Moving Points in Nephrology

Vitamin D and Parathyroid Hormone in General Populations: Understandings in 2009 and Applications to Chronic Kidney Disease

Manraj Johal and Adeera Levin

Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada

Vitamin D is now recognized as an important prohormone in health and disease. Its role in immunoregulation and cardiovascular and bone health has become topical in the lay press and the medical press in the past 5 yr. The target audience for this review includes the interested clinician and researchers. The prevalence of chronic kidney disease in the general population has further increased the interest and perhaps the applicability of findings of population studies. The basic physiology of vitamin D and receptor activation and biologic importance is reviewed, as well as various vitamin D analogues and nomenclature. Issues related to measurement of vitamin D and parathyroid hormone have the potential to complicate the clinical use of these tests and should be understood by all clinicians so as to ensure informed decision making and stimulate interest in participation in clinical trials. The epidemiology of vitamin D deficiency and supplementation in association with health status and disease status is reviewed, and issues related to association *versus* causation are highlighted. Some recommendations for pragmatic approaches and study design are suggested.

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Vitamin D is an important prohormone and parathyroid hormone (PTH) an important hormones in both health and disease. In the past decade, there has been an increasing appreciation of the complexity and importance of their regulation and actions in both medical and lay press.

The purpose of this review is to update the nonexpert reader with respect to our current understanding of these prohormones/hormones in general populations, with some reference to those particularly with early chronic kidney disease (CKD). It is beyond the scope to give a comprehensive review of the biology of both hormones, but this has been done recently in an excellent review by Holick (1).

The thesis of this article is that the biologic effects of vitamin D and PTH are diverse and affect most organ systems, the epidemiology of deficiencies and excesses congruent with the known biology, and that those in the general population have abnormalities of both of these hormones that have similar consequences to those seen in populations with CKD. Associative studies have described disease states with deficiencies of vitamin D and improved patient outcomes with the use of vitamin D therapies. Unfortunately, as in much of medicine, there are limited randomized, controlled trials to guide clinicians as to best practices in the timing, dosing, and follow-up of administration of vitamin D. Nonetheless, improved understanding will come through the development of both mechanistic and treatment trials designed with sufficient rigor, informed by basic science and translational work ongoing in the field.

Vitamin D Nomenclature

In clinical practice, confusion remains regarding the various compounds known collectively as vitamin D. Table 1 describes the vitamin D_2 and D_3 compounds and their derivatives so as to ensure clarity. The products of vitamin D hydroxylation lead to 25-hydroxyvitamin D_2 [$25(OH)D_2$] and 25-hydroxyvitamin D_3 [$25(OH)D_3$], ercalcidiol and calcidiol, respectively, which are collectively referred to as 25-hydroxyvitamin D. The second hydroxylation of these compounds leads to the production of 1,25-dihydroxyvitamin D_2 [$1,25(OH)_2D_2$] and 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], ercalcitriol and calcitriol respectively, which are collectively referred to as 1,25-dihydroxyvitamin D (Table 1).

There are important differences between 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. 25-Hydroxyvitamin D has a long half-life (approximately 3 wk) and is the best measure of vitamin D status. No consensus in the literature defines the reference ranges for vitamin D insufficiency or vitamin D deficiency; however, according to current reference ranges and literature, clinicians have been alerted to the diagnosis of insufficiency when 25-hydroxyvitamin D levels fall below 30 ng/ml and of outright deficiency when levels fall below 15

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Correspondence: Dr. Adeera Levin, Department of Medicine, Division of Nephrology, University of British Columbia, St. Paul's Hospital, 1081 Burrard, Room 60101A, Vancouver BC, Canada V6Z 1Y8. Phone: 604-682-2344, ext. 62232; Fax: 604-806-8120; E-mail: alevin@providencehealth.bc.ca

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Table 1. Vitamin D nomenclature[a]

Parameter	D_2 and Derivatives	D_3 and Derivatives	Collective Terminology
Parent compound			
abbreviation	D_2	D_3	D
full term	Vitamin D_2	Vitamin D_3	Vitamin D
synonym	Ergocalciferol	Cholecalciferol	
Product of first hydroxylation			
abbreviation	25(OH)D_2	25(OH)D_3	25(OH)D
full term	25-Hydroxyvitamin D_2	25-Hydroxyvitamin D_3	25-Hydroxyvitamin D
synonym	Ercalcidiol	Calcidiol	
Product of second hydroxylation			
abbreviation	1,25(OH)2 D_2	1,25(OH)D_3	1,25(OH)D
full term	1,25-Dihydroxyvitamin D_2	1,25-Dihydroxyvitamin D_3	1,25-Dihydroxyvitamin D
synonym	Ercalcitriol	Calcitriol	

[a] Adapted from reference (5).

ng/ml. Serum levels of 25-hydroxyvitamin D reflect nutritional intake and endogenous synthesis; however, there is known seasonal, geographic, and ethnic variation in levels and accumulating data regarding age-related differences as well. None of the current reference ranges or definitions has taken these factors into consideration.

Calcitriol has a short half-life (4 to 6 h) and exists at circulating levels 1/1000 of those of 25-hydroxyvitamin D. Multiple factors affect the conversion of calcitriol from calcidiol by 25-hydroxyvitamin D-1 α hydroxylase enzyme. Although this predominantly occurs in the kidney, there is also a significant ability to convert calcidiol extrarenally. The renal conversion is regulated by PTH, estrogen, calcitonin, prolactin, calcium, and phosphate and is inhibited by its product calcitriol, fibroblast growth factor 23 (FGF-23) and metabolic acidosis. It is interesting that extrarenal conversion occurs in the skin, colon, prostate, macrophages, and other organs by mitochondrial 25-hydroxyvitamin D-1 α hydroxylase enzyme, although the regulatory processes for this conversion are not well understood.

PTH has a key role in calcium and phosphate homeostasis. It simulates the synthesis of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by activating the 25-hydroxyvitamin D-1 α hydroxylase enzyme and decreases the activity of 25-hydroxyvitamin D-24-hydroxylase (which inactivates 1,25-dihydroxyvitamin D). PTH indirectly modulates intestinal calcium absorption by stimulating the activation of 1,25-dihydroxyvitamin D synthesis, in addition to causing excretion of phosphate by the renal tubular cells. It has additional roles in terms of activation of cardiac myocytes and, hence, left ventricular hypertrophy (LVH) (2), as well as having vasoactive properties, including hypertension. It has also been implicated in the metabolic syndrome as a contributor to impaired glucose tolerance and dyslipidemia. Whether these latter effects are *via* relationship with vitamin D or independent is not clear.

Assay Variation and Measurement Issues

There is important and accumulating literature regarding variability in assays, especially as regards measurement of circulating levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and PTH. It is beyond the scope of this article to review these in detail; however, it is important and of significant consequence for clinical decision making to appreciate that there is between-laboratory and interassay variation of sufficient size (>35%) to be concerning. Souberbielle and others (3,4) have described this in detail. The implications for the diagnosis of hypovitaminosis D or hyperparathyroidism (and ultimately evaluation of response to therapy) are obvious when the variability is that great. Thus, clinicians are encouraged to understand which assay is being used, to know and understand the implications of change in assay. During this time of change and with increasing awareness of these issues, it is prudent to encourage patients to use the same laboratory for all measurements. These issues have been raised and explained in detail in the recent Kidney Disease: Improving Global Outcomes Chronic Kidney Disease related Mineral and Bone Disorders (KDIGO CKD MBD) guidelines (5).

There are a number of different assays for PTH, and these have evolved over time. Second-generation intact PTH assays are most common, and standardization and improvements in the assays are ongoing. There is a circadian rhythm to PTH secretion, which is individual and has been described in detail (6). Furthermore, a publication described the need to contextualize PTH normal ranges within the context of vitamin D status (7), especially as regards the elderly. The authors described nicely issues related to cutoff points contextualized to vitamin D status and demonstrated different potentially pathologic ranges on the basis of this approach. Specifically, the diagnosis of vitamin D deficiency is substantially lower when one takes into consideration concomitant PTH levels in those who are older than 65 yr.

Collection methods, processing, and assay type can also affect the measurement (8). Thus, again, the clinician is advised against making diagnoses on the basis of single values or decisions as to treatment changes on the basis of values obtained under different circumstances or from different laboratories using different assays.

The concept of interassay variation may also cause clinicians to question the range of values currently recognized as being indicative of abnormal vitamin D levels. The measurements of 25-hydroxyvitamin D and PTH may explain some inconsistent correlations of hormone levels and clinical outcomes.

It is possible that the current perspective of widespread vitamin D deficiency may be overemphasized or overinterpreted in the normal population, and, if so, then clinical decisions and vitamin D replacement may need to be more conservatively addressed. Alternatively, if indeed these are true deficiencies, then it may be that the presence of an isolated deficiency, without association of other biochemical or hormonal abnormalities, may not confer the same risk as a deficiency identified in association with other conditions. The presence of mitigating biologic processes (*e.g.*, receptor activation, receptor number) may be important in explaining the dissociation between the prevalence of deficiencies of vitamin D and disease incidence. It is difficult to imagine that if 50% of adolescents and 80 to 100% of community-living elderly can be classified as truly having vitamin D deficiency, then the levels have the same implications in all individuals. One would certainly expect a much higher incidence of disease than is currently seen.

Biology of Vitamin D and Vitamin D Receptor

During the past decade, the central importance of this hormone, the ubiquitous presence of the vitamin D receptor (VDR), and its role in various key regulatory processes has led to a plethora of studies in both basic and clinical sciences. For an excellent review of the current understanding of the area, the reader is referred to Holick (1).

Vitamin D deficiencies are associated with numerous problems: Osteoporosis and fractures, muscle strength, and falls and, most interesting, an association with cancer (9), autoimmune diseases, diabetes, and cardiovascular disease (CVD). The geographic distribution of cancer prevalence is clearly associated with geographic latitude and 25-hydroxyvitamin D levels/exposure to sunlight (10). Of note, some of this association has been found to be mediated through VDR genotype differences. A number of different genotypes that increase the risk for malignancies have been described (11,12). Publications have reviewed the association of various VDR genes with osteocalcin, PTH, and bone mineral density. There have been attempts to use calcitriol and other vitamin D analogs on tumor-derived endothelial cells and in the treatment of some cancers. The most success, however, has been seen in the treatment of psoriasis.

The role of vitamin D and VDR in inhibition of antigen cell maturation and function, smooth muscle cell proliferation (13), and inflammatory processes is becoming increasingly well described in animal and human studies. The modulation of matrix metalloproteinase 3 and C-reactive protein status implicates it in the process of vascular disease and athero- and arteriosclerosis (14). The important role of vitamin D in renin regulation and, hence, BP control, podocyte function, and proteinuria has been consistently shown.

General Populations, Common Conditions, and Association with Vitamin D Deficiencies

Numerous publications describe deficiencies in general populations, in association with latitude, age, and season. It is estimated that up to 40 to 75% of the general elderly population may have deficiency, and numerous authors have documented deficiencies in adolescent and prepubertal children and young adults of various backgrounds (15). It is interesting that irrespective of the laboratory diagnosis associated with levels <30 ng/ml is the finding that these deficiencies of vitamin D are associated with higher PTH levels and loss of muscle strength and muscle mass (13), bone mass, concentration, and cognitive impairment (16). In general populations, 1,25-dihydroxyvitamin D has been found to be inversely correlated with coronary calcification (17), and 25-hydroxyvitamin D levels predicted incidence of CVD events in the National Health and Nutrition Examination Survey (NHANES) cohort.

Renin and Vitamin D

There is conflicting information in general populations regarding vitamin D deficiency and hypertension. Resnick *et al.* (18) described an inverse relationship between serum renin and 1,25-dihydroxyvitamin D levels in patients with essential hypertension. This clinical finding is corroborated by a series of animal experiments that described stimulating of the renin-angiotensin-aldosterone system in knockout mice that lacked either VDR or 25-hydroxyvitamin D-1 α hydroxylase gene (19). More recently, Bodyak *et al.* (20) described LVH and hypertension in knockout mice, which can be reversed or salvaged with administration of vitamin D.

From a clinical perspective, Forman *et al.* (21) described in 2005 the results of a pooled analysis using three prospective cohorts from the general population: Two Nurse Health Study cohorts and Health professional follow-up study. They used a semiquantitative assessment of vitamin D intake using detailed dietary questionnaire and found no difference in BP according to imputed 25-hydroxyvitamin D levels. This is the only study not to find a difference at all and, given the method, may not be of relevance. It is interesting that there have been a few analyses of 25-hydroxyvitamin D levels in NHANES II, which described higher prevalence of hypertension and of albuminuria in a population-based cohort of 15,000 patients who were randomly selected from noninstitutionalized groups (22).

Does Vitamin D Supplementation Affect Outcomes?

The evidence that supplementation affects outcomes is variable and confusing. With respect to reducing bone fractures,

there have been numerous negative studies and some positive. Those that are positive all used dosages of vitamin D >700 IU/d, with a wide range (700 to 100,000 IU). Furthermore, in some studies, there was a reduction in fracture rate without reduction in mortality (23), whereas in others there was no change in fracture rate but improved muscle strength (tested as grip strength) and mobility, and reduced risk for falling has been described (24). In another negative study, the risk for cancer (the secondary outcome) was reduced in those who received vitamin D, although fractures (the primary outcome) was not (25).

In a small but well-conducted study that used three cohorts of patients Agarwal *et al.* (26) investigated the antiproteinuric effect of paracalcitol in patients with CKD. Patients had a range of GFR from 10 to 60, and results showed a significant reduction in proteinuria (as measured on dipstick) in the entire group according to use of vitamin D analogue, and that finding was seen as well in the subgroup of patients who were already receiving angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. This is interesting in light of congruence with animal models, effect on renin, podocyte function, *etc.*, all modulated through the VDR.

Additional Findings in General and High-Risk Populations

Population-based studies often include, either intentionally or unintentionally, those with impaired kidney function (CKD). In these populations, it is often interesting to determine the prevalence of abnormalities. The Kidney Early Evaluation Program (KEEP), run by the National Kidney Foundation, attracts people in the general population who are at risk for CKD (family history, history of hypertension, diabetes, or African descent) to be evaluated for CKD and associated anomalies. A recent publication (27) described >4000 patients with modest elevations of PTH. Importantly, the highest tertile of PTH was associated with prevalent CVD, as determined by history. The importance of these studies lies in the association of disease state and the relatively modest elevations of PTH. Unfortunately, 25-hydroxyvitamin D levels are not available for that cohort. In a similar vein, we described relatively early rises in PTH and decline in 1,25-dihydroxyvitamin D levels in a general population sample of 1814 patients (28). The population was distributed in the four geographic areas of the United States, samples were taken at the same time of the year (June through October), and all samples were analyzed in the same laboratory. Of note, 1,25-dihydroxyvitamin D levels seemed to decline at every tertile of GFR in those with estimated GFR ranging from 60 to 80 ml/min at baseline; the reduction in 1,25-dihydroxyvitamin D levels precedes the rise in PTH, which occurs at GFR of approximately 45 to 50 ml/min, long before any discernible change in phosphate or calcium can be detected (Figures 1 and 2). The prevalence of deficiency of the hormones (1,25-dihydroxyvitamin D and 25-hydroxyvitamin D) and excess of PTH, as defined conservatively according to laboratory values, is most apparent for 1,25-dihydroxyvitamin D and PTH, which seem to be a trend with the GFR; the changes in 25-hydroxyvitamin D levels do not seem prevalent until much lower GFR levels are reached (<30 ml/min). In a separate analysis of the same cohort, Gutierrez *et al.* (29) described that black individuals have more 25-hydroxyvitamin D deficiency than do white individuals at all levels of GFR. This is congruent with other information regarding race and lower 25-hydroxyvitamin D levels. In yet-unpublished data from the same cohort, we describe an association between low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels and higher urine albumin-to-creatinine ratio levels, as well as difference in IL-6 associated with lower levels of both hormones, which further suggests the potential relationship among inflammation, vitamin D deficiency, and albuminuria (30). Addi-

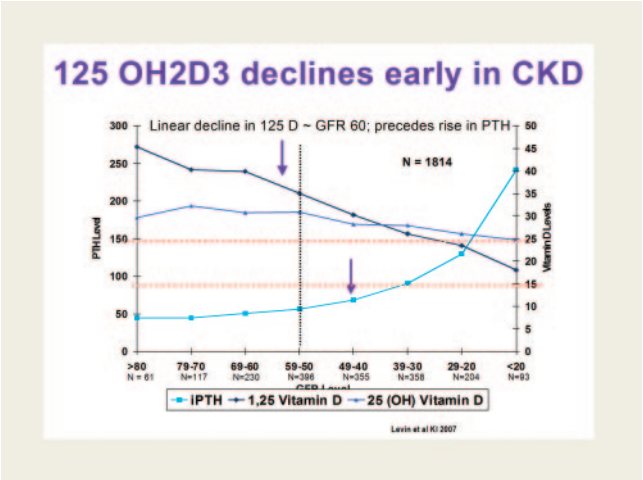

Figure 1. 1,25-Dihydroxyvitamin D has been shown to decline earlier in the progression of CKD, as early as GFR levels of approximately 60 to 80. It can also be seen that the decreasing levels of 1,25-dihydroxyvitamin D precede the increases in PTH. Adapted from reference (30).

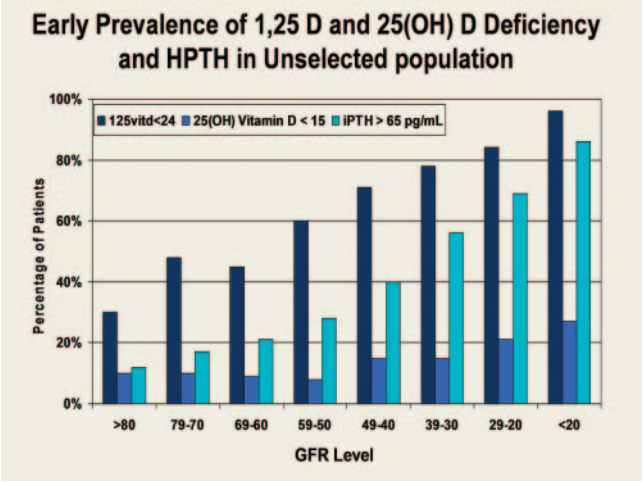

Figure 2. Prevalence of deficiencies of 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, and hyperparathyroidism (HPTH) in an unselected population. Note that the deficiencies of 1,25-dihydroxyvitamin and HPTH begin relatively early and increase linearly as GFR declines, whereas prevalence of 25-hydroxyvitamin deficiency remains constant over the range of GFR.

tional studies are obviously needed to assess whether vitamin D compounds ameliorate inflammation and albuminuria in CKD and, more general, the relationship between inflammatory cytokines and 25-hydroxyvitamin D levels.

Most recently, Ravani *et al.* (31) reported on 25-hydroxyvitamin D levels and patient outcomes in CKD. They evaluated 168 new referrals to nephrologists, followed them from 2 to 6 yr, and evaluated death or dialysis as major outcomes. Of note is the consistent relationship demonstrated between 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels, PTH, and levels of each of the vitamin D hormones. The levels of 25-hydroxyvitamin D predicted both kidney and patient survival, but the levels of 1,25-dihydroxyvitamin D did not. It may be that the number of patients was too small and levels of 1,25-dihydroxyvitamin D too variable to permit appropriate discrimination or that 1,25-dihydroxyvitamin D is simply not a good marker in this cohort. Using a VA database of those with GFR of approximately 34 ml/min, Shoben *et al.* (32) described 1418 patients with CKD and nephrology follow-up and demonstrated a calcitriol supplementation survival advantage.

To understand further the physiologic consequences of vitamin D deficiency in various at risk populations, we investigated the status of vitamin D and PTH and the relationship to arterial stiffness in three cohorts of patients: Two cardiac and one established CKD. Despite estimated GFR values in the cardiac group in the 54-ml/min range, there was an association of arterial stiffness, as measured by sphygmacor apparatus, with lower GFR, higher phosphate (within the normal range), and lower 1,25-dihydroxyvitamin D levels. 25-Hydroxyvitamin D levels were not different between the groups and did not correlate with stiffness (33). It is interesting that in the same group irrespective of GFR, those with LVH were more likely to have higher PTH levels.

Perspectives on Vitamin D and PTH in General Populations and Those with CKD

It seems from the basic animal and clinical data that vitamin D and PTH have important and complex roles in maintaining a variety of essential regulatory functions in health. Abnormalities of these prohormones/hormones in the general population are associated with immunoregulatory abnormalities, muscle and bone abnormalities, cognitive dysfunction, and cardiovascular effects. Moreover, the complexity of those interactions is even more interesting in an era when the role of FGF-23 and Klotho, as important modulators of aging processes, is evolving. It is beyond the scope of this article to review the fascinating story of FGF-23 and Klotho in relation to phosphate excretion, regulation of PTH and vitamin D syntheses, and health and disease. The current understanding includes that FGF-23 decreases PTH secretion and increases Klotho expression in PTH glands, that FGF-23 concentrations are elevated in dialysis patients, and that it seems to inhibit calcitriol synthesis and Klotho expression. Furthermore, FGF-23 predicts progression in CKD (34). The reader is referred to excellent comprehensive articles on this topic (35–37).

The general population has an increasing incidence of CVD, diabetes, metabolic syndrome, and cancer rates. It is tempting to speculate the relationship among these conditions and the seemingly prevalent finding of vitamin D deficiency in developed countries.

Furthermore, CKD is often described as an accelerated aging process: Loss of regulation of hormones that are important to maintenance of bone, cardiovascular, and immune function health. These are in keeping with the increasing prevalence of CVD, diabetes, and cancer in the aging population. CKD populations similarly have a high incidence of these conditions, which may be linked to protracted exposure to abnormal internal milieus (such as occurs with vitamin D deficiency and PTH excess), and potentially to amplification of the effects of this dysregulation as a result of other "uremic" factors. The clinical implications of minor aberrations of these hormones for all individuals is not clear, yet from our understanding of the biology, it is likely that minor irregularities in the axis leads to profound cellular changes with long-term consequences.

Patients who are suspected of developing vitamin D deficiency or insufficiency may be tested where the results of the tests will alter management. This will depend on the various health care environments and cost-benefit ratios that various systems and physicians ascribe to testing for deficiency *versus* treating for suspected deficiency. Vitamin D deficiency can have several causes, and the pattern of laboratory values with respect to 25-hydroxyvitamin D and PTH and in response to vitamin D supplementation may help lead to identification of the underlying pathology. The most common cause of vitamin D deficiency that results in hyperparathyroidism is CKD. Although there are recommendations for annual monitoring of high-risk groups or evaluation in response to therapy, given the assay variability and high prevalence of the condition, practitioners and health care systems need to evaluate critically the utility of this strategy (33). It may be more prudent to evaluate which consequences of vitamin D deficiency (*e.g.*, hyperparathyroidism) are being targeted and supplement those patients. There is no consensus as to whether measuring 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D is of value in clinical practice after supplementation with different agents.

The measurements of both 25-hydroxyvitamin D and PTH remain problematic in clinical practice, so individual practitioner are asked to understand better the nuances of those measurements and the need to repeat them, act on trends, and contextualize them; however, the bulk of the epidemiologic evidence supports the biology and underscores the importance of vitamin D and PTH in health and disease. Additional studies are required to examine the ranges of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in the general populations, in association with known effects of those hormones, so as to establish population means and definitions of deficiencies. In addition, studies to assess impact of fixed-dosage regimens, *versus* targeting values, in large populations would be beneficial. Through appropriate discovery and interventional studies, we will better understand and capitalize on the importance of these prohormones/hormones.

Disclosures

None.

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