Vitamin D. Bone Health and a Lot More

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Vitamin D is not a vitamin in the strict sense of the word. It is not an essential component of diet and, it is perfectly possible, in most latitudes, to obtain it through exposure to the sun, because it is synthesized in the skin through the influence of ultraviolet sunlight. For it to become functional it needs to undergo hydroxylation in the liver, where it is converted to 25-hydroxi-vitamin D_3 (25-OHD_3), which is the circulating form, and then another hydroxylation in the renal tubule. In the kidney it becomes $1,25(OH)_2D_3$, or calcitriol, the true D hormone, with physiologic actions in individuals of all ages. While the majority of vitamins participate or act as cofactors in determined biochemical reactions, calcitriol exerts its action through binding with its nuclear receptor and a mechanism similar to steroidal hormones. The best-known physiologic function of this hormone is regulation of calcium (Ca) and phosphorus (P) metabolism, with the goal of maintaining steady levels of these ions in the blood, and an adequate mineralization of the skeleton. Through its direct action on intestinal cells, the kidneys, parathyroid glands, and bones, it increases the intestinal absorption of Ca and P into plasma, produces a mobilization of Ca from the bone through the action of parathyrine, and increments it reabsorption in the distal renal tubules. Calcium carries out 2 predominant physiologic roles; in the bone, and in the form of a salt, it constitutes a structure, and in the extracellular fluid and the cytosol, it is very important in a great variety of biochemical processes and requires strict regulation of its concentration. These processes are initiated with the activation of the specialized tubules of the cell membrane, the calcium channels, which allow for the entry of this ion into the cell to form the calcimodulin complex, a molecule which is determinant in the activation of different protein kinase systems.[1] The cell, under these conditions, alters it polarity and facilitates the activation or inactivation of different enzyme systems that play a role in multiple phenomenon's such as neurotransmission, muscle contraction, and relaxation, cell migration and transmigration and the liberation of secretion products such as hormones, or neurotransmitters, among many others.[1,2]

D hormone has actions in other tissues such as the prostate, mammary glands, gonads, muscle, heart, brain, skin, colon, or pancreas. These target tissues present receptors for nuclear vitamin D (VDR),[3] where $1,25(OH)_2D_3$ binds after penetrating the cell and acts through the activation of specific gene transcription, to regulate the differentiation and cell proliferation or hormonal secretion, though all of the physiologic functions that it has in all of these tissues is not fully understood. The discovery of VDR in cells of the immune system, such as T lymphocytes, macrophages, and antigen presenting cells such as dendritic cells,[4,5] indicates that it participates also in the immune system where it acts as an important modulator of its function. Many tumor cells[6] also have VDR.

The renal tubule is the main source of circulating $1,25(OH)_2D_3$ which is obtained after the metabolism of 25-OHD_3 by the effect of the 25(OH)D-1α-hydroxilase (1-OHase) enzyme of the P450 cytochrome system.[7] It has been demonstrated that different tissues such as the placenta or skin, the mammary tissue, lymph nodes, colon, pancreas or prostate, and different cells such as lymphocytes or activated macrophages, express 1-OHase, and therefore have the capacity to produce $1,25(OH)_2D_3$.[8]

This locally synthesized D hormone would have an autocrine and paracrine effect, not completely identified, but with a role in the regulation of cell growth, differentiation, and function.[9] The presence of 1-OHase also has been demonstrated on cancer cells.[10,11]

Numerous studies worldwide have demonstrated that vitamin D insufficiency is a common problem. It is frequent at all ages and as a result of the combination of a series of factors such as race, the degree of exposure to sunlight, latitude, aging, and the ingestion of vitamin D. There is evidence of the role that vitamin D plays during development[12] or the severity of osteoporosis,[13] because secondary hyperthyroidism causes an increase in bone remodeling, a negative bone balance and an increment in the risk for fracture. A severe and maintained deficit of vitamin D also leads to deficient mineralization of the skeleton and the appearance of rickets and osteomalacia. Vitamin D insufficiency also causes muscle weakness and

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an increment in the risk of falling.[14] In Spain, this deficiency has been demonstrated in subjects of all ages[15-17] and especially in older institutionalized residents,[18] or with hip fractures.[19]

It seems evermore evident that the relationship between hypervitaminosis D and different autoimmune diseases, arterial hypertension or some types of cancer, and the hypothesis to explain this relationship is that in a situation of hypervitaminosis D the activity of 1-OHase would be limited by a lack of substrate.[20] In experimental animal models have demonstrated that the deficit of vitamin D exacerbates intestinal inflammatory disease and multiple sclerosis[21,22]; additionally, these same illnesses, as well as type 1 diabetes mellitus or rheumatoid arthritis can be avoided in predisposed animals if treated early with $1,25(OH)_2D_3$.[21-24] Epidemiological studies propose that the ingestion of vitamin D reduces the risk of presenting illnesses such as rheumatoid arthritis,[25] multiple sclerosis,[26] or certain types of cancer such as breast, prostate, or pancreatic cancer.[27-29] In addition, the degree of solar ultraviolet radiation and/or the serum concentrations of vitamin D have been inversely correlated with the incidence, severity or mortality of different types of cancer.[30-32] There is a seasonal variance in the prognosis of cancers such as colon, breast or pancreatic cancer, or Hodgkins lymphoma, which suppose a greater survival when the diagnosis have been carried out in summer or fall, and coincide with larger serum concentrations of calcidiol.[33] The possibility of dissociating the hypercalcemic action from the cell differentiation actions has stimulated the search for analogs of vitamin D that could be useful in the treatment of cancer or as an immunosuppresant,[34] in the same way that they are currently used for the treatment of psoriasis.[35]

The action of the sun provides an adequate synthesis of vitamin D in the equatorial belt, but is insufficient in other regions during winter, whose length is more or less variable depending on the latitude. This situation leads commonly to the supplementation of vitamin D. The determination of serum $25\text{-}OHD_3$ is an indicator of the reserve of vitamin D, and in spite of the great importance that having adequate serum concentration represents for health, this determination is not standardized. Also, there is no general consensus, with respect to which are the reference serum values, and this determination is not performed systematically either in the clinic nor in cases in which a deficiency is suspected. The Consensus Document 2006 of the Spanish Society of Rheumatology on postmenopausal osteoporosis[36] recommends that a $25\text{-}OHD_3$ determination be asked for at least on the first visit of a patient who is being evaluated for osteoporosis, but this advice should probably be applied to all individuals at risk for hypovitaminosis D, in addition to controlling the serum concentrations of the patients in treatment to insure that sufficient values have been achieved. Different authors consider that 30-40 ng/mL should be an acceptable serum concentration of $25\text{-}OHD_3$, because values under this level are associated with variable degrees of hypothyroidism.[37,38] It is evermore evident that the dose of 800 U per day of cholecalcipherol, which is the commonly recommended dose, is insufficient to normalize the reserve of vitamin D in patients with a deficit of this vitamin, having the capacity to increase the baseline concentration of $25\text{-}OHD_3$ in only 8 ng/mL.[38] To normalize this concentration, larger doses, such as 10 000 U a day of vitamin D_2 are needed, for as long as 3 months of treatment,[39] or using a more efficacious metabolite such as calcidiol at a dose of 16 000 U weekly and for 4 weeks.[40] We must be aware of the importance that knowing the dose of vitamin D that our patients are taking has, because only when we insure a sufficient ingestion of vitamin D will we be able to provide for their bone health and probably much more.

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