathway that promotes hair follicle differentiation and modulates Wnt-induced tumor formation. This investigation is an example of recent research providing a deeper understanding of the involvement of vitamin D in cancer-related mechanisms.

Studies have linked vitamin D deficiency to colon, prostate, breast, ovarian, lymphoma, and other devastating cancer types. It is has been stated that increasing the population’s average circulating 25(OH)D level to ~50 ng/ml would prevent ~58,000 new cases of prostate cancer annually. However, upper level dose limits are critical since effective therapeutic levels may produce hypercalcemia. This information is based on observational studies combined with randomized trials. Vitamin D guidelines for cancer prevention have focused on the relationship between high levels of vitamin D (e.g., >800 IU) and reduced risk of breast, colon, lung, and prostate cancer. However, epidemiological evidence is inconsistent, and the role of vitamin D in cancer prevention remains unclear.

An enhanced level of vitamin D through sun exposure or dietary intake does not result in a measurable increase of 1,25(OH)D production but does result in a measurable increase of 25(OH)D concentration. The kidney is not the only location of 25(OH)D hydroxylation; a wide variety of tissues, including skin, breast, colon, lung, and brain have the enzymatic ability to metabolize 25(OH)D into 1,25(OH)D. It has been suggested that raising levels of 25(OH)D in the bloodstream provides enough 25(OH)D substrate to enable various tissue types to use locally synthesized 1,25(OH)D for protection against uncontrollable cell growth and maturation, and malignancy risk. Cell growth and maturation control may be attributed to the antiangiogenic properties of vitamin D. Mantell, et al., showed 1,25(OH)D treatment on “activated” endothelial cells significantly inhibited vascular endothelial growth factor (VEGF)-induced endothelial cell sprouting and elongation, a required stage in the angiogenic process. An additional in vivo study showed 1,25(OH)D treatment produced tumors were less vascularized then tumors formed in mice without 1,25(OH)D treatment. Previous research findings regarding vitamin D and cancer have led to the creation of a new cancer etiology model, referred to as DINOMIT (disjunction, initiation, natural selection, overgrowth, metastasis, involution, and transition). The model describes the loss of communication between cells as the driver in cancer development. This new model differs significantly from the carcinogenesis and cancer stem cell models. Cedric Garland, UCSD said “In this new model, we propose that this loss may play a key role in cancer by disrupting the communication between cells that is essential to healthy cell turnover, allowing more aggressive cancer cells to take over.” When there are adequate vitamin D levels, cells adhere, communicate, and act as mature epithelial cells but with inadequate vitamin levels, they may lose their stickiness along with their identity as differentiated cells, and revert to a stem cell-like state. Garland further stated “vitamin D may halt the first stage of the cancer process by re-establishing intercellular junctions in malignancies having an intact vitamin D receptor.” Although the DINOMIT model and other scientific reports presented in this article provide a strong explanation for the beneficial value of vitamin D, additional research and long-term clinical studies are needed to fully understand the impact of vitamin D in human disease prevention.

References

5. The vitamin D receptor is a Wnt effector that controls hair follicle differentiation and specifies tumor type in adult epidermis. Palmer, H.G. et al., PLoS ONE, 3(1), e1483.