Vitamin D in Critical Illness

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Introduction

Vitamin D is well known for its regulatory effects on calcium and phosphate homeostasis and its role in the maintenance of bone integrity. Over the past decade, there have been data from biochemical and molecular genetic studies that point to vitamin D having a much wider role than just maintenance of calcium and phosphate metabolism. Vitamin D and its synthetic analogues have been shown to have anticancer properties as well as to modulate the immune system. Recently, vitamin D deficiency has been reported in critically ill patients [1, 2]. However, it is still unclear how this deficiency affects patient outcomes in intensive care. The focus of this chapter is to examine the role of vitamin D in the body, with discussion of its effects on mineral and bone metabolism as well as its pleiotropic effects and the role it may play in the pathophysiology of critical illness.

Historical Perspective

The clinical manifestations of rickets were first described in the 17th century by Whistler and Glisson. The sentinel observations of the British medical epidemiologist and missionary, Theodore Palm, were crucial to the discovery and characterization of the physiology of vitamin D and its role in the prevention of rickets. He noted a lower incidence of rickets in children living in the tropics and attributed this to the beneficial effects of sunlight. Sir Edward Mellanby experimentally confirmed this in dogs, where he showed that dogs isolated from sunlight developed rachitic bones. McCollum discovered the compound that is now known as vitamin D. The two major forms of vitamin D (D2 and D3) are shown in Table 1. Vitamin D1 is a combination of ergocalciferol and lumisterol in a 1:1 ratio. Vitamin D3 undergoes two sequential hydroxylation steps, 1-hydroxylation in the liver and a subsequent 25-hydroxylation in the kidney resulting in the physiologically active 1-25 dihydro-

<table>
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<tr>
<th>Form</th>
<th>Chemical name</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Vitamin D2</td>
<td>Ergocalciferol</td>
<td>Made in plants, fungi and invertebrates, not produced in vertebrates. Precursor is ergosterol</td>
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<tr>
<td>Vitamin D3</td>
<td>Cholecalciferol</td>
<td>Made in the skin of humans when sunlight reacts with 7-dehydrocholesterol and converts it to cholecalciferol.</td>
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xycholecalciferol (1,25(OH)\(_2\)D\(_3\)). Only a small fraction of 1,25(OH)\(_2\)D\(_3\) circulates in the plasma as the free fraction, most of it is bound to vitamin D binding proteins.

**Circadian Rhythm of Vitamin D**

Cholecalciferol, being a secosterol is subject to circadian variation just like cortisol. Studies of 1,25(OH)\(_2\)D\(_3\) levels in normal volunteers have demonstrated a small, but significant diurnal variation in levels [3]. In post-menopausal women, however, a significant circadian rhythm in 1,25(OH)\(_2\)D\(_3\) levels has been observed with a nadir level in the morning followed by a rise to a plateau level (14% > nadir) during the day [4].

**Pleiotropic Effects of Vitamin D**

1,25(OH)\(_2\)D\(_3\) exerts its molecular effects by binding to the vitamin D receptor [5, 6]. Vitamin D receptors are nuclear receptors and binding of 1,25(OH)\(_2\)D\(_3\) to the vitamin D receptor results in target gene transcription. These receptors are ubiquitous as demonstrated by the response in most tissues to administration of 1,25(OH)\(_2\)D\(_3\). Further research into the mechanism of action of these receptors brought to fore the more subtle, pleiotropic effects of this hormone, which are distinctly different from its effects on bone and mineral homeostasis (Fig. 1.).

**Vitamin D and the Musculoskeletal System**

As noted, 1,25(OH)\(_2\)D\(_3\) acts as the ligand for vitamin D receptor and the hormone-receptor complex results in calcemic and phosphatemic effects. Low calcium stimulates secretion of parathyroid hormone (PTH) and 1,25(OH)\(_2\)D\(_3\) by the kidney resulting in calcium absorption in the kidney and in the intestines. Phosphate absorption in the intestine is stimulated by 1,25(OH)\(_2\)D\(_3\). In addition, osteoblasts secrete fibroblast growth factor 23 (FGF 23), a phosphaturic hormone to regular phosphate and calcium metabolism relative to 1,25(OH)\(_2\)D\(_3\). FGF 23 lowers the levels of 1,25(OH)\(_2\)D\(_3\) and suppresses the absorption of phosphate from the kidneys. The 1,25(OH)\(_2\)D\(_3\)-vitamin D receptor complex also controls production of 1,25(OH)\(_2\)D\(_3\) by feedback loops – most of the mineral effects of 1,25(OH)\(_2\)D\(_3\) are attenuated by inactivating the DNA binding function of vitamin D receptors [5]. Osteoblasts also synthesize phosphate-regulating endopeptidase homolog, X-linked (PHEX), which regulates protein degradation to reduce FGF 23 synthesis, thus allowing continued renal phosphate reabsorption. PHEX levels are also regulated by 1,25(OH)\(_2\)D\(_3\), which represses its expression. Mutations in PHEX lead to development of X-linked hypophosphatemia. Thus, 1,25(OH)\(_2\)D\(_3\) regulates calcium and phosphate homeostasis by regulating PTH, FGF 23 and PHEX.

Various anabolic and catabolic genes involved in bone formation and resorption are also regulated by 1,25(OH)\(_2\)D\(_3\). The anabolic genes include: a) RP5, b) Runx2, c) TRPV 6 and d) Npt2c. Catabolic genes regulated include a) PTH and b) RANKL. Hence, 1,25(OH)\(_2\)D\(_3\) plays a pivotal role not only in regulating the minerals that are critical for bone formation but also by altering the expression of various genes needed for bone remodeling [5].