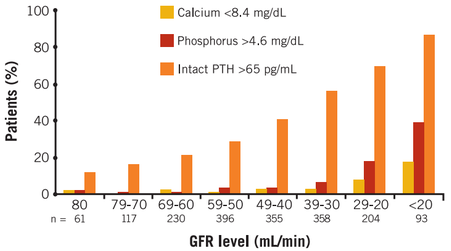
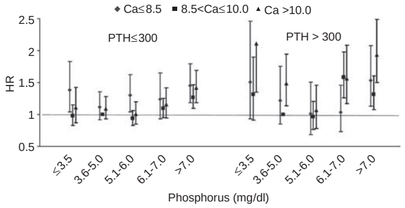
Secondary Hyperparathyroidism

- Occurs as a response to declining kidney function in order to maintain calcium/phosphorus homeostasis and bone turnover. However, secondary hyperparathyroidism may have a negative impact on bone turnover and mineralization and, in its severe forms, may lead to bone abnormalities such as osteitis fibrosa cystica.
- May also lead to pruritus, calciphylaxis (calcific uremic arteriolopathy), cardiovascular disease (CVD), neuromuscular disturbances, and mortality.

Prevalence of abnormal serum calcium, phosphorus, and intact PTH by GFR[9]



Risk of all-cause mortality associated with combinations of baseline serum phosphorus and calcium categories by PTH level (pg/mL)*[2]



In the graph above, mortality risks are associated with combinations of calcium and phosphorus categories and two PTH categories (≤ 300 pg/mL, >300 pg/mL).[2] In patients with PTH levels of ≤ 300 pg/mL, patients with calcium levels ≤ 8.5 mg/dL appeared to be at greatest risk at all phosphorus levels. In patients with PTH levels > 300 pg/mL, patients with calcium levels >10.0 mg/dL appeared to be at greatest risk.

* A prospective cohort study that included 25,588 patients on hemodialysis therapy (CKD Stage 5) in 12 countries during the course of a decade. Separate models for mortality risk by PTH categories included ≤100 pg/mL, 101-300 pg/mL, 301-600 pg/mL and >600 pg/mL. 31% of patients had PTH levels >300 pg/mL, 11% of which had PTH levels >600 pg/mL.[2]

Definition of CKD-MBD[1]

A systemic 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

Definition of renal osteodystrophy

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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11) Souberbielle J, Roth H, Fouque D. Parathyroid hormone measurement in CKD. *Kidney Int.* 2010; 77:93-100.

12) World Health Organization (WHO). Expert Committee on Biological Standardization (ECBS). WHO international collaborative study of the proposed 1st international standard for parathyroid hormone 1-84, human, recombinant. 2009.

Grade for Strength of Recommendation	Strength	Wording[1]	Grade for Quality of Evidence[1]	
Level 1	Strong	"We recommend...should"	A	High
Level 2	Weak	"We suggest...might"	B	Moderate
			C	Low
			D	Very Low

NOTE: Ungraded statements are used in areas where guidance was based on common sense and/or the question was not specific enough to undertake a systematic evidence review.[1]

On all panels of this resource, G stands for Guideline.[1]

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Managing PTH IN CKD-MBD

Insights for Dialysis

AS KIDNEY FUNCTION DECLINES, there is a progressive disruption in the metabolism of calcium, phosphorus, vitamin D and parathyroid hormone (PTH).

Patients with secondary hyperparathyroidism may develop abnormalities of all components of Chronic Kidney Disease–Mineral Bone Disorder (CKD-MBD).*

Excessively high or low levels of PTH, calcium and/or phosphorus have been associated with an increased risk of mortality in patients on dialysis (CKD stage 5).[1-8]

An Overview of the Biochemical and Hormonal Abnormalities of CKD-MBD

EARLIER CKD STAGES → PROGRESSION OF CKD → LATER CKD STAGES

↓ Kidney Function	Deterioration of mineral homeostasis	↓ Phosphorus excretion	↓ Conversion of 25(OH)D, $1,25(OH)_2D_3$	Kidney fails to respond to PTH and FGF-23	Possible consequences
	↑ Disruptions in phosphorus, calcium, circulating hormones (PTH, 25[OH] D, $1,25(OH)_2D_3$, other vitamin D metabolites, FGF-23, growth hormone)	Hyperphosphatemia ↑ PTH ↓ $1,25(OH)_2D_3$ ↑ FGF-23	↓ Intestinal calcium absorption ↑ PTH	Downregulation of Vitamin D receptor Resistance to actions of PTH	Bone abnormalities, fractures, extraskeletal calcification, cardiovascular disease, mortality

Abbreviations: PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; FGF-23, fibroblast growth factor–23

* See back panel for CKD-MBD definition.

Variability in CKD-MBD
Biochemical Measurements

Establishing a narrow target range for serum intact PTH is difficult because assays can differ in their measurement of accumulating PTH fragments.[1,10] Experts have looked for ways to help clinicians reduce some of the interassay and biological variability.[11, 12]

Equivalent concentrations obtained with each PTH assay, when the value measured with the Allegro assay is 150, 300, or 1000 ng/L[10]

Assay	PTH (ng/L)	PTH (ng/L)	PTH (ng/L)	Median Bias (%)
Allegro intact PTH	150	300	1000	0
N-tact PTH IRMA	83	160	517	-44.9 (-68.0; -26.2)
PTH IRMA Immunotech	188	369	1216	23.9 (-6.1; 108.3)
ELISA-PTH	149	311	948	-1.6 (-24.3; 47.2)
Total intact PTH IRMA	134	262	857	-14.5 (-41.5; 23.5)
DSL PTH IRMA	323	638	2108	123.0 (53.1; 188.9)
DSL PTH ELISA	264	523	1734	79.6 (-8.0; 180.9)
Elecsys PTH	161	311	1011	7.3 (-13.8; 80.3)
Immulite 2000 intact PTH	212	410	1334	37.8 (3.8; 130.8)
PTH-ACS 180	185	374	1256	18.8 (-9.9; 69.4)
PTH AdviaCentaur	168	342	1154	9.5 (27.6; 55.6)
Intact PTH advantage	174	339	1109	14.6 (-10.4; 72.2)
LIAISON N-tact PTH	111	223	748	-23.4 (-68.2; -1.9)
Ca-PTH IRMA	84	165	543	-44.8 (-65.6; -22.8)
BioIntact PTH advantage	109	214	704	-27.6 (-53.0; 12.5)

DSL, diagnostic system laboratories; ELISA, enzyme-linked immunosorbent assay; IRMA, immunoradiometric assay; PTH, parathyroid hormone.

IN REPORTS OF LABORATORY TESTS for patients with CKD stages 3-5D, KDIGO recommends that clinical laboratories 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 the appropriate interpretation of biochemistry data. *G 3.1.6 (1B).*[1]

Monitoring and Management of CKD–MBD

Management is generally focused on: • Lowering high serum phosphorus • Maintaining calcium • Treating abnormal PTH level

In patients with CKD stages 3-5D, KDIGO recommends that therapeutic decisions be based on trends rather than on a single laboratory value taking into account all available CKD-MBD assessments. *G 3.1.4 (1C)*[†]

KDIGO recommends monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity in adults beginning in CKD stage 3, *G 3.1.1 (1C)*, and suggest baseline 25(OH)D levels might be measured. *G 3.1.3 (2C)*[†]

Reasonable Monitoring Intervals for CKD Stage 5D[1]

- Serum Calcium and Phosphorus: Every 1-3 months *G 3.1.2 (not graded)*
- PTH: Every 3 - 6 months *G 3.1.2 (not graded)*
- Alkaline Phosphatases: Every 12 months or more often when PTH is elevated *G 3.1.2 (not graded)*
- 25(OH)D: Repeat testing determined by baseline values and therapeutic interventions. Correct vitamin D deficiency and insufficiency using treatment strategies recommended for the general population. *G 3.1.3 (2C)*

In patients receiving treatment for CKD-MBD, or in whom biochemical abnormalities are identified, increase the frequency of measurements to monitor for trends and treatment efficacy and side effects. *G 3.1.2 (not graded)*[†]

Suggested Ranges[1]

PTH
Observational studies consistently report an increased relative risk of death in CKD stage 5D patients who have PTH values at the extremes, defined as less than two or greater than nine times the upper normal limit of the assay. KDIGO suggests that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range. *G 4.2.3 (2C)*

Serum Phosphorus
Lower elevated phosphorus towards normal range *G 4.1.1 (2C)*

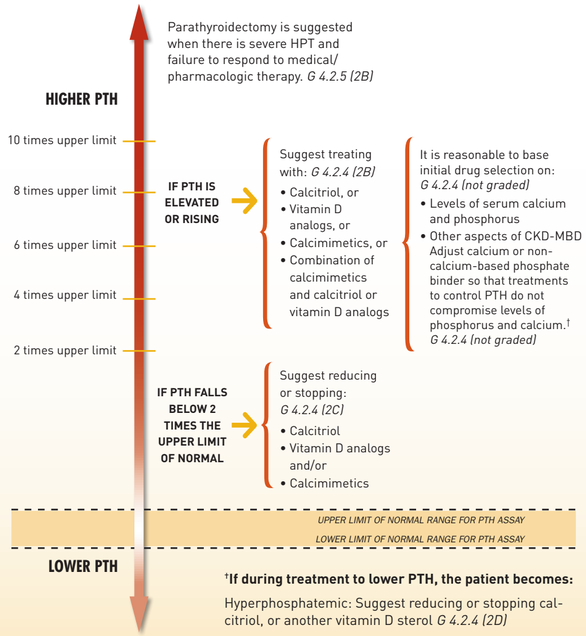
Serum calcium
Maintain within normal range *G 4.1.2 (2D)*

Lowering High Serum Phosphorus and Maintaining Calcium[1]

In patients with hyperphosphatemia	Suggested approach:
	• Limit dietary phosphate intake alone or in combination with other treatments. *G 4.1.7 (2D)*
	• Use a dialysate calcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L). *G 4.1.3 (2D)*
	• Use phosphate binding agents. *G 4.1.4 (2B)* Suggest the choice of binder should take into account: *G 4.1.4 (not graded)*
	  • CKD stage
	  • Presence of other components of CKD-MBD
	  • Concomitant therapies
	  • Side-effect profile.

In patients with hyperphosphatemia and persistent or recurrent hypercalcemia	Recommend restricting dose of: *G 4.1.5 (1B)* • Calcium-based phosphate binders and/or • Calcitriol or vitamin D analog.
In patients with hyperphosphatemia and arterial calcification and/or adynamic bone disease and/or if serum PTH levels are persistently low	Suggest restricting the dose of calcium-based phosphate binders. *G 4.1.5 (2C)*

Treating Abnormal PTH Level[1]



†If during treatment to lower PTH, the patient becomes:

Hyperphosphatemic: Suggest reducing or stopping calcitriol, or another vitamin D sterol *G 4.2.4 (2D)*

Hypercalcemic: Recommend reducing or stopping: Calcitriol, or another vitamin D sterol *G 4.2.4 (1B)*

Hypocalcemic: Suggest reducing or stopping calcimimetics depending on severity, concomitant medications, and clinical signs and symptoms. *G 4.2.4 (2D)*

BIOCHEMICAL ABNORMALITIES are the primary indicators for the diagnosis and management of CKD-MBD. Thus, changes in serum PTH need to be interpreted together with serum calcium and phosphorus. PTH-altering treatment should be expected to change not only PTH level, but also calcium and phosphorus levels.

A Trends Approach
to Interpreting the PTH Result

Two Patients have been receiving hemodialysis and treatment for CKD-MBD. Initial therapy was based on levels of serum calcium and phosphorus, and other aspects of CKD-MBD. Each patient has the same PTH level after 6-months. However, when you consider the trend in both patients' results over 6 months, the approach to adjusting each patient's treatment could be different.

Lab Results	Patient 1	Patient 2
Baseline	PTH: 70 pg/mL Ca: 10.4 mg/dL P: 5.6 mg/dL ALP: 50 IU/L	PTH: 845 pg/mL Ca: 8.8 mg/dL P: 4.6 mg/dL ALP: 236 IU/L
After 3 months of treatment	PTH: 205 pg/mL Ca: 9.6 mg/dL P: 5.0 mg/dL ALP: 84 IU/L	PTH: 557 pg/mL Ca: 9.2 mg/dL P: 5.0 mg/dL ALP: 165 IU/L
After 6 months of treatment	**PTH: 350 pg/mL** Ca: 8.8 mg/dL P: 4.0 mg/dL ALP: 165 IU/L	**PTH: 350 pg/mL** Ca: 9.6 mg/dL P: 5.3 mg/dL ALP: 120 IU/L

*Reference ranges: PTH 10-65 pg/mL; Ca 9.02–11.02 mg/dL; P 3.0–4.49 mg/dL; ALP 30-130 units/L
ALP, alkaline phosphatase; Ca, calcium; P, phosphorus; PTH, parathyroid hormone;

What are the trends?

Patient 1

- PTH results show an increasing trend
- Serum calcium shows a slightly downward trend, but is within reference range;
- Serum phosphorus shows a slightly downward trend;
- ALP shows an increasing to above the upper limit of normal.

Patient 2

- PTH results show a decreasing trend
- Serum calcium shows a slightly upward trend, but is within reference range;
- Serum phosphorus shows a slightly upward trend beyond the upper limit of normal;
- ALP shows a decreasing trend to within the normal reference range.

Address the marked change in PTH trend. Account for other available CKD-MBD assessments. Adjustments to Consider

- Lower PTH to avoid progressive increase and excessively high levels by treating with calcitriol, or Vitamin D analogs, or calcimimetics, or a combination of these options
- Adjust calcium or non-calcium-based phosphate binder so that treatments to control PTH do not compromise levels of phosphorus and calcium
- Consider increasing frequency of measurements to monitor for trends and treatment efficacy and side effects
- Reduce or stop calcitriol, Vitamin D analogs and/or calcimimetics in order to maintain PTH within 2-9 times the upper normal limit of assay
- Consider increasing frequency of measurements to monitor for trends and treatment efficacy and side effects