

The Role of the Vitamin D Endocrine System in Health and Disease

Vitamin D is not only a vitamin, but also a hormone. $1,25(\text{OH})_2\text{D}_3$ and $1,25(\text{OH})_2\text{D}_2$ are the principal vitamin D mediators that regulate bone and mineral metabolism in humans. There are, however, other actions of $1,25(\text{OH})_2\text{D}_3$ —and probably $1,25(\text{OH})_2\text{D}_2$ —that have not been well recognized by practitioners. This article reviews current concepts in this field.

The circulating $25(\text{OH})\text{D}_3$ level reflects the availability of vitamin D₃ and is thought to be the best indicator of vitamin D levels. Feedback mechanisms play pertinent roles, as they do in the other endocrine systems. For example, $1,25(\text{OH})_2\text{D}_3$ decreases the level of $25(\text{OH})\text{D}_3$. $1,25(\text{OH})_2\text{D}_3$ in excess also decreases its own level by shifting the synthesis of $25(\text{OH})\text{D}_3$ to $24,25(\text{OH})_2\text{D}_3$ instead of continuing to synthesize $1,25(\text{OH})_2\text{D}_3$.

Other factors regulating the synthesis of $1,25(\text{OH})_2\text{D}_3$ include parathyroid hormone (PTH), which stimulates 1α -hydroxylase activity, as do low dietary phosphate and hypophosphatemia. Hyperphosphatemia, in contrast to hypophosphatemia, decreases 1α -hydroxylation. Several other hormones secondarily affect $1,25(\text{OH})_2\text{D}_3$ levels. Estrogen, for

example, increases $1,25(\text{OH})_2\text{D}_3$ because vitamin D binding protein is increased.

Synthesis of $1,25(\text{OH})_2\text{D}_3$ occurs to some extent in organs other than the kidney, eg, in patients with sarcoidosis who are anephric. Ectopic synthesis also occurs during pregnancy, as placental and decidual cells produce the hormone.

Substantial evidence has accumulated that the mechanism of action of $1,25(\text{OH})_2\text{D}_3$ is similar to that of other steroid hormones, in that the hormone-receptor complex is associated with DNA in the nucleus. Here it either initiates the synthesis of specific RNA encoding proteins or mediates a selective repression of gene transcription. The $1,25(\text{OH})_2\text{D}_3$ receptor protein is expressed in almost every tissue examined so far.

With respect to calcium metabolism, $1,25(\text{OH})_2\text{D}_3$, in concert with PTH and calcitonin (CT), acts on bone, intestine, and kidney. $1,25(\text{OH})_2\text{D}_3$ plays a role in the regulation of osteoblast function, although its effect on bone growth and mineralization is probably not mediated directly via osteoblasts. As for osteoclast activity, which contributes to bone resorption: administration of $1,25(\text{OH})_2\text{D}_3$ in-

creases the number of osteoclasts found in rats.

In the parathyroid gland $1,25(\text{OH})_2\text{D}_3$ decreases PTH release by increasing serum calcium and by a direct short-loop feedback message that inhibits the synthesis of PTH through an interaction with the prepro-PTH gene. In the intestine, it stimulates the influx of calcium and phosphorus from the lumen through the intestinal wall and into the plasma. For calcium, this is done by activating an increased production of calbindin-D in the intestinal wall which, in turn, enhances calcium absorption.

The authors also discuss at length the role of $1,25(\text{OH})_2\text{D}_3$ in involutional osteoporosis, rickets, granulomatous diseases, cellular growth and differentiation, interaction with the hematopoietic system, effects on lymphocytes, and interaction with cancer cells.

Reichel H, Koeffler HP, Norman AW. *N Engl J Med* 1989;320:980.

Editor's comment—*This is a lengthy and excellent review of the contributions of vitamin D to both normal and pathologic conditions. The data and concepts are up to date. Readers interested in the details of vitamin D metabolism are encouraged to use this article as a reference.*

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