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Invited critical review

Vitamin D activities and metabolic bone disease

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ABSTRACT

Vitamin D activity requires an adequate vitamin D status as indicated by the serum level of 25-hydroxyvitamin D and appropriate expression of genes coding for vitamin D receptor and 25-hydroxyvitamin D 1α-hydroxylase, the enzyme which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Vitamin D deficiency contributes to the aetiology of osteomalacia and osteoporosis. The key element of osteomalacia, or rickets in children, is a delay in mineralization. It can be resolved by normalisation of plasma calcium and phosphate homeostasis independently of vitamin D activity. The well characterised endocrine pathway of vitamin D metabolism generates plasma 1,25-dihydroxyvitamin D and these endocrine activities are solely responsible for vitamin D regulating plasma calcium and phosphate homeostasis and protection against osteomalacia. In contrast, a large body of clinical data indicate that an adequate serum 25-hydroxyvitamin D level improves bone mineral density protecting against osteoporosis and reducing fracture risk. Recent research demonstrates that the three major bone cell types have the capability to metabolise 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D to activate the vitamin D receptor and modulate gene expression. Dietary calcium intake interacts with vitamin D metabolism at both the renal and bone tissue levels to direct either a catabolic action on bone through the endocrine system when calcium intake is inadequate or an anabolic action through a bone autocrine or paracrine system when calcium intake is sufficient.

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1. Introduction

Osteoporosis is a debilitating metabolic bone disease that weakens the architecture of bone and decreases bone mass and strength resulting in an increase in the risk of fracture. Many factors may contribute to the pathogenesis of osteoporosis but the net result on bone is the same: there is a disturbance to the remodelling process that results in increased bone resorption and/or decreased bone formation. This process disrupts bone microarchitecture resulting in an increased susceptibility to fracture, which is associated with significant morbidity and mortality and places a major burden on health care systems.

Treatment modalities include anti-resorptive therapies such as bisphosphonates, selective oestrogen receptor modulators, hormone replacement therapy or anabolic therapies including strontium ranelate and teriparatide (parathyroid hormone). Dietary vitamin D and calcium supplementation is often considered as adjunct therapy for treating established osteoporosis or as a strategy to prevent its development. An unresolved question with regard to vitamin D supplementation remains over the critical level of serum 25-hydroxyvitamin D_3 (25D) required to adequately reduce the incidence of osteoporotic fractures. For

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the clinical laboratory handling increased numbers of requests for assays of serum 25D, assessment of vitamin D status for the elderly in relation to osteoporosis and risk of fracture is critical for optimal clinical care. The clinical benefits of vitamin D supplementation to correct vitamin D deficiency have been best demonstrated in this field. In contrast, the evidence base for the benefits of an adequate vitamin D status for risk of other diseases is weak. Such evidence largely arises from population studies demonstrating a simple association between increased risk of disease and a low serum 25D level [1].

Recent analysis indicates a dose response for vitamin D supplements with the highest dose (800 to 2000 IU vitamin D/day) demonstrating a 30% reduction in the risk of hip fracture and 14% reduction in the risk of any nonvertebral fracture in the elderly [2]. This evidence has been strengthened by re-analysis of data from the Women's Health Initiative clinical trial indicating a similar reduction in the risk of hip fracture in postmenopausal women aged 50 to 79 years taking a daily supplement of 400 IU vitamin D3 and 1000 mg calcium daily [3]. However, the significance of vitamin D in the prevention and treatment of osteoporosis remains controversial and its role in maintenance of bone health is yet to be fully explicated. Seminal discoveries that the three major bone cell types express both the vitamin D receptor (VDR) [4], and the 25-hydroxyvitamin D_3 1α-hydroxylase (CYP27B1) enzyme [5–7] which converts 25D to the biologically active metabolite 1,25-dihydroxyvitamin D (1,25D) [8], raised the notion that vitamin D may exert autocrine or paracrine activities within bone tissue.

Vitamin D deficiency and insufficiency are increasingly recognised in most communities, and coupled with an ageing population, it is important to review the effects of vitamin D activities on bone health, particularly in relation to osteoporosis and fracture risk. This information is critical for clinical laboratories to optimise their service to clinicians and their patients.

2. Vitamin D deficiency: a cause of rickets

It has been known since the early 1900s that severe vitamin D deficiency results in the metabolic bone disease rickets (in children), or osteomalacia (in adults) [9]. The 21st century has revealed links between vitamin D deficiency and a wide range of pathologies including osteoporosis (also a metabolic bone disease), cardiovascular disease, depression, inflammation and immunity, respiratory infections, arthritis, gastrointestinal tract conditions and other pathologies (reviewed in Ref. [10]). Clinical guidelines to define levels of serum 25D defining an adequate vitamin D status are controversial. The prestigious Institute of Medicine (IOM) report recommended vitamin D adequacy at a serum level of greater than 50 nmol/L for the population [11]. Others have recommended vitamin D sufficiency for individual patients at a serum 25D level of greater than 75 nmol/L with vitamin D insufficiency at serum 25D levels between 20 and 75 nmol/L and vitamin D deficiency at levels less than 20 nmol/L [12]. Importantly, it is the serum level of 25D, as opposed to the serum 1,25D level, that determines vitamin D status and that correlates with a range of clinical outcomes including risk of osteoporotic fracture [1].

When serum levels of 25D are deficient, insufficient substrate is available for the renal 25-hydroxyvitamin D3 1α-hydroxylase (CYP27B1) enzyme to generate adequate serum 1,25D, the biologically active form of vitamin D. The major activities of serum 1,25D are to maintain plasma calcium and phosphate homeostasis [13]. The kidney is capable of markedly up-regulating expression of CYP27B1 by some 40-fold under the influence of the calciotropic hormone parathyroid hormone (PTH) and hypocalcemia [14]. The marked up-regulation of CYP27B1 enzyme levels in the kidney under such conditions allows for continued production of 1,25D at lower levels of 25D substrate. Clinical data [15] and rodent model data [16] indicate that under these conditions adequate serum 1,25D levels can be maintained with serum 25D levels of 20 nmol/L or greater. Under these conditions serum 1,25D is adequate to maintain intestinal calcium absorption [15] as well as to act at the kidneys to maximise renal tubular reabsorption of calcium and to act on bone to stimulate calcium and phosphate flow into the plasma pool by stimulating bone resorption.

When serum 25D levels fall below 20 nmol/L substrate levels for the kidney CYP27B1 are limiting and serum 1,25D levels fall with concomitant reduction in intestinal calcium absorption and presumably all of the endocrine activities of serum 1,25D. At these levels serum free (or ionised) calcium levels begin to fall markedly with concomitant marked increases in serum PTH levels [15]

3. Vitamin D depletion: a cause of osteoporosis

Significant clinical evidence indicates that vitamin D deficiency at a level less severe than that which causes osteomalacia contributes to osteoporosis as indicated by an increase in the risk of hip fracture in the elderly [17]. Meta-analyses of case-control studies conducted over some 30 years clearly demonstrate the strong association between a decreased serum 25D level and increased risk of hip fracture amongst the elderly [18]. It is intriguing that this relationship does not extend to serum 1,25D and hip fracture [19]. The causal relationship between a low vitamin D status and hip fracture has been established through the conduct of randomised, placebo-controlled clinical trials (RCTs) of vitamin D supplementation, usually in combination with a calcium supplement, to assess the effect on risk of fracture. Trials conducted by Chapuy et al. in 1992 and 2002 established evidence that vitamin D and calcium supplementation reduced the risk of hip and nonvertebral fractures in the elderly [20,21]. A subsequent trial showed that supplementation with both vitamin D and calcium can improve hip bone density, but an effect on risk of fracture was not detectable [22]. The quality of such trials has varied markedly particularly with regard to dose of vitamin D, compliance with the study treatment and interaction with dietary supplements that subjects were taking before the start of the trials and continued to take during the trial. Meta-analyses of the outcomes of RCTs have provided conflicting interpretations. However, when dose of vitamin D is considered and combined with meta-regression analysis, a significant benefit of vitamin D at a dosage between 800 and 2000 IU per day and calcium has been consistently established [2].

An intriguing issue arising from these studies is the fact that only the serum 25D level, the prohormone, relates to the development of osteoporosis and fracture risk rather than the level of serum 1,25D, the biologically active metabolite. Furthermore meta-analysis of fracture prevention trials when 1,25D was administered instead of vitamin D found no reduction in fracture risk [23]. These data are in contradistinction to the regulation of plasma calcium and phosphate homeostasis and the resolution of osteomalacia which demonstrate it is the serum 1,25D level which relates to these indices as discussed above. These observations have raised the question of the mechanism by which serum 25D modulates bone cell activities critical to the development of osteoporosis.

4. Local metabolism of vitamin D regulates bone turnover

The importance of serum 25D for skeletal health in humans is related to the ability of the bone cells to actively metabolise this prohormone. Mutations in the gene encoding the CYP27B1 enzyme ablates vitamin D activity through inadequate conversion of the substrate to its active form, resulting in the condition vitamin D dependent rickets type I (VDDR I). The multiplicity of abnormalities seen in this disease mimics those seen in hereditary vitamin-D resistant rickets (HVDRR) with 1,25D levels deficient or absent because of the lack of enzymatic conversion. A number of mutations have been found in the CYP27B1 gene including missense mutations, deletions, duplications and splice site mutations that are all linked to patients displaying an array of skeletal abnormalities [24].

Extra-renal synthesis of 1,25D plays a key role in the regulation of cell growth and differentiation at various sites of the body, including