Henry Ford Hospital Medical Journal

Volume 36 | Number 3 Article 12

9-1988

Vitamin D Metabolism in Health and Disease

Norman H. Bell

Vitamin D Metabolism in Health and Disease

Norman H. Bell, MD*

1,25-Dihydroxyvitamin D_3 Receptor Structure and Function

In this portion of the program the most recent information concerning factors that regulate the production and biologic action of 1,25-dihydroxyvitamin D, the most active metabolite of vitamin D, in normal and disease states was presented. Haussler (1) described the structure and functional domains of the receptor for 1,25-dihydroxyvitamin D. The human receptor is a polypeptide containing 427 amino acids with an N-terminal DNA binding domain (150 amino acids) and a C-terminal hormone binding domain (226 amino acids) that are separated by a "hinge" (51 amino acids). The DNA binding region contains two "zinc fingers" that are thought to be important in binding of the 1,25-dihydroxyvitamin D-receptor complex to DNA (see below). The vitamin D receptor bears a striking resemblance to other nonpolypeptide hormonal receptors including the glucocorticoid receptor, estrogen receptor, retinoic acid receptor, and thyroid receptor (1). Not surprising is the finding that there is a high degree of homology among the receptors at the DNA binding site. Haussler indicated that 1,25-dihydroxyvitamin D_3 upregulates its receptor, that phosphorylation may occur in this process, and that upregulation may be physiologically important by amplifying gene regulation and biologic action. Although the mechanisms by which 1,25-dihydroxyvitamin D regulates gene expression are not known, Haussler proposed a model in which phosphorylation of the vitamin D receptor is catalyzed by casein kinase and the hormone-receptor-DNA complex initiates transcription (1).

Hereditary Resistance to 1,25-Dihydroxyvitamin D: Pathophysiology, Diagnosis, and Treatment

Liberman and Marx (2) indicated that five defects in hereditary vitamin D-dependent rickets, type II, have been described based on studies of cellular uptake and nuclear binding of ^{3}H-1,25-dihydroxyvitamin D_3. These are outlined as follows:

Type I: no binding of hormone to soluble cell extract or nuclei.

Type II: reduced binding capacity with normal binding affinity to soluble cell extract and nuclei (reduced number of receptors).

Type III: reduced binding affinity with normal binding capacity (normal number of receptors).

Type IV: normal binding affinity and capacity to soluble cell extract and no nuclear uptake.

Type V: near-normal binding affinity and capacity to soluble cell extract and abnormal elution of hormone-receptor complex from heterologous DNA-cellulose.

Type VI was not described but would include patients with posttranscription defects who should show normal binding and nuclear uptake of 1,25-dihydroxyvitamin D_3 and normal elution of hormone-receptor complex from heterologous DNA-cellulose. Patients with types III and IV disease respond to large doses of 1,25-dihydroxyvitamin D_3, whereas patients with types I, II, and V disease respond poorly or not at all.

Based on these findings and assuming that receptor defects are qualitative (and result from point mutations) and not quantitative (and do not result from lack of expression), it can be predicted that the structure of the 1,25-dihydroxyvitamin D-binding domain of the receptor is abnormal in patients with type I disease and that structure of the DNA binding domain is abnormal in patients with type V disease. It is now known that two separate mutations exist in type V disease. Point mutations have been identified in each of the two "zinc fingers" which account for the lack of response to 1,25-dihydroxyvitamin D_3 in vivo and abnormal nuclear uptake of the 1,25-dihydroxyvitamin D_3-receptor complex in vitro in two different families with vitamin D-dependent rickets, type II (Pike JW, personal communication). These results emphasize the importance of the structure of the cysteine-containing loops or "zinc fingers" in binding of the 1,25-dihydroxyvitamin D_3-receptor complex for biologic function of the vitamin. Studies are in progress in Dr. Pike's laboratory to determine whether abnormal structure of the 1,25-dihydroxyvitamin D-binding domain of the receptor or abnormalities in posttranscription events are responsible for expression of the disease in other patients. He proposes to transfect cells that have an abnormal receptor with the gene for the normal vitamin D receptor to determine whether a defective receptor fully accounts for the disease in a given patient.

The Role of Phosphorus in Modulating Vitamin D Metabolism in Health and Disease

Previous studies in rats showed the importance of dietary phosphate in regulating the production of 1,25-dihydroxyvitamin D (3). Thus, phosphate intake varied directly with renal production of the metabolite. Also, previous studies demonstrated the importance of restriction of phosphate intake in preventing secondary hyperparathyroidism in chronic renal failure (4). Morris et al (5) showed that changes in phosphate intake regulate the renal production of 1,25-dihydroxyvitamin D and serum 1,25-dihydroxyvitamin D in normal subjects. They also

*Research Department, Medical University of South Carolina, Charleston.
Address correspondence to Dr. Bell, Research Department, Medical University of South Carolina, 109 B Street, Charleston, SC 29403.

showed that phosphate restriction prevents inhibition of the renal synthesis of 1,25-dihydroxyvitamin D and secondary hyperparathyroidism even in patients with modest reductions in glomerular filtration rate. Their studies indicate, therefore, that dietary intake of phosphorus should be limited early in the course of renal disease to prevent the development of secondary hyperparathyroidism and its sequelae.

Clinical Disorders of Phosphorus and Vitamin D Metabolism

Nesbitt et al (6) presented evidence that the renal tubular reabsorption of phosphate and renal synthesis of 1,25-dihydroxyvitamin D are closely linked. Thus, TmP/GFR or tubular phosphate reabsorption and plasma 1,25-dihydroxyvitamin D varied directly with each other in patients with X-linked hypophosphatemic rickets, tumor-induced osteomalacia, and tumoral calcinosis. However, there was poor correlation between TmP/GFR and plasma 1,25-dihydroxyvitamin D in patients with hereditary hypophosphatemic rickets and hypercalciuria. In this disorder, circulating 1,25-dihydroxyvitamin D was increased and responsible for the hypercalciuria. They suggested that the proximal renal tubular site at which phosphate is reabsorbed may be important in the regulation of renal synthesis of 1,25-dihydroxyvitamin D and that the interrelation of these two processes, which appear to be linked, is complex.

Abnormal Vitamin D and Calcium Metabolism in Sarcoidosis and Related Diseases

Hypercalcemia caused by increased circulating 1,25-dihydroxyvitamin D is a potentially preventable cause of renal failure and death in patients with sarcoidosis. Liel and colleagues (7) developed a means to identify patients who may be at risk to develop hypercalcemia. Their method is based on the fact that feedback regulation of circulating 1,25-dihydroxyvitamin D normally occurs in response to increases in dietary calcium. They found in a small number of patients with sarcoidosis and active disease, in contrast to normal subjects in whom serum 1,25-dihydroxyvitamin D declined in response to increases in dietary calcium, that serum 1,25-dihydroxyvitamin D did not change. These results were interpreted to mean that since the production of 1,25-dihydroxyvitamin D is not normally regulated, it must be synthesized at extrarenal sites in patients with active disease. Thus, patients with active disease may be at risk for developing hypercalcemia. In fact, one of the patients developed hypercalcemia in the course of a summer.

The Effects of Race and Body Habitus on the Vitamin D Endocrine System

Blacks and obese subjects have a greater bone mass than whites and nonobese individuals and are at less risk for developing osteoporosis and fractures of the hip (8). Blacks and obese whites also show decreases in serum 25-hydroxyvitamin D and urinary calcium and increases in serum 1,25-dihydroxyvitamin D and urinary cyclic adenosine 3′,5′-monophosphate as compared to nonobese white men and women. It remains unclear whether the altered vitamin D endocrine system in these subjects is related to the increased bone mass.

References

1. Haussler MR. 1,25-Dihydroxyvitamin D_3 receptor structure and function. In: Kleerekoper M, Krane SM, eds. Clinical disorders of bone and mineral metabolism. New York: Mary Ann Liebert, Inc, 1989 (in press).
2. Liberman UA, Marx SJ. Hereditary resistance to 1,25-dihydroxyvitamin D: Pathophysiology, diagnosis, and treatment. In: Kleerekoper M, Krane SM, eds. Clinical disorders of bone and mineral metabolism. New York: Mary Ann Liebert, Inc, 1989 (in press).
3. Tanaka Y, DeLuca HF. The control of 25-hydroxyvitamin D metabolism by inorganic phosphorus. Arch Biochem Biophys 1973;154:566-74.
4. Slatopolsky E, Caglar S, Pennell JP, et al. On the pathogenesis of hyperparathyroidism in chronic experimental renal insufficiency in the dog. J Clin Invest 1971;50:492-9.
5. Morris RC Jr, Halloran BP, Portale AA. The role of phosphorus in modulating vitamin D metabolism in health and disease. In: Kleerekoper M, Krane SM, eds. Clinical disorders of bone and mineral metabolism. New York: Mary Ann Liebert, Inc, 1989 (in press).
6. Nesbitt T, Davidai GA, Brazy PC, Drezner MK. Clinical disorders of phosphorus and vitamin D metabolism. In: Kleerekoper M, Krane SM, eds. Clinical disorders of bone and mineral metabolism. New York: Mary Ann Liebert, Inc, 1989 (in press).
7. Liel Y, Basile J, Bell NH. Abnormal vitamin D and calcium metabolism in sarcoidosis and related diseases. In: Kleerekoper M, Krane SM, eds. Clinical disorders of bone and mineral metabolism. New York: Mary Ann Liebert, Inc, 1989 (in press).
8. Epstein S, Bell NH. The effects of race and body habitus on the vitamin D endocrine system. In: Kleerekoper M, Krane SM, eds. Clinical disorders of bone and mineral metabolism. New York: Mary Ann Liebert, Inc, 1989 (in press).