



Editorial

Vitamin D and bone and beyond



This collection of 12 review articles is directed at but not limited to the impact of vitamin D on bone and mineral metabolism, selecting topics with relevance to clinical conditions involving vitamin D levels, metabolism, and therapeutic application. Each article is preceded by a clinical anecdote to highlight the relevance of the following discussion to the clinical situation being described. The goal of this collection is to illustrate the important role vitamin D plays in bone and mineral metabolism and how alterations in vitamin D levels and its subsequent metabolism can lead to disease.

The first three manuscripts document the global extent of vitamin D deficiency and discuss its management. Chakhtoura et al. (Chakhtoura, n.d.) discuss the prevalence of vitamin D deficiency in the Middle East and North Africa (MENA). They reviewed 41 observational studies and 14 randomized controlled trials (RCT). The extent of vitamin D deficiency, identified by the authors as < 20 ng/ml, ranged up to 96% in a number of studies, with mean values varying between 11 and 20 ng/ml. Conditions identified as predisposing to vitamin D deficiency included female gender, increased age, BMI, veiling, winter, lower socioeconomic status, and increased latitude. The RCTs tended to show that 1000–2000 IU vitamin D daily was required to maintain a level of 25 hydroxyvitamin D [25(OH)D] above 20 ng/ml. Outcome parameters included both skeletal and extraskeletal effects including diabetes mellitus. The review by Lips and de Jongh focused on vitamin D deficiency in immigrants, in particular non western individuals migrating into western countries (Lips, n.d.). Severe vitamin D deficiency, defined by the authors as < 20 nmol (8 ng/ml), existed in nearly 50% of such populations. Deficiency was attributed to darker pigmentation, substantial covering of the skin, consumption of diets that lack both vitamin D and calcium. The symptoms of vitamin D deficiency are well described and age dependent with occasional convulsions in infants due to the low calcium levels, flaring of wrists and knees in children with bowing of the legs, fatigue, muscle weakness, bone pain in older children and adults, who may also present with pseudofractures. Laboratory studies show low serum calcium and phosphate with high alkaline phosphatase levels. Treatment is with vitamin D and calcium, the amounts adjusted for age. The article by Thandrayen and Pettifor is directed at the roles of both vitamin D and calcium in nutritional rickets (Thandrayen, n.d.). Although vitamin D deficiency is generally considered the major cause of rickets, this article stresses the role of calcium deficiency as well. The description of rickets in this article is detailed and focused on the pediatric population who are prone to rickets

from lack of vitamin D and/or calcium with proper management requiring both dietary components. Calcium deficiency in the sub-Saharan African populations studied by the authors develops because of limited dairy products following weaning especially in the lower social economic groups along with diets rich in phytate cereals and/or green leafy vegetables with high oxalate content.

The next two chapters deal with the laboratory diagnosis of vitamin D deficiency. The article by Galior et al. discusses the 10 year experience at the Mayo Clinic assessing 25(OH)D levels by LC-MS/MS (Singh, n.d.). This article describes the use of LC-MS/MS in comparison with that of immunoassays, and provides the rationale for LC-MS/MS becoming the gold standard for measuring 25(OH)D in blood. Moreover, LC-MS/MS enables the measurement of multiple vitamin D metabolites in the same sample at the same time. The review describes the efforts to reduce variability in measurements between laboratories when used with standards such as those provided by the US National Bureau of Standards and Technology (NIST). The article by Bhan et al. discusses the use of bone biopsies and their histologic assessment for the diagnosis of osteomalacia (Rao, n.d.). Although this is an invasive procedure and not commonly done, when performed following dual labeling with fluorescent probes to measure dynamic changes in bone turnover, it is the most definitive means of making the diagnosis. An important point introduced by the authors is that osteomalacia is not always easy to diagnose and can be confused with other conditions including cancer. The authors discuss a number of causes of osteomalacia providing clear criteria for distinguishing osteomalacia due to vitamin D deficiency from that due to phosphate deficiency, although in many situations both are present.

Rickets and osteomalacia are not only caused by dietary insufficiency of calcium, phosphate, and vitamin D, but can be a consequence of other conditions. The article by Florenzano et al. discusses a unique type of tumor that secretes FGF23, the syndrome known as tumor induced osteomalacia (Collins, n.d.). FGF23 induces osteomalacia at least in part by increasing phosphate wasting by the kidney and limiting the renal production of 1,25 dihydroxyvitamin D (1,25(OH)2D). The authors describe a recent finding that a fibronectin and fibroblast growth factor receptor-1 (FGFR1) fusion gene is expressed in these tumors that may serve as a tumoral driver. These tumors are generally small and difficult to find. The article discusses both diagnosis, methods of localization, and treatment of these tumors. Corbeels et al. describe in their review what might be considered as an

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iatrogenic cause of bone disease, bariatric surgery, focusing on the alterations in calcium and vitamin D handling following such surgery (Corbeels, n.d.). Bariatric surgery leads to a reduction in calcium and vitamin D absorption generally with secondary hyperparathyroidism and subsequent bone loss, but other mechanisms may also contribute to the loss of bone and increased risk of fractures. These include weight reduction per se with decreased mechanical loading and loss of adipokines such as leptin and adiponectin. These and other potential mechanisms resulting in post surgical bone loss are reviewed in this article.

Alterations in vitamin D metabolism also impact bone and mineral homeostasis. Bikle et al. review the role of extra renal CYP27B1, the enzyme producing the active form of vitamin D, 1,25(OH)2D (Bikle, n.d.). Unlike the CYP27B1 in the kidney, extrarenal CYP27B1 is generally not regulated by PTH, calcium or 1,25(OH)2D. Rather in tissues such as keratinocytes and macrophages, CYP27B1 activity is stimulated by inflammatory cytokines such as tumor necrosis factor and interferon- γ . Thus a number of granulomatous diseases lead to increased 1,25(OH)2D production and hypercalcemia unchecked by the mechanisms that otherwise regulate 1,25(OH)2D production by the kidney. Moreover, extrarenal CYP27B1 is widely expressed in both normal and malignant tissues. This article reviews these locations and their potential biologic significance. The article by Schlingmann et al. reviews the consequences of CYP24A1 mutations as underlying a significant proportion of what had been referred to as cases of idiopathic infantile hypercalcemia (IIH) (Schlingmann, n.d.). CYP24A1 serves as degradative enzyme for 25(OH)D and 1,25(OH)2D, such that inactivating mutations in CYP24A1 lead to increased levels of the would suggest that IIH is a term now out of date with the finding of a least one cause of IIH and findings that such mutations are also found in adults presenting with hypercalcemia during pregnancy or frequent kidney stone formation.

Bone is not the only target of vitamin D. The review by Gunton and Girgis focuses on muscle (Gunton, n.d.). Muscle weakness is a well known symptom of vitamin D deficiency, but whether fully differentiated myocytes contain the vitamin D receptor, and so are direct targets of 1,25(OH)2D, remains controversial. However, this article provides evidence that it is. Moreover, this article provides a balanced and extensive review of the RCTs that have examined the impact of vitamin D supplementation on muscle function and falls as they reach the overall conclusion that although “vitamin D supplementation generally reduces the risk of falls in frail, older individuals (at doses > 700 IU d), dose-dependent effects have not been clearly established with the exception of a significantly *higher* risk of falls in subjects receiving single mega-doses”. Perwad focuses on the kidney with particular attention to the pathologic events disrupting bone and mineral homeostasis in patients with chronic kidney disease (CKD) (Perwad, n.d.). Although numerous disturbances to bone and mineral metabolism develop with the onset and progression of CKD, the roles of FGF23, PTH, and 1,25(OH)2D are high on the list. In this article Perwad reviews the key role that the kidney plays in vitamin D metabolism and calcium and phosphate handling, the regulation of such processes by

PTH and FGF23, how CKD disrupts these processes leading to bone disease and vascular calcification, and the difficulties in managing such patients.

Among the numerous biological tissues outside the musculoskeletal system that are potential targets for vitamin D, cancer ranks very high. Compelling animal and cellular studies in combination with a large number of epidemiologic studies indicate that vitamin D and/or its active metabolites and analogs should be useful therapy for a wide range of cancers. However, RCTs have in general not shown the expected beneficial effects seen in these animal and epidemiologic studies. The article by Trump discusses the mechanisms by which 1,25(OH)2D and analogs could block cancer development and reviews epidemiologic evidence for the cancer protective effects of vitamin D (Trump, n.d.). The article then discusses RTCs and what may have contributed to their lack of success. As an example Trump discusses the two trials by Novoclea using high dose calcitriol (1,25(OH)2D) as adjuvant therapy for prostate cancer that came to different conclusions regarding the efficacy of calcitriol, perhaps related to changes in trial design. The article provides recommendations for future RTCs with 1,25(OH)2D and its analogs.

We believe the reader will find these articles informative, and although not exhaustive, will provide illustrative examples of the role of vitamin D in modern medicine.

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