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Vitamin D signaling in calcium and bone homeostasis: A delicate balance

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Loss-of-function mutations in genes involved in the vitamin D/vitamin D receptor system have clearly evidenced its critical role for mineral and skeletal homeostasis. Adequate levels of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the active form of vitamin D are therefore required and depend on sufficient sunlight exposure or dietary intake. Intestinal calcium absorption is a primary target of 1,25$(OH)_2$D action and this pathway indirectly promotes calcium incorporation in bone. Severe vitamin D deficiency may thus decrease bone quality and leads to osteomalacia, whereas less severe deficiency increases the risk of osteoporosis and bone fractures. On the other hand, high vitamin D levels together with low dietary calcium intake will increase bone resorption and decrease bone mineralization in order to maintain normal serum calcium levels. Appropriate dietary calcium intake and sufficient serum vitamin D levels are thus important for skeletal health. Dosing of calcium and vitamin D supplements is still debated and requires further investigation.

Introduction

Nearly a century ago it was found that vitamin D can be obtained by photosynthesis in the skin or by dietary intake. After being metabolized to its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], exerts

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its genomic actions by binding and activating a nuclear transcription factor, the vitamin D receptor (VDR) [1]. Inactivating mutations in the VDR leads in humans and mice to rickets, characterized by hypocalcemia, secondary hyperparathyroidism, high levels of $1,25(OH)_2D$, hypophosphatemia and a rachitic bone phenotype [2,3]. Typical for the bone phenotype is the enlargement of the growth plates and the decrease in calcium incorporation in the bone matrix, resulting in reduced bone quality. Nutritional rickets, caused by vitamin D deficiency is still endemic in several parts of the world [4,5], but can be prevented completely by vitamin D supplementation. Because vitamin D deficiency frequently occurs in the elderly and is associated with fractures, vitamin D supplementation is also recommended in these individuals [6]. However, several issues are still heavily debated including the dosage of vitamin D supplementation and which subjects require treatment. A possible explanation for the discussion is that the direct role of vitamin D signaling in calcium handling tissues, especially in bone, is not yet fully elucidated. We will first discuss mechanistic insights obtained in transgenic mouse models that help understanding how vitamin D action in different tissues contributes to calcium homeostasis. In the second part, current data from observational studies and randomized controlled trials will be discussed with regard to vitamin D supplementation of different age groups.

Mechanistic insight obtained from transgenic mouse models

VDR signaling and intestinal calcium transport

VDR is a major regulator of intestinal calcium absorption

In order to maintain normal serum calcium levels, calcium is absorbed in the intestine and reabsorbed in the kidney depending on the body's needs. Whenever intestinal and renal calcium fluxes are insufficient to effectively adjust serum calcium levels, the bone will serve as an additional pool of calcium during this negative calcium balance. $1,25(OH)_2D$ is considered as the primary factor to regulate intestinal calcium transport [7] (Fig. 1). Consistent herewith, adult mice that lack the *Vdr* display reduced intestinal calcium absorption [8,9]. Also mice with specific deletion of the *Vdr* in the intestine show a comparable decrease in calcium absorption [10]. The importance of this $1,25(OH)_2D$-mediated intestinal calcium absorption for calcium and bone homeostasis has been evidenced by several studies. Indeed, the hypocalcemia and bone phenotype of *Vdr* null mice are rescued when the VDR is reintroduced exclusively in the intestine [11] or when these mice are given a high calcium/high lactose diet [12,13]. A similar phenotype is observed in mice with inactivation of *Cyp27b1*, the enzyme that produces $1,25(OH)_2D$ [14,15]. In relation with the rescue diet, the high calcium and lactose content of mother's milk may explain why the mineral and bone phenotype of *Vdr* null mice only develops after weaning [13,15,16]. On the other hand, intestinal-specific *Vdr* null mice preserve normal serum calcium levels, despite reduced intestinal calcium absorption, because calcium is mobilized from the bone [10] (Fig. 2). These findings highlight that adequate intestinal calcium absorption is required to acquire and preserve bone mass and bone quality.

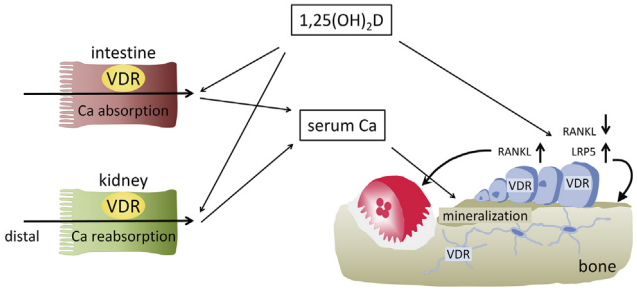

Fig. 1. Model of normal calcium balance: normal serum $1,25(OH)_2D$ levels promote intestinal calcium absorption, when dietary calcium supply is low-normal to normal, and stimulate renal calcium reabsorption in the distal tubules. These pathways deliver sufficient calcium for adequate bone matrix mineralization. VDR signaling in osteoprogenitors increases RANKL expression and stimulates osteoclastogenesis, whereas VDR action in mature osteoblasts has anti-catabolic actions, by decreasing RANKL, and anabolic activity by increasing LRP5 expression.