Vitamin D Effect on Bone Mineral Density and Fractures

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KEYWORDS

• Vitamin D • Osteoporosis • Osteomalacia • Calcium • Fracture • Bone density

KEY POINTS

- Vitamin D was identified as the cause and cure of osteomalacia.
- Vitamin D influences skeletal mineralization principally through the regulation of intestinal calcium absorption.
- Meta-analyses of vitamin D trials show no effects on bone density or fracture risk when the baseline 25-hydroxyvitamin D is greater than 40 nmol/L.
- Provision of vitamin D supplements to those at risk of 25-hydroxyvitamin D levels less than 40 nmol/L is supported by current evidence, but untargeted supplementation is not.
- A daily dose of 400 to 800 IU vitamin D_3 is usually adequate.

INTRODUCTION

Although the syndrome of rickets has been recognized for hundreds of years, the role of vitamin D in its genesis and treatment was only documented in the early twentieth century, when both sunlight exposure and cod liver oil supplements were found to be curative.[1] These discoveries suggested that vitamin D was good for bone, and it has been regarded by some as a skeletal tonic since that time. However, more recent investigations have demonstrated that this is an oversimplification, and that the primary role of the vitamin D endocrine system is to maintain normocalcemia and normophosphatemia, thus permitting normal skeletal mineralization. The principal way in which vitamin D does this is through regulation of intestinal absorption of these minerals.

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The most striking abnormality in vitamin D receptor (VDR) knockout mice is the presence of osteomalacia.[2] This osteomalacia can be reversed either by provision of high intakes of calcium and phosphate sufficient to normalize serum concentrations[3] or by the selective expression of the VDR in enterocytes alone.[4,5] These findings are complemented by the demonstration that selective knockout of VDR in enterocytes reproduces the skeletal abnormalities seen in the systemic knockout.[6] Thus, enterocytic VDR expression is necessary and adequate to maintain normal skeletal mineralization.

VDR is expressed in bone, mainly in osteoblasts and osteocytes, where its main role is to stimulate bone resorption, consistent with the function of the vitamin D endocrine system in the maintenance of circulating calcium levels. VDR in osteoblastic cells does this by regulating RANKL and osteoprotegerin to promote osteoclastogenesis.[7,8] Selective knockout of VDR in bone results in increases in bone mass.[6,8,9] These findings are corroborated by a study in which femora from either wild-type or VDR knockout mice were transplanted into normal mice.[9] VDR-knockout bone in a wild-type environment had a 40% higher bone mineral density (BMD) than the wild-type bone in the same environment. Further corroboration comes from human studies showing that single large doses of vitamin D increase bone resorption markers,[10–12] that vitamin D intoxication is associated with sustained increases in bone resorption,[13] and that correction of vitamin D intoxication is associated with increases in BMD.[14] A second direct effect of vitamin D on bone is to increase local pyrophosphate levels resulting in inhibition of mineralization.[6] This vitamin D effect is also consistent with vitamin D being a procalcemic factor rather than a direct stimulator of bone growth and mineralization, as many clinicians have tended to regard it. The finding that high levels of vitamin D or its metabolites can increase bone resorption and impair mineralization suggests that incautious use of vitamin D or its metabolites could adversely affect bone, and there are studies of high-dose calciferol or vitamin D metabolites that show increased bone loss[15] or fractures.[16,17]

WHAT IS VITAMIN D DEFICIENCY?

Profound loss of vitamin D signaling results in hypocalcemia and osteomalacia. Partial loss of signaling (eg, from vitamin D deficiency) stimulates parathyroid hormone (PTH) secretion leading to increased bone resorption and increased renal retention of calcium, but with maintenance of serum calcium levels within the normal range. In this situation, bone mineralization is maintained, but at the expense of bone mass. Preventing such secondary hyperparathyroidism is the principal rationale for using vitamin D in the management of osteoporosis. Interestingly, many individuals with markedly reduced levels of 25-hydroxyvitamin D (eg, <25 nmol/L) do not develop secondary hyperparathyroidism,[18,19] for reasons that are unclear. Arabi and colleagues[20] have demonstrated that accelerated loss of BMD is only observed in vitamin D–deficient older adults who also have secondary hyperparathyroidism, and Sayed-Hassan and colleagues[19] report that BMD is not related to 25-hydroxyvitamin D in a D-deficient cohort, but is related to PTH. Similarly, in a bone biopsy study of sudden death subjects, at serum 25OHD levels less than 12 ng/mL (30 nmol/L), more than half of the population studied failed to demonstrate osteoid accumulation, indicating that factors other than low 25OHD contribute to osteomalacia.[21] Thus, many individuals do not appear to suffer adverse effects from levels of 25-hydroxyvitamin D that are associated with bone loss or undermineralization in others. Whether this is related to their diet (eg, intake of calcium or of calcium binders such as phytates) or to other factors (such as the efficiency of renal calcium conservation) is unclear. This variability between individuals may contribute to the variability seen in the outcomes of trials of vitamin D as an intervention.