Vitamin D and the Parenteral Nutrition Patient

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Vitamin D is a prohormone produced in the skin epidermis when irradiated with sunlight or ultraviolet light B. It is also absorbed from food or supplements. Vitamin D must be converted to 25-hydroxyvitamin D_3 (circulating form) and finally to the hormone, 1a,25-dihydroxyvitamin D_3, before it can function. This hormone acts through a single nuclear receptor. The details of these conversions and molecular biology of the action of vitamin D_3 are summarized. The physiologic functions of vitamin D have been expanded beyond the mineralization of the skeleton to include modulation of the immune system, terminal differentiation in several tissues, suppression of malignant cells, and anabolic activity in the skeleton and in the renal–cardiovascular system. Epidemiologic studies have associated vitamin D deficiency with an increased risk of colorectal and breast cancers and an increased risk of autoimmune diseases, such as multiple sclerosis, type 1 diabetes, and cardiovascular events. Thus, vitamin D is essential not only for the skeleton but also many other organ systems. Recommendations for 25-hydroxyvitamin D_3 levels for PN patients are presented.

Vitamin D and Health

Over the past 5 years, there has been an enormous rebirth of interest in vitamin D from the public health point of view. The basis for the current excitement harkens back to the discovery of the vitamin D endocrine system. Before that discovery, the role of vitamin D in animal and human physiology was deemed to be the mineralization of the skeleton and hence prevention of the disease rickets in children and osteomalacia in the adult.[1] In fact, some textbooks indicated that vitamin D is not required after childhood because the growth of the skeleton had ceased.[2] This, of course, is false; vitamin D is required throughout life for skeletal health because it plays a major role in the remodeling system in addition to the requirement for mineralization that repairs the skeleton.[3–5]

Vitamin D Metabolism

The delineation at the physiologic level of the mechanism of action of vitamin D occurred with the discovery that vitamin D_3 itself is biologically inactive[3] and must be metabolized first in the liver to 25-hydroxyvitamin D_3 (25-OH-D_3) and subsequently in the kidney to 1α,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) before it can carry out its well-known functions in calcium and phosphorus metabolism resulting in the healing of rickets and osteomalacia.[4,5] There is little doubt then that vitamin D plays an essential role in bone health, and in subsequent sections, the molecular mechanisms whereby it brings these actions about are discussed.

The Vitamin D Receptor

Continued pursuit of the vitamin D endocrine system based in the kidney revealed that the vitamin D hormone, that is, 1,25-$(OH)_2D_3$ functions primarily, if not exclusively, through a nuclear receptor.[6,7] This vitamin D receptor (VDR) was first described in 1975[8] and 1976,[9] and several laboratories attempted isolation of the VDR for approximately a decade. Importantly, radiolabeled 1,25-$(OH)_2D_3$ when administered to animals was found to localize in the nuclei in the target organs, suggesting a nuclear mechanism.[10] Although the receptor was extensively purified by 2 laboratories, it was never purified to homogeneity. These laboratories used the partially purified receptor to produce monoclonal antibodies directed to the VDR from 1982 to 1986.[11,12] This resulted in the cloning of the VDR in rats in the DeLuca group and in human cells by the O'Malley, Haussler, and Pike group in 1988.[13,14] Of great interest was the finding, using either radiolabeled ligand or the antibodies to the receptor, that the receptor is found in many tissues not in any way associated with calcium and phosphorus homeostasis required for bone health and growth.[15–17] This led to the speculation that vitamin D may play other important roles in addition to skeletal mineralization and bone remodeling.

Expanded View of Vitamin D Function

The discovery that VDR in tissues not involved with calcium and bone ultimately resulted in discovery of new functions of vitamin D. Clearly, vitamin D plays a

Abbreviations used in this paper: 1, 25-$(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; 25-OH-D_3, 25-hydroxyvitamin D_3; CYP450, cytochrome P-450; PN, parenteral nutrition; PTH, parathyroid hormone; TPN, total parenteral nutrition; VDR, vitamin D receptor; VDRE, vitamin D-responsive element.

0016-5085/09/$36.00
doi:10.1053/j.gastro.2009.07.075

significant role in the immune system, cellular differentiation, the development of the giant osteoclast, and some circumstances, as a regulator of cell cycle being useful in the treatment of proliferative diseases such as cancer and psoriasis. These findings have led epidemiologists to examine the relationship of vitamin D to a wide number of abnormalities giving rise to the idea that vitamin D may be very important in reducing the incidence of autoimmune disease, colorectal cancer, breast cancer, and heart attacks.[18–20] This, therefore, signals the importance of vitamin D for all subjects including those relying on parenteral nutrition (PN). This presentation is devoted to that idea.

The Production and Metabolism of Vitamin D

Although vitamin D was originally discovered as a vitamin by McCollum et al,[21] our current knowledge reveals very clearly that vitamin D is not a vitamin but a prohormone that is normally produced in skin under the influence of ultraviolet light.[22] As illustrated in Figure 1, the production of vitamin D in skin is from the cholesterol metabolite, 7-dehydrocholesterol, which absorbs ultraviolet light between 282 and 310 nM producing previtamin D, a compound that has little biological activity, but that slowly isomerizes to the vitamin D form.[23] Vitamin D thus produced in the skin is transported to the liver where it begins it metabolic alterations for function. In the liver, it undergoes 25-hydroxylation primarily due to a cytochrome P-450 (CYP450) enzyme yet to be positively identified but believed to be the CYP450 2R1.[24,25] However, that enzyme has not yet been knocked out and, therefore, we cannot yet conclude that it is the enzyme responsible for the initial activation step of vitamin D to produce 25-OH-D_3, which is the circulating form of vitamin D. Although another candidate has been suggested as the CYP450 that activates vitamin D to 25-OH-D_3, it is clear that that enzyme, that is, the CYP27A1, is not required for the activation of vitamin D as revealed by a null mutant mouse model.[26]

25-OH-D_3 is the form of vitamin D that is measured to determine the vitamin D status of any patient. However, 25-OH-D_3 under normal circumstances is not biologically active, but must be metabolized further to its final hormonal form, 1,25-$(OH)_2D_3$. A biological activity due exclusively to 25-OH-D has not been found; thus, it is currently believed that 1,25-$(OH)_2D_3$ is the functional form of vitamin D. The process producing 1,25-$(OH)_2D_3$ takes place primarily, if not exclusively, in the kidney, particularly in the proximal convoluted tubule cells.[27,28] The enzyme responsible for this conversion is the CYP27B1. It has been cloned, and has been rendered null by mutation in mice. Most important is that vitamin D-dependency rickets type I, which was discovered in 1953 by Prader represents a defect in this enzyme[29] and,

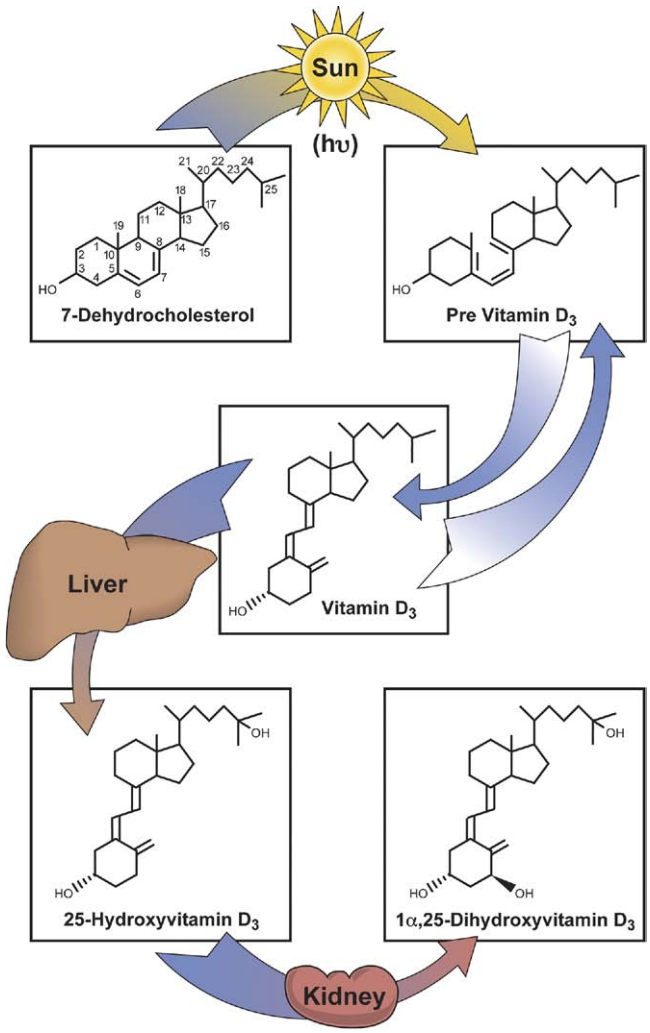

Figure 1. The production of vitamin D in skin and its conversion through the liver to the major circulating form, 25-OH-D_3, and its conversion to the final vitamin D hormone, 1,25-$(OH)_2D_3$, in the proximal convoluted tubule cells of the kidney.

in fact, many kindreds have now been identified illustrating the mutations resulting in this form of disease.[30,31] This disease can be cured by large amounts of vitamin D or 25-OH-D_3 but only physiologically with 1,25-$(OH)_2D_3$. These mutations themselves illustrate the vitamin D endocrine system and the essential role played by the CYP27B1. Vitamin D-dependency rickets type I and the 3 different reports of the null mutant mice[28,32,33] prove conclusively that the vitamin D endocrine system is true and is certainly functional in man.

There is considerable interest in the possibility that small amounts of the CYP27B1 might exist in other cells and tissues, giving rise to an autocrine/paracrine function in the vitamin D system.[34] Although this may still be true, conclusive in vivo evidence is lacking. Certainly cells and tissues explanted in vitro can produce 1,25-$(OH)_2D_3$. Furthermore, in certain disease states, extrarenal production of 1,25-$(OH)_2D_3$ is clearly evident, as, for example, in