

REVIEW

Osteoporosis and the role of vitamin D and calcium—vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency

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Introduction

The skeleton consists of cortical bone (70–80%) and trabecular bone (20–30%). In the normal axial skeleton, about 25% of the anatomic bone volume is specific bone tissue and 75% bone marrow and fat, but this varies widely between different parts of the skeleton. Of the specific bone tissue, only 60% is bone mineral and 40% is organic matter, mainly collagen. Bone marrow consists of a stroma, myeloid tissue, fat cells, blood vessels, sinusoids and some lymphatic tissue. The yellow marrow contains mainly fat cells and the red marrow mainly erythropoietic tissue elements. With advancing age, the proportion of red marrow decreases as red marrow is replaced with yellow marrow, although at any age, the proportion of yellow and red marrow varies with the skeletal site.

Bone tissue is a complex, metabolically active organ of which the bone mineral is composed essentially of calcium and phosphate salts. These salts account for about two-thirds of the total dry weight of bone and most of total body calcium and phosphate. They are essential for normal skeletal growth, the maintenance of skeletal mechanical integrity and as a pool for the extracellular calcium compartment. The body contains about 1000 g (2500 mmol) of calcium, of which 9 g (225 mmol) is in the soft tissues, 1 g (25 mmol) in the extracellular fluid compartment and the remainder in bone.

The parathyroid hormone–vitamin D axis

The homeostasis of extracellular ionized plasma calcium (ECF-Ca^{2+}) is tightly regulated by a number

of hormones, of which parathyroid hormone and vitamin D play a major role (Figure 1). Vitamin D is derived from plant (vitamin D₂; ergocalciferol) and animal sources (vitamin D₃; cholecalciferol) in the diet and synthesized in the skin (vitamin D₃) by ultraviolet radiation of 7-dehydrocholesterol. Vitamin D₂ and vitamin D₃ are biologically interchangeable although they differ in their rates of metabolism.

Vitamin D (D₃ and D₂ collectively) is transported to the liver, bound to a specific α -globulin (vitamin D-binding protein) and to a small extent albumin and lipoproteins. It is hydroxylated to 25-hydroxylated vitamin D—25(OH)D; calcidiol—which is the major circulating vitamin D metabolite in the body. This passes to the kidney where it is further hydroxylated by 1 α -hydroxylase to form 1,25-dihydroxy vitamin D—1,25(OH)₂D. This is the active metabolite and increases ECF-Ca^{2+} by increasing calcium and phosphate absorption from the gut and mobilizing calcium from bone.

Parathyroid hormone is synthesized by the parathyroid gland and maintains the short-term homeostasis of ECF-Ca^{2+} through its effects on the kidney (increased calcium re-absorption) and mobilization of calcium from the labile bone pool. A more sustained response is produced through the regulation of the renal production of 1,25(OH)₂D [1]. Parathyroid hormone is the major regulator of 1,25(OH)₂D production, although serum calcium and serum phosphate also affect its production.

Vitamin D and skeletal pathophysiology

The mechanical integrity and structure of skeleton is maintained by the constant remodelling of bone which

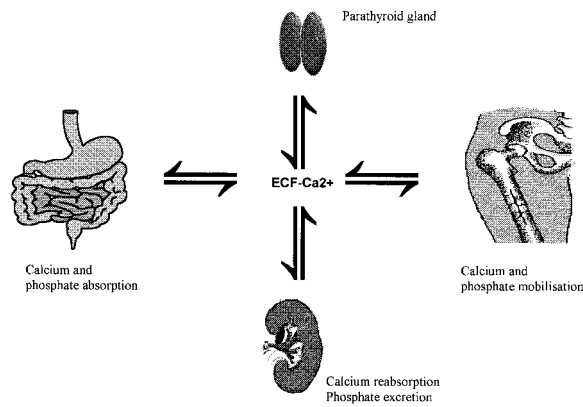


Figure 1. The parathyroid hormone-vitamin D axis.

responds to the normal physiological and pathological skeletal stresses of daily living. The required intakes of calcium and vitamin D increase with age, which unfortunately, these increased levels are seldom achieved.

Vitamin D deficiency and insufficiency

The major causes of vitamin D deficiency are poor nutrition, deprivation of sunlight, consequent decline in the synthesis of cutaneous vitamin D₃ and decreased renal hydroxylation of 25(OH)D by the ageing kidney [2–4].

Long-lasting and severe vitamin D deficiency leads in adults to osteomalacia and in children to rickets (a bone disorder characterized by typical biochemical and bone abnormalities), along with defective mineralization, severe secondary hyperparathyroidism, hypocalcaemia, hypophosphataemia and an increase in total alkaline phosphatase. Vitamin D deficiency can be confirmed by measuring 25(OH)D levels which are usually very low and often undetectable. The prevalence is high in the institutionalized and housebound elderly population [5, 6].

Vitamin D insufficiency (subclinical vitamin D deficiency) is increasingly being recognized as a distinct pathological entity. In contrast to vitamin D deficiency, it is characterized by mild secondary hyperparathyroidism, normocalcaemia and normal bone mineralization. The initial fall in ionized plasma calcium stimulates parathyroid hormone secretion, which in turn stimulates renal 1 α -hydroxylase and increases 1,25(OH)₂D production. This restores serum calcium to the normal set-point for that individual [7], but at the expense of increased bone turnover, and prevents the emergence of osteomalacia [8, 9].

The increase in 1,25(OH)₂D in response to the parathyroid hormone stimulus in vitamin D deficiency has nevertheless been found to be inappropriate and remains within the mid-low normal laboratory reference range [10, 11]. This may be partly related to the degree of substrate [25(OH)D] deficiency and possibly

impaired 1 α -hydroxylation of the ageing kidney, despite normal renal function [12]. Vitamin insufficiency is common in adults and in older people living at home. Chapuy and co-workers [13] found that 39% of healthy ambulatory elderly women recruited from the general community in France had a 25(OH)D level of <12 ng/ml. In a further study, they investigated the vitamin D status of a middle-aged general adult urban population (aged 45–65 years) and found that 14% had a 25(OH)D level of <12 ng/ml [14].

Untreated, vitamin D insufficiency progresses to bone loss and thus increased risk of fracture, but this is further compounded with ageing. Peak bone mass is achieved around the age of 20–30 years, followed by a period of consolidation and then an age-related decline in osteoblastic function, leading to an excess of bone resorption over formation and consequent bone loss. Peak bone mass and rate of bone loss are important in the development of osteoporosis. However when there is vitamin D insufficiency, bone resorption is amplified, further increasing fracture risk. This pathophysiological process has been recognized in patients presenting with osteoporotic hip fractures and occurs also in fit elderly people with established vertebral osteoporosis [15], which encompasses most osteoporotic patients presenting to doctors.

The threshold serum concentration of 25(OH)D that defines vitamin D insufficiency has been the subject of much research over the last few years. An early sign of vitamin D insufficiency is the secondary increase in serum parathyroid hormone, which may still be within the 'upper normal range' [16, 17]. A recent study has shown a parathyroid hormone threshold effect when serum 25(OH)D was ≤ 31 ng/ml [14]. The recommended diagnostic threshold and relationship to bone turnover markers and bone mineral density of the three vitamin D subgroups are shown in Table 1 [18].

Therapeutic intervention

Calcium therapy

In adults, calcium supplementation reduces the rate of age-related bone loss [19]. A review of 20 prospective studies concluded that calcium supplementation reduced bone loss on average by about 1% per year in postmenopausal women [20]. The effect of calcium in reducing the incidence of fractures has, however, been inconsistent. Recker *et al.* [21] found that 1200 mg of calcium daily reduced the incidence of vertebral fractures in women with low calcium intakes and with one or more vertebral fracture, but did not reduce the risk of the first vertebral fracture. In contrast, Chevalley *et al.* [22] observed a marked reduction in the incidence of first vertebral fracture with calcium supplementation, although all patients were vitamin D-replete. Fewer studies

Table 1. The relationship of the biochemical indices, bone turnover and bone mineral density in vitamin D deficiency, insufficiency and sufficiency

	Deficiency	Insufficiency	Sufficiency
25(OH)D, ng/ml	0–5	5–30	>30
Parathyroid hormone	High	High normal	Normal
1,25(OH) ₂ D	Low/normal	Low normal	Normal
Bone turnover	High	High normal	Normal
Bone	Osteomalacia/low bone mass	Low bone mass	Normal

25(OH)D, 25-hydroxylated vitamin D (calcidiol); 1,25(OH)₂D, 1,25-dihydroxy vitamin D.

have examined the relationship between calcium and hip fracture risk, and these have produced conflicting results [23, 24]. No studies have evaluated the effects of calcium to reduce the risk of a second hip fracture in vitamin D-insufficient subjects.

Vitamin D therapy

Lips *et al.* [25] and Ooms *et al.* [26] have shown that daily supplementation with small doses of vitamin D₂ or vitamin D₃ (10–20 µg/day) can reduce the secondary hyperparathyroidism induced by vitamin D insufficiency and increase bone mineral density, but there have been no prospective randomized controlled trials to evaluate the effect on vertebral fracture rates. Studies on hip fracture reduction, as with calcium, have produced conflicting results. Lips *et al.* [27] showed that 400 IU vitamin D daily for three and a half years had no effect on reducing hip fractures and, although most subjects were vitamin D-replete, further sub-analysis on the vitamin D-deficient patients similarly showed no significant reduction in hip fracture rate. In contrast, Heikinheimo *et al.* [28] showed that vitamin D given annually by intramuscular injection (300 000 IU) resulted in a decrease in non-vertebral fractures, although sub-analysis only showed a statistically significant reduction in upper limb but not hip fractures. No studies have evaluated the effect of vitamin D in the reduction of second hip fracture in patients with vitamin D insufficiency.

Combination vitamin D and calcium

The use of combination vitamin D and calcium therapy has nevertheless shown a consistent reduction in non-vertebral fractures. Chapuy *et al.* [29] showed that supplementation with 1.2 g calcium and 800 IU vitamin D₃ over 18 months resulted in a 43% reduction in hip fractures and a 32% reduction in the total number of non-vertebral fractures in institutionalized, vitamin D-insufficient elderly women compared with the placebo group, with a mean reduction of 47% in secondary hyperparathyroidism. Previous osteoporotic fractures were present in some of these patients, but sub-analysis of prevalent fractures and the reduction in

second fractures was not carried out. Dawson-Hughes and co-workers' study of patients over the age of 65 years living at home showed that treatment for 3 years with 500 mg of calcium plus 700 IU of vitamin D₃ increased bone mineral density at both hip and spine [30]. The reduction of non-vertebral fractures was of a similar magnitude to that in Chapuy and co-workers' study, but the absolute numbers of fractures in the study were small. In this study it was unclear what proportion of patients were vitamin D-insufficient, although there was a 33% mean reduction in parathyroid hormone.

Conclusion

Vitamin D and calcium are important in the mechanical and structural integrity of the skeleton. Subclinical vitamin D deficiency (vitamin D insufficiency) is common in the fit, active elderly population and leads to an amplification of age-related bone turnover, bone loss and thus increased risk of fracture, mediated by secondary hyperparathyroidism. Daily supplementation with vitamin D can reduce the secondary hyperparathyroidism and increase bone marrow density but only combination calcium and vitamin D therapy has been shown to be effective in reducing non-vertebral fractures.

Key points

- Vitamin D and calcium are important in the mechanical and structural integrity of the skeleton.
- Subclinical vitamin D deficiency (vitamin D insufficiency) is common in the fit, active elderly population and leads to an amplification of age-related bone turnover, bone loss and thus increased risk of fracture, mediated by secondary hyperparathyroidism.
- Daily supplementation with vitamin D can reduce the secondary hyperparathyroidism and increase bone marrow density but only combination calcium and vitamin D therapy has been shown to be effective in reducing non-vertebral fractures.

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