There is growing evidence that disturbances in vitamin D metabolism are associated independently with vitamin D deficiency. Experi-
mental animal data link renin-angiotensin-aldosterone system (RAAS) inhibitors, notably angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), to vitamin D deficiency. More investigations and randomized trials need to be performed to elucidate the mechanistic underpinnings of these findings.

### References


**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).\(^1\)

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**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.\(^3\)

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**CKD-MBD\(^1\)**

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

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**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 systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

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**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.\(^0\)**

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**Clinicians should:**

- Base therapeutic decisions on trends rather than a single laboratory value, taking into account all available CKD-MBD assessments.\(^0\)**
- Evaluate individual values of serum Ca and P together to guide clinical practice rather than the mathematical construct of the Ca×P product.\(^0\)

---

**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.\(^0\)
Treatment of Abnormal PTH Levels in CKD-MBD (KDIGO)

**GFR, glomerular filtration rate**

**FGF-23, fibroblast growth factor-23**

The predictive value of PTH for underlying bone histology is poor when PTH values are between approximately Lower PTH and accumulating PTH fragments and there is interassay variability.

If PTH is progressively increasing and/or native vitamin D.

(Treat with calcitriol or vitamin D analogs.)

• Calculate PTH, parathyroid hormone

HPT, hyperparathyroidism

(Parathyroidectomy is rarely needed; consider presence of primary HPT.)

• Reduce dietary phosphorus.

• Vitamin D sterol

When there is severe HPT and no control PTH do not compromise levels of:

Base initial drug selection on:

• Clinical signs & symptoms

• Severity

• Calcium and PTH, and decreased 1,25(OH)2D3, resulting in decreased intestinal calcium absorption, hypercalcemia and hypophosphatemia, survival, vascular calcification, albuminuria.

As kidney function declines, the ability of the kidneys to appropriately excrete a phosphate load is diminished, leading to hyperphosphatemia, elevated PTH, and decreased 1,25(OH)2D3, resulting in decreased gastrointestinal calcium absorption, hypercalcemia and hypophosphatemia, survival, vascular calcification, albuminuria.

The dependence of serum calcium on vitamin D metabolites, and the 1,25(OH)2D3, results in a U-curve type of relationship between serum 1,25(OH)2D3 and disease mortality.

The impact of vitamin D or VDR activation therapies on survival is generally focused on correcting biochemical and hormonal abnormalities in an effort to limit their consequences.

Emerging Science on VDR Activation

Treat with calcimimetics, or vitamin D analogs, or calcitriol, or vitamin D sterol.

Emerging Science on VDR Activation

■ Albuminuria/Proteinuria

■ Vascular/Valvular Calcification

■ Osteodystrophy

■ Metabolic bone disease

■ Periostitis

■ Perineal osteitis

■ Pathophysiologic changes in soft tissues

■ Pathophysiologic changes in the skin

■ Pathophysiologic changes in bone

■ Pathophysiologic changes in muscle

■ Pathophysiologic changes in the cardiovascular system

■ Pathophysiologic changes in the musculoskeletal system

• Calcimimetics, or a vitamin D sterol

CALCIMIMETICS

CALCITRIOL

CALCIDIOL

ALFACALCIDOL

PARACALCIODOL

VDR activators activate the VDR.

ALFACALCIDOL

CALCITRIOL

CALCIDIOL

PARACALCIODOL

Maximum PTH in the forearm circulation was even in PTH changes in the other forearm when PTH was higher in the other forearm.

Calcimimetics do not correct hypercalcemia and hypophosphatemia, and they do not decrease serum PTH levels.

A comprehensive list of the difference between SER and ordinary analgesics can be found in the diagram.
Treatment of Abnormal PTH Levels in CKD-MBD (KDIGO)

- ARB, angiotensin receptor blocker
- ACE, angiotensin converting enzyme

• The predictive value of PTH for underlying bone histology is poor when PTH values are between approximately
  30 and 150 pg/mL. The optimum PTH level is not known.†

• Vitamin D deficiency

- If intact PTH is above the upper limit of normal, assess for modifiable factors.
- If PTH is progressively increasing and not responding to medical/pharmacologic therapy, consider primary hyperparathyroidism.

- Parathyroidectomy is suggested when there is severe HPT and failure to respond to medical/pharmacologic therapy.

- Maintain PTH at 2 to 9 times upper normal limit for assay depending on:
  - Clinical signs & symptoms
  - Serum Ca and P

- Combination of calcimimetics
- Calcimimetics, or a Vitamin D analogs, or
- Combination of calcimimetics and a Vitamin D analogs

- Parathyroidectomy is rarely needed; consider presence of primary HPT.

Pathophysiology of CKD-MBD

Emerging Science on VDR Activation

- The ability of the kidneys to appropriately excrete a phosphate load is decreased in CKD-MBD, leading to a progressive decoordination in mineral homeostasis, with disruption of normal calcium and phosphate balance.

- Conversion of 25(OH)D3 to 1,25(OH)2D3 is impaired, reducing the plasma levels of 1,25(OH)2D3.

- VDR activation with associated elevations in levels of FGF-23.

- Recent observational studies have suggested that survival benefit with the endocrine (PTH-lowering and calcium increasing) effects of vitamin D analogues is independent of renal conversion.

- Studies also showed a U-curve type of relationship between serum 1,25(OH)2D3 level and arterial calcification.

- In a cohort study, treatment with paricalcitol (29,021 patients) compared to calcitriol (38,378 patients) was associated with an approximately 20% lower mortality risk. In an adjusted analysis, the risk reduction was approximately 30% lower in patients with albuminuria compared to patients without albuminuria.

- Investigators concluded that paricalcitol has a different effect on vascular calcification compared to calcitriol in CKD patients. However, more research is needed to clarify the precise mechanisms by which VDR activation affects vascular calcification.

Emerging Science on VDR Activation

- Recent experimental studies have suggested that vitamin D analogues may have different effects on vascular calcification compared to calcitriol.

- The use of vitamin D analogues is supported by current evidence. However, more research is needed to clarify the precise mechanisms by which VDR activation affects vascular calcification in vivo.
**Treatment of Abnormal PTH Levels in CKD-MBD (KDIGO)**

**GFR, glomerular filtration rate**
**FGF-23, fibroblast growth factor-23**

Abbreviations:

†Establishing narrow target ranges for serum intact PTH is difficult because:
- Higher PTH values are less predictive of underlying bone histology when PTH values are between approximately two and nine times the upper normal laboratory range.
- With progressive deterioration of kidney function, bone becomes increasingly resistant to the actions of PTH.

**Lower PTH values are also problematic as:***
- Vitamin D deficiency
- Hypocalcemia

If PTH is progressively increasing and/or native vitamin D and/or VDRA, vitamin D receptor activator do not achieve adequate control PTH do not compromise the ability to appropriately excrete a phosphate load is diminished, leading to hyperphosphatemia, elevated PTH, and decreased 1,25(OH)2D3, resulting in decreased intestinal absorption and calcium reabsorption, or to reabsorb calcium, and to increase the intestinal absorption of calcium. This includes calcium reabsorption from the bone.

**COMMONLY USED NOMENCLATURE**

<table>
<thead>
<tr>
<th>Vitamin D sterol</th>
<th>Vitamin D derivative</th>
<th>Vitamin D analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,25(OH)2D3</td>
<td>Calcifediol</td>
<td>Calcitriol</td>
</tr>
<tr>
<td>Cholecalciferol</td>
<td>Ergocalciferol</td>
<td>Doxercalciferol</td>
</tr>
</tbody>
</table>

**ENHANCING SCIENCE ON VDR ACTIVATION**

Emerging Science on VDR Activation

- **Endothelium/Valvular Calcification**
  - Experimental studies in rats suggest that treatment with vitamin D analogues reduces arterial calcification extent and reduces arterial calcification in vivo in rats. Further evaluation in humans is required to determine the effects of cardiac death in patients with vitamin D analogues.
  - Experimental studies of vitamin D analogues in aortic valve stenosis patients demonstrated a significant reduction in calcification. Further evaluation in humans is required to determine the effects of vitamin D analogues on aortic valve disease.

- **Vascular/Valvular Calcification**
  - Experimental studies in rats suggest that treatment with vitamin D analogues reduces arterial calcification extent and reduces arterial calcification in vivo in rats. Further evaluation in humans is required to determine the effects of vitamin D analogues on arterial calcification.

- **Bone**
  - Vitamin D analogues have been shown to reduce bone mineral density in experimental studies in rats. Further evaluation in humans is required to determine the effects of vitamin D analogues on bone mineral density.

- **Heart Function**
  - Experimental studies in rats suggest that treatment with vitamin D analogues reduces arterial calcification extent and reduces arterial calcification in vivo in rats. Further evaluation in humans is required to determine the effects of vitamin D analogues on arterial calcification.

- **Pathophysiology of CKD-MBD Emerging Science on VDR Activation**
  - Studies suggest that vitamin D analogues have been shown to reduce bone mineral density in experimental studies in rats. Further evaluation in humans is required to determine the effects of vitamin D analogues on bone mineral density.
Treatment of Abnormal PTH Levels in CKD-MBD (KDIGO)

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

FGF-23, FGF-23
Ca, calcium
ACE, angiotensin converting enzyme

- The predictive value of PTH for underlying bone histology is poor when PTH values are between approximately
- There are methodologic problems with the measurement of
  - Lower
  - PTH
  - Accumulating PTH fragments and there is interassay variability.

- Lower
- Hyperphosphatemia
- Hyperparathyroidism
- Hypocalcemia
- Limit of assay despite correction of
- If PTH is progressively increasing and

- CKD STAGE 3-5 NOT ON DIALYSIS
- CKD STAGE 5 DIALYSIS

- Treat with calcitriol or calcimimetics, or a
- VDRA, vitamin D receptor activator

- Parathyroidectomy is suggested when there is severe HPT and failure to respond to medical/pharmacologic

- Combination of calcimimetics
- • Calcitriol, or
- • Calcimimetics, or a

- Reduces or stops:
  - Calcium may cause hypercalcemia if
  - Phosphate binder should be
  - Ca or non-calcium-based

- Base initial drug selection on
  - Concomitant medications
  - Severity
  - Serum Ca and P

- **Reclassified as H05BX (anti-parathyroid agents) instead of A11CC (vitamin D and analogues) by the World Health Organization.

Pathophysiology of CKD-MBD

Emerging Science on VDR Activation

- ALFACALCIDOL
- No
- No
- CHOLECALCIFEROL
- No
- No

- Vitamin D sterol
- Synthetic derivative

- VDRA
- Anti-parathyroid agent
- VDRA
- Vitamin D derivatives

- VDR activators activate the VDR.

- Selective VDRA may have greater effect on VDR in the parathyroid than those in the intestines and bone.

- VDR activation mediates the process of vascular calcification.11

- Experimental studies showed differential effects of calcimimetics and calcitriol on extraosseous calcification, the former

- Investigators concluded that paricalcitol has a different effect

- Recent observational studies have suggested that survival

- Survival

- Not consistent across studies, but generally support higher

- AKF, chronic kidney disease

- CKD, chronic kidney disease
- HD, hemodialysis
There is growing evidence that disturbances in vitamin D metabolism and PTH suppression. In humans, vitamin D has been shown to be independent of paricalcitol's effect on hemodynamics and albuminuria. 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 albuminuria.

In a large-scale randomized trial, doxercalciferol was shown to improve the rate of regression of cardiac hypertrophy in dialysis patients. In light of these findings, the PRIMO study (Paricalcitol Capsules Benefits in Renal Aldosterone Blockade) was conducted to investigate the potential of the selective vitamin D receptor activator doxercalciferol in reducing albuminuria and inflammation. The Selective Vitamin D Receptor Activator for Albuminuria and Intact PTH (SVDRA) study, which was designed to investigate the potential of the selective vitamin D receptor activator doxercalciferol in reducing albuminuria and inflammation, was also initiated.

Lower calcidiol and calcitriol were associated independently with increased risk of death in CKD stage 4. However, the role of vitamin D in the prevention of cardiovascular disease and kidney health remains controversial.

Emerging Science on VDR Activation

**References**

Emerging Science on VDR Activation in Cardiovascular and Kidney Health

**MBD**

**CKD**

**Heart Function**

**VDR Activation**

**References**

**The Role of VITAMIN D and VITAMIN D RECEPTOR ACTIVATORS**

Emerging Science on VDR Activation in Cardiovascular and Kidney Health

MBD

CKD

Heart Function

VDR Activation

What’s Inside

• VDR-MBD
  • Management of MBD in CKD

Emerging Science on VDR Activation

• Conclusions
  • Critical players in CKD-MBD
  • Novel Therapies

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MBD

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