Vitamin D and Bone Health in Adults and the Elderly

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1. INTRODUCTION

Vitamin D is one of the principle hormonal regulators of calcium homeostasis in the body. Besides being critically important for calcium and phosphate absorption in the intestine, vitamin D is essential for normal mineralization of bone and has major regulatory effects on bone cells in the bone remodeling unit. In addition to distant skeletal and intestinal effects, the active form of vitamin D, 1,25-dihydroxyvitamin D$_3$ [1,25(OH)$_2$D$_3$], also regulates its own synthesis in the kidney and parathyroid hormone (PTH) secretion in the parathyroid gland. These multisystem effects firmly establish the importance of this hormone in the maintenance of skeletal health. Moreover, perturbations in vitamin D synthesis, secretion, or action have been implicated as potential pathogenetic factors in the development of osteoporosis. For these reasons, there has been sustained interest in vitamin D and 1,25(OH)$_2$D$_3$ as therapeutic agents in several metabolic bone disorders. However, the relationship between active vitamin D and its metabolites and calcified tissue components is complex and redundant. Hence a thorough understanding of the role vitamin D plays in the bone remodeling process (either directly or indirectly) is extremely important. In turn, complete delineation of the physiologic role of vitamin D in mineral homeostasis illustrates why vitamin D deficiency, especially in the elderly, is now being recognized as a major public health issue.

This chapter focuses on the role of vitamin D in skeletal remodeling, its relationship to osteoporosis/osteomalacia, and the utility of vitamin D analogs as therapeutic modalities for various metabolic bone diseases.

2. BONE REMODELING AND ITS RELATIONSHIP TO VITAMIN D HOMEOSTASIS

2.1. Physiology of Remodeling: The Bone Multicellular Unit

The adult skeleton is not static but rather undergoes dynamic renewal in a process commonly known as remodeling or turnover. During this carefully orchestrated process, bone dissolution or resorption is followed by new bone formation (1). At the end of this process, the quantum of bone, which is resorbed, is matched by newly deposited bone
matrix. In general, the remodeling cycle takes between 100 and 130 d, and this process permits mechanical competence to be maintained and calcium homeostasis to be preserved.

Remodeling is controlled by various hormonal and skeletal factors that influence the behavior of the basic multicellular unit (BMU), the basic functional unit of bone turnover. The BMU is composed of three types of cells, the osteoclast, the osteoblast (OB), and the osteocyte. Each has a defined role in remodeling and each has unique regulatory circuits that control activity during active skeletal turnover.

OBs are bone-forming cells that are derived from progenitor cells of mesenchymal origin (2). These mononucleated cells serve to synthesize and secrete collagen and proteoglycan complexes that constitute osteoid and also play a major role in matrix mineralization (3). OBs may also regulate ionic channels and movement of cations/anions in and out of bone fluid (2,3). In addition, mature OBs secrete several protein products that may be critical to the process of mature bone formation; these include osteocalcin (bone gla protein) and alkaline phosphatase (4). OBs form a layer of cells that cover bone surfaces and lay down matrix in humans at a rate of approx 100 μm²/d of matrix volume/d (5).

Fully differentiated and premature OBs are regulated by two major calcitropic hormones [PTH and 1,25(OH)₂D₃], systemic mediators (growth hormone, insulin, thyroxine, glucocorticoids and sex steroids), and skeletal growth factors (e.g., insulin-like growth factor-I, prostaglandins, transforming growth factor-β, several cytokines). Each of these is involved in a cascade of events that initiate and propagate bone formation. Several key skeletal growth factors are also regulated by calcitropic hormones.

Osteoblasts are terminally differentiated (2). Once these cells lay down new bone, the OB can undergo apoptosis or bury itself within skeletal matrix and become another cell, the osteocyte. The osteocyte maintains cytoplasmic and vascular connections with osteoblasts on the surface of bone (6). Although it appears inert by microscopic analysis, the osteocyte serves two roles: (1) as a transducer for mechanical loading; and (2) to modulate minute to minute exchange of minerals within the matrix (6,7).

Osteoclasts are large multinucleated giant cells that arise from hematopoietic stem cells in the bone marrow (8). These cells are responsible for bone resorption through four major mechanisms: carbonic anhydrase production, proton secretion by the osteoclast, calcium-dependent adenosine triphosphatase activity, and the sodium/potassium pump (9). As might be predicted, osteoclastic activity is also tightly regulated by 1,25(OH)₂D₃, PTH, and calcitonin. The recruitment and differentiation of premature osteoclasts from stem cells are also under the control of hematopoietic growth factors including granulocyte/macrophage colony-stimulating factor (GM-CSF) and several interleukins (10). These peptides are released by osteoblasts during initial activation of the remodeling cycle. In contrast to the deliberate and orchestrated process of bone formation, which is completed in 2.5–3 mo, bone resorption can be accomplished in 2–5 d (1).

The remodeling cycle begins when osteoblasts are activated; this in turn leads to the release of osteoclast-activating substances that accelerate recruitment and differentiation of osteoclast precursor cells. During bone resorption, growth factors that activate and recruit surface osteoblasts are released from the skeletal matrix. This permits coupling between these two distinct processes. The cycle is finished when bone formation and matrix maturation is complete. Calcitropic hormones act at every point in the remodeling cycle through all three cell types. In fact, 1,25(OH)₂D₃ is a major regulator of bone turnover, and its effects are profound in both physiologic and pathologic states.