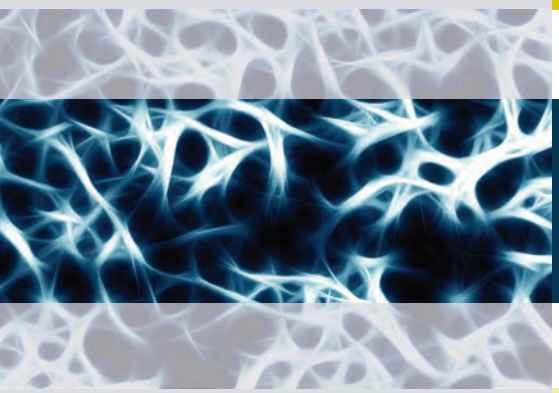


The Role of VITAMIN D *and* VITAMIN D RECEPTOR ACTIVATORS *in Cardiovascular and Kidney Health*

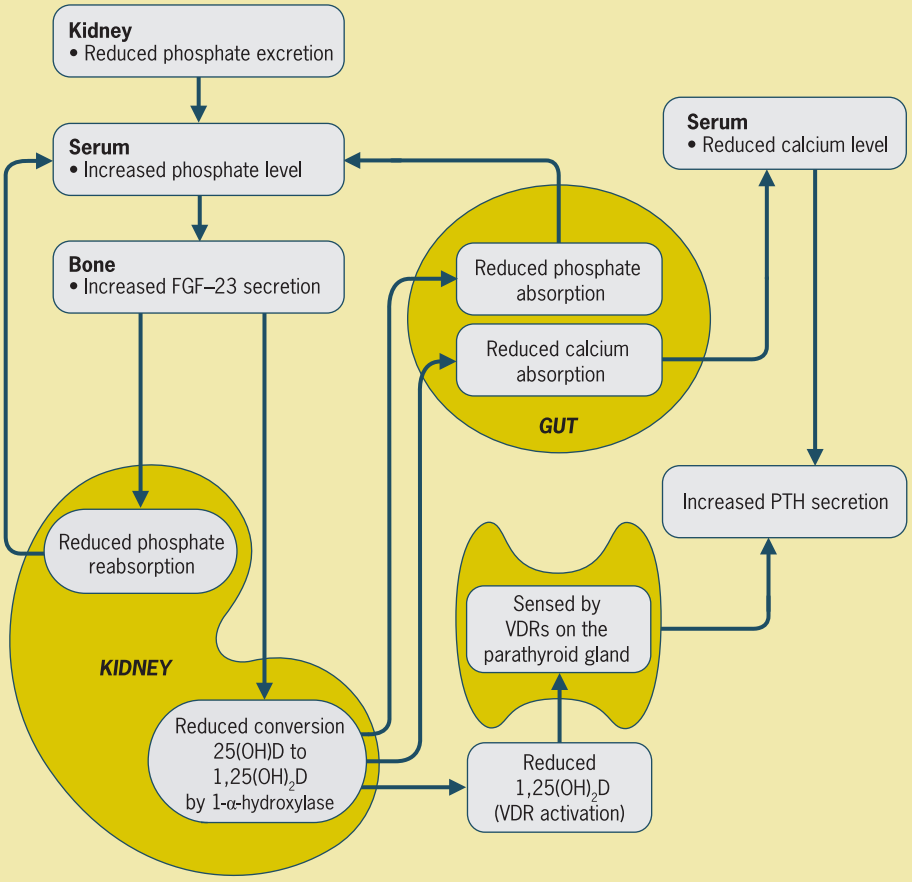
What's Inside...

CKD-MBD

- Management of Abnormal PTH (KDIGO)

Emerging Science on VDR Activation

- Survival
- Vascular/Valvular Calcification
- Albuminuria/Proteinuria
- Heart Function



CKD
Chronic Kidney Disease

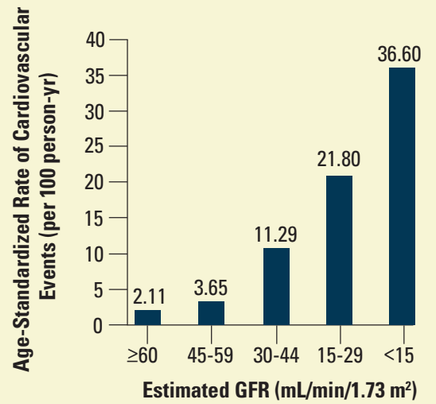
MBD
Mineral and Bone Disorder

GFR Levels Associated With Cardiovascular Disease in CKD

Lower level of estimated glomerular filtration rate (eGFR) was associated with a greater burden of cardiovascular disease (CVD).[1]

CKD-related Mineral Bone Disorder Includes CVD

Numerous cohort studies have demonstrated associations between disorders of mineral metabolism and fractures, CVD, and mortality. These observational studies have broadened the focus of CKD-related mineral bone disorder to include CVD. All three of these processes (abnormal mineral metabolism, abnormal bone, and extraskeletal calcification) are closely interrelated and together make a major contribution to the morbidity and mortality of patients with CKD.[3]

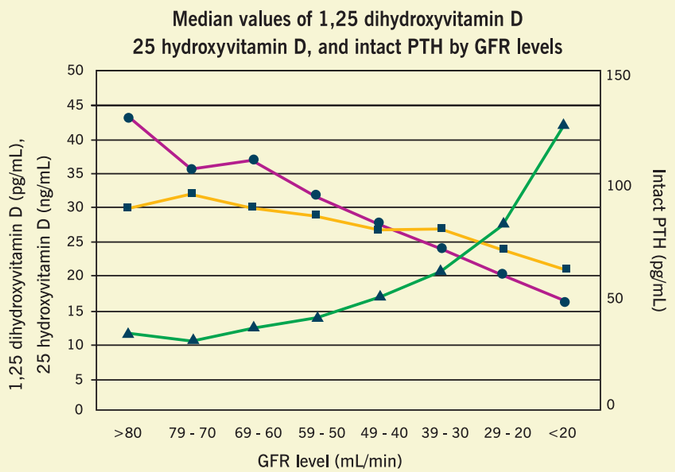


STAGE 3 CKD
(GFR 30–59 mL/min/1.73 m^2) CVD events occur at a rate of 3.65%–11.29% per year[2]

STAGE 4 CKD
(GFR 15–29 mL/min/1.73 m^2) CVD events occur at a rate of 21.80% per year[2]

GFR Levels Associated With $1,25(OH)_2D_3$, 25(OH)D and Intact PTH[4]

- 1,25 Dihydroxyvitamin D_3 (pg/mL)
- 25 hydroxyvitamin D_3 (ng/mL)
- Intact PTH (pg/mL)



CKD-MBD[3]

A systematic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth or strength
- Vascular or other soft tissue calcification

Renal Osteodystrophy[3]

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systematic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

Severe hyperparathyroidism (HPT) is associated with morbidity and mortality in patients with CKD stages 3–5D. Observational studies consistently report an increased relative risk of death in CKD stage 5D patients who have PTH values at the extremes (less than two or greater than nine times the upper normal limit of the assay).[3]
Once developed, severe HPT may be resistant to medical/pharmacologic therapy and may persist following transplantation. Progressive increases of PTH should be avoided.[3]

Frequency of Monitoring for CKD-MBD

CKD STAGE	STAGE 3 (30–59 mL/min/1.73 m^2)	STAGE 4 (15–29 mL/min/1.73 m^2)	STAGE 5 (<15 mL/min/1.73 m^2)	STAGE 5 DIALYSIS (<15 mL/min/1.73 m^2)
SERUM CALCIUM	Every 6–12 months *(G 3.1.2)*	Every 3–6 months *(G 3.1.2)*	Every 1–3 months *(G 3.1.2)*	Every 1–3 months *(G 3.1.2)*
SERUM PHOSPHORUS	Every 6–12 months *(G 3.1.2)*	Every 3–6 months *(G 3.1.2)*	Every 1–3 months *(G 3.1.2)*	Every 1–3 months *(G 3.1.2)*
PTH	On baseline level & CKD progression *(G 3.1.2)*	Every 6–12 months *(G 3.1.2)*	Every 3–6 months *(G 3.1.2)*	Every 3–6 months *(G 3.1.2)*
ALKALINE PHOSPHATASES		Every 12 months or more often when PTH is ↑ *(G 3.1.2)*	Every 12 months or more often when PTH is ↑ *(G 3.1.2)*	Every 12 months or more often when PTH is ↑ *(G 3.1.2)*
25(OH)D	Measure and repeat testing on baseline values and therapeutic interventions. Correct vitamin D deficiency and insufficiency using treatment strategies recommended for the general population. *(G 3.1.3)*			

CLINICAL LABORATORIES SHOULD:
Inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate appropriate interpretation of biochemistry data.*(G 3.1.6)*

Clinicians should:

- Base therapeutic decisions on trends rather than a single laboratory value, taking into account all available CKD-MBD assessments.*(G 3.1.4)*
- Evaluate individual values of serum Ca and P together to guide clinical practice rather than the mathematical construct of the CaxP product.*(G 3.1.5)*

All CKD stages:

- If receiving treatment for CKD-MBD, or if biochemical abnormalities are identified, increase the frequency of measurements to monitor for trends and treatment efficacy and side effects.*(G 3.1.2)*

Treatment of Abnormal PTH Levels in CKD-MBD (KDIGO)

CKD STAGE 3-5 NOT ON DIALYSIS

Higher PTH

Parathyroidectomy is suggested when there is severe HPT and failure to respond to medical/pharmacologic therapy. *(G 4.2.5)* (Parathyroidectomy is rarely needed; consider presence of primary HPT.)

If PTH is progressively increasing and remains persistently above the upper limit of assay despite correction of modifiable factors. *(G 4.2.2)*

→ Treat with calcitriol or vitamin D analogs. *(G 4.2.2)*

If intact PTH is above the upper normal limit of the assay, evaluate:

- Hyperphosphatemia
- Hypocalcemia
- Vitamin D deficiency

(G 4.2.1)

→
- Reduce dietary phosphorus.
- Treat with phosphate binders.
- Treat with calcium supplements, and/or native vitamin D.

(G 4.2.1)

Normal PTH range varies with type of assay. The optimum PTH level is not known. †*(G 4.2.1)*

Lower PTH

†Establishing narrow target ranges for serum intact PTH is difficult because[3]:

- Studies demonstrate that the median intact PTH increases and the range widens with progressive CKD.
- There are methodologic problems with the measurement of PTH, because assays differ in their measurement of accumulating PTH fragments and there is interassay variability.
- With progressive deterioration of kidney function, bone becomes increasingly resistant to the actions of PTH.
- The predictive value of PTH for underlying bone histology is poor when PTH values are between approximately two and nine times the upper normal laboratory range.

Abbreviations:

ACE, angiotensin converting enzyme
ARB, angiotensin receptor blocker
Ca, calcium
FGF-23, fibroblast growth factor-23
GFR, glomerular filtration rate
P, phosphorus
HPT, hyperparathyroidism
PTH, parathyroid hormone
VDRA, vitamin D receptor activator

CKD STAGE 5 DIALYSIS

Higher PTH

Parathyroidectomy is suggested when there is severe HPT and failure to respond to medical/pharmacologic therapy. *(G 4.2.5)* (Parathyroidectomy is rarely needed; consider presence of primary HPT.)

If PTH is elevated or rising: *(G 4.2.4)*

→ Treat with:
- Calcitriol, or
- Vitamin D analogs, or
- Calcimimetics, or a
- Combination of calcimimetics and calcitriol or vitamin D analogs

(G 4.2.4)

→ Base initial drug selection on levels of:
- Serum Ca and P
- Other aspects of CKD-MBD

(G 4.2.4)

Ca or non–calcium-based phosphate binder should be adjusted so that treatments to control PTH do not compromise levels of P and Ca *(G 4.2.4)*

Maintain PTH at 2 to 9 times upper normal limit for assay *(G 4.2.3)*. If PTH changes in either direction, initiate or change therapy to get it back within this range. *(G 4.2.3)*

Upper Limit of Normal

Lower Limit of Normal

If iPTH falls below 2 times the upper limit of normal: *(G 4.2.4)*

→ Reduce or stop:
- Calcitriol
- Vitamin D analogs and/or
- Calcimimetics

(G 4.2.4)

Lower PTH

TREATING COMPLICATIONS

HYPERPHOSPHATEMIA

Reduce or stop:
- Calcitriol, or
- Vitamin D sterol *(G 4.2.4)*

When there is severe HPT and no response to medical/pharmacologic therapy – parathyroidectomy *(G 4.2.5)*

HYPERCALCEMIA

Reduce or stop:
- Calcitriol, or
- Vitamin D sterol

(G 4.2.4)

HYPOCALCEMIA

Reduce or stop calcimimetics depending on:
- Severity
- Concomitant medications
- Clinical signs & symptoms

(G 4.2.4)

COMMONLY USED NOMENCLATURE

COMPOUND	ACTIVE	SELECTIVE*	ALSO KNOWN AS	WHO ATC CODES
ERGOCALCIFEROL	No	No	Vitamin D Vitamin D_2 Vitamin D sterol Native vitamin D VDRA** 25,D	A11CC01
CHOLECALCIFEROL	No	No	Vitamin D Vitamin D_3 Vitamin D sterol Native vitamin D VDRA 25,D	A11CC05
CALCIDIOL	No	No	Vitamin D 25(OH)D 25(OH)D_3 25,D 25-Hydroxyvitamin D_3 25-Hydroxyvitamin D 25-Hydroxycholecalciferol Vitamin D sterol VDRA Calcifediol	A11CC06
CALCITRIOL	Yes	No	Vitamin D 1,25$(OH)_2D_3$ 1,25-Dihydroxyvitamin D_3 1,25-Dihydroxyvitamin D 1,25D Dihydroxycholecalciferol Vitamin D sterol VDRA	A11CC04
ALFACALCIDOL	No	No	Vitamin D D_3 analogue Synthetic derivative Vitamin D sterol Prodrug 1-α vitamin D derivatives VDRA 1,25D	A11CC03
PARICALCITOL	Yes	Yes	Vitamin D D_2 analogue Synthetic derivative Vitamin D sterol Anti-parathyroid agent VDRA 19–Nor 1,25D	H05BX02***

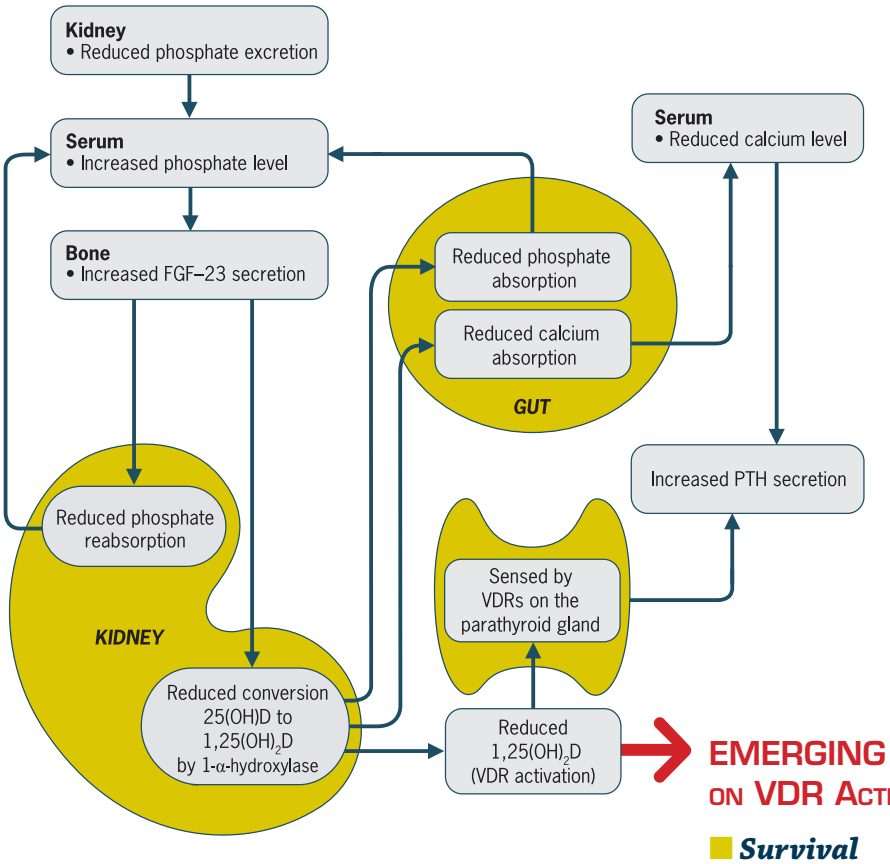
*Selective VDRAs are thought to interact with the VDR at different affinities depending on the cell type, resulting in differing levels of VDR activation and upregulation. A selective VDRA may have greater effect on VDR in the parathyroid than those in the intestines and bone.
**VDR activators activate the VDR.
***Reclassified as H05BX (anti-parathyroid agents) instead of A11CC (vitamin D and analogues) by the World Health Organization.

Pathophysiology of CKD-MBD

AS KIDNEY FUNCTION DECLINES, there is a progressive deterioration in mineral homeostasis, with disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. These include PTH, 25-hydroxycholecalciferol [$25(OH)D_3$], 1,25-dihydroxycholecalciferol [$1,25(OH)_2D_3$] and other vitamin D metabolites, FGF-23, and growth hormone.

The ability of the kidneys to appropriately excrete a phosphate load is diminished, leading to hyperphosphatemia, elevated PTH, and decreased $1,25(OH)_2D_3$, resulting in decreased VDR activation with associated elevations in levels of FGF-23. Conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ is impaired, reducing intestinal calcium absorption and increasing PTH.

The kidney fails to respond adequately to PTH which normally promotes phosphaturia and calcium reabsorption, or to respond to FGF-23 which also enhances phosphate excretion. In addition, there is evidence at the tissue level of downregulation of the VDR and of resistance to the actions of PTH. Therapy is generally focused on correcting biochemical and hormonal abnormalities in an effort to limit their consequences.



EMERGING SCIENCE ON VDR ACTIVATION:

- ***Survival***
- ***Vascular/Valvular Calcification***
- ***Albuminuria/Proteinuria***
- ***Heart Function***

Emerging Science on VDR Activation

STUDIES SUGGEST THERE ARE DIFFERENCES between the various vitamin D therapies used for PTH suppression, gastrointestinal calcium absorption, hypercalcemia and hyperphosphatemia, survival, vascular calcification, albuminuria and proteinuria, and heart function.[3, 5-14] Recent data suggest a potential role for 25(OH)D in a number of tissues, independent of renal conversion.[15-18] In patients with CKD, levels of serum 25(OH)D are commonly insufficient or deficient. Consideration may need to be given to managing autocrine (local inflammation and cell cycle regulation), as well as to the endocrine (PTH-lowering and calcium increasing) effects of vitamin D, calcitriol, and its analogues.[3]

Survival

Recent observational studies have suggested that survival on dialysis may be improved by VDR activation therapy.[19-22] In a cohort study, treatment with paricalcitol (29,021 patients) was reported to provide a survival advantage compared to calcitriol (38,378 patients).[10] In an adjusted analysis, the mortality rate was 16% lower using paricalcitol versus calcitriol.

This finding was not confirmed in a study with 7,731 patients that assessed doxercalciferol[22] or in the recent DOPPS analysis, in which no relationship was detected between the use of vitamin D and outcome using an instrumental-variable approach. However, when a patient-level approach to the analysis was used, there was an apparent survival benefit with vitamin D use, as previously reported suggesting a significant degree of residual confounding.[23] An association between VDR activation therapy and better survival was also reported in a cohort of 58,058 hemodialysis (HD) patients. This study demonstrated an association between the administration of any dose of paricalcitol and greater survival in HD patients.[20]

Vascular/Valvular Calcification

There are no prospective studies in humans that have evaluated the impact of vitamin D or VDR activation therapies on arterial calcification. A recent observational study showed a U-curve type of relationship between serum $1,25(OH)_2D_3$ and arterial calcification in children and adolescents with CKD stage 5D.[24] No such association existed between serum 25(OH)D and arterial calcification.

No independent association of serum 25(OH)D or $1,25(OH)_2D_3$ levels with arterial calcification was observed in adults with CKD stage 5.[25] However another report identified an association between 25(OH)D deficiency and the magnitude of vascular calcification.[26] Studies did show an association of arterial calcification with arterial pulse wave velocity.[25,26]

Experimental studies showed differential effects of calcimimetics and calcitriol on extraosseous calcification, the former being neutral or protective, the latter being a dose-dependent risk factor for calcification.[27-29] The experimental data supporting less toxicity of vitamin D analogues compared to calcitriol is not consistent across studies, but generally suggests there is less calcification with equivalent PTH lowering using vitamin D analogues.[11,12,27,30]

Experimental studies in rats suggest that treatment with paricalcitol in CKD patients may potentially have less of an effect on vascular calcification than doxercalciferol. The effects were independent of the serum CaxP suggesting independent mechanisms. Further evaluation in humans is required to clarify the precise mechanisms by which VDR activation mediates the process of vascular calcification.[11]

Another experimental study, which examined the differential effects of VDR activation on vascular calcification reported that calcitriol increased calcification of vascular smooth muscle cells (VSMCs) cultured in calcification media. An effect was not present when cells were incubated with paricalcitol. Investigators concluded that paricalcitol has a different effect than calcitriol in VSMC calcification, which may explain part of the differences observed in clinical settings.[31]

Emerging Science on VDR Activation

Albuminuria/Proteinuria

Low calcidiol and calcitriol were associated independently with increased albuminuria in CKD patients not on dialysis.[32] Paricalcitol demonstrated an antiproteinuric effect in CKD.[13] Authors of a randomized trial in CKD patients not on dialysis concluded that reduction in albuminuria and inflammation was seen to be independent of paricalcitol's effect on hemodynamics and PTH suppression.[33]

Combination therapy with an ARB and doxercalciferol showed synergistic effects against diabetic nephropathy as a result of blockade of the ARB-induced compensatory renin increase.[34]

The Selective Vitamin D Receptor Activator for Albuminuria Lowering (VITAL) Study (results expected late 2009) is investigating the effectiveness of paricalcitol in reducing abuminuria levels when added to ACE inhibitor or ARB therapy in patients with type 2 diabetic nephropathy.[35]

Heart Function

There is growing evidence that disturbances in vitamin D homeostasis may lead to the development of hypertension. Mortality in patients with congestive heart failure (CHF) is associated independently with vitamin D deficiency. Experimental animal data link renin-angiotensin-aldosterone system (RAAS) activation, cardiac function, left ventricular (LV) mass, and cardiac microvascularity to vitamin D status.[14] Paricalcitol treatment was shown to slow the development of LVH and LV dysfunction in high salt-induced cardiac hypertrophy and cardiac dysfunction in rats.[36] In humans, vitamin D has been associated with improved cytokine profile (decrease in proinflammatory tumor necrosis factor-α and increase in anti-inflammatory interleukin-10) in patients with CHF and regression of cardiac hypertrophy in dialysis patients. In light of these findings, a randomized trial is under way to address whether paricalcitol reduces left ventricular hypertrophy (LVH) in patients not on dialysis.[14]

The PRIMO study (Paricalcitol Capsules Benefits in Renal Failure Induced Cardiac Morbidity), expected to be completed in 2010, is currently evaluating the effects of oral paricalcitol versus placebo on the progression or regression of LVH.

CONSIDERABLE RESEARCH HAS BEEN DONE to advance the understanding of the effects of vitamin D and VDR activation in health and CKD. More investigations and randomized trials need to be performed to elucidate the mechanistic underpinnings of these effects to determine if these therapies improve patient centered outcomes such as mortality, hospitalizations, fractures, and quality of life.

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