How Vitamin D Works on Bone

Tomohiko Yoshida, MD, PhD[a], Paula H. Stern, PhD[b,*]

KEYWORDS

• Vitamin D • Mineralization • Bone resorption • Rickets • Osteomalacia • Fracture • Analogues

KEY POINTS

- Vitamin D is important for the normal development and maintenance of bone.
- Our understanding of the actions of vitamin D on bone has been advanced by the elucidation of its activation pathway and the cloning of the vitamin D receptor.
- The preponderance of evidence indicates that $1,25(OH)_2D_3$ enhances bone mineralization through its effects to promote calcium and phosphate absorption.
- Although $1,25(OH)_2D_3$ stimulates bone resorption in vitro, treatment in vivo can prevent bone loss and fracture, through several potential mechanisms.
- The development of vitamin D analogues has provided new therapeutic options.

INTRODUCTION

Vitamin D is involved in calcium and phosphate metabolism in bone, intestine, and kidney. Several clinical and animal studies indicate that the physiologic effects of vitamin D extend beyond these tissue sites. Adequate vitamin D levels have a role in muscle integrity,[1–4] cancer prevention,[5–8] innate and acquired immune responses,[9,10] and cardiovascular morbidity and mortality.[11–14] Although these extraskeletal effects of vitamin D have recently attracted attention, the actions on bone, which have been recognized for many years, are still not fully understood. This article summarizes the effects of vitamin D on bone and highlights issues that are not yet resolved.

VITAMIN D METABOLISM AND ACTIONS

Vitamin D is produced from previtamin D_3, and is in part provided by dietary sources. Previtamin D_3 is generated from the vitamin D_3 precursor, 7-dehydrocholesterol, in the skin after sunlight exposure (ultraviolet B light),[15–17] and is then readily converted

[a] Division of Endocrinology, Diabetes and Metabolism, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan; [b] Department of Molecular Pharmacology and Biological Chemistry, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue, Chicago, IL 60611, USA
* Corresponding author.
E-mail address: p-stern@northwestern.edu

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to vitamin D_3. Vitamin D_3 is hydroxylated in the liver to make 25-hydroxyvitamin D_3 ($25(OH)D_3$), and further hydroxylated in the kidney to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$, calcitriol), the active form.[18]

In book III of *The Persian Wars* (500–600 BC), the beneficial effect of physiologically produced vitamin D on bone was indirectly implicated by the description of the difference in skulls between the Egyptians and the Persians.[19] The skulls of the Persians were weaker than those of the Egyptians, and the explanation for this was that the Persians had their heads covered by turbans, whereas the heads of the Egyptians were more exposed to sunlight because they had their heads shaved. Later, in the early twentieth century, ultraviolet light came into use as a treatment of rickets.[20] Around the same time, specific dietary deficiencies in phosphorous and photosynthesized fat-soluble vitamins were found to have a causal role in the development of rickets.[21–25] After the discovery that irradiation of some dietary components conferred antirachitic properties,[26,27] the metabolism of vitamin D was investigated,[28,29] providing a basis of our current understanding of the dietary and metabolic mechanisms of osteomalacia.

VITAMIN D RECEPTOR AND ITS EFFECTS ON BONE MINERALIZATION

Before the cloning of vitamin D receptor (VDR), the action was predicted by the observation of hereditary vitamin-D–resistant rickets, or vitamin-D–dependent rickets type II (VDDRII) (OMIM 277440).[30,31] A brother and sister presented with hypocalcemia caused by calcium malabsorption, and manifested secondary hyperparathyroidism with hypophosphatemia and high serum concentrations of $1,25(OH)_2D_3$. The male proband failed to walk unsupported by age 20 months, possibly because of muscular weakness. High doses of ergocalciferol or 1,25-dihydroxycholecalciferol were required to obtain radiographic healing, but the bowing deformities of the tibias and femurs were remarkable (genu varum) and required corrective surgery. Radiologic pictures of the patient showed diffusely decreased bone mineral density (BMD), subperiosteal resorption, and a pseudofracture of the left ischiopubic ramus.

The skeletal action of vitamin D became more evident after the discovery, cloning, and expression of VDR.[32–35] Through the screening of human intestine (jejunum) and T47D (human ductal breast epithelial tumor cell line) cell cDNA libraries, complementary DNA clones encoding the human VDR were isolated. The cloned sequences were transfected into COS-1 cells, and the protein encoded by the cDNA was comparable with the native receptor in terms of the binding affinity to $1,25(OH)_2D_3$, binding preferences for other vitamin D metabolites, and sedimentation characteristics with VDR antibody.[35] Vitamin D and its metabolites have a unique characteristic as to flexibility in structure, and the VDR have had to adapt to the conformational mobility of its ligand. Five carbon-carbon single bonds in the intact 8-carbon side chain,[36] the chair-chair inversion of the cyclohexanelike A-ring,[37] and the rotation around B-ring[38] allow $1,25(OH)_2D_3$ to be highly conformationally mobile.

VDR belongs to the steroid hormone nuclear receptor superfamily, and has been shown to regulate both gene transcription as well as rapid responses such as the opening of voltage-gated Ca^{2+} channels,[39] and stimulation of intestinal Ca^{2+} absorption.[40] These rapid responses of VDR seem to be mediated through the membrane-bound VDR in caveolae[41,42] or through a variety of receptor types located within or near the plasma membrane or caveolae.[43] Protein-disulfide isomerase-associated 3 is hypothesized to be one of these receptors, and was shown to directly inhibit mineralization in osteoblastlike MC3T3-E1 cells through phospholipase A_2-dependent rapid release of prostaglandin E_2 (PGE_2), activation of protein kinase C, and regulation of bone-related gene transcription.[44]