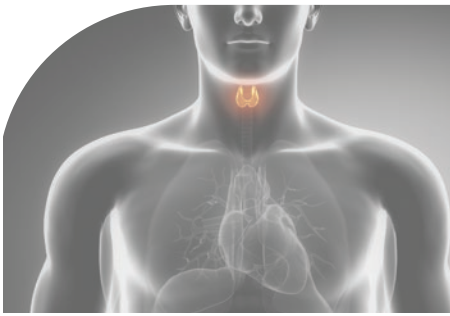
Parathyroid Hormone and Secondary Hyperparathyroidism in Chronic Kidney Disease

Stage 5D



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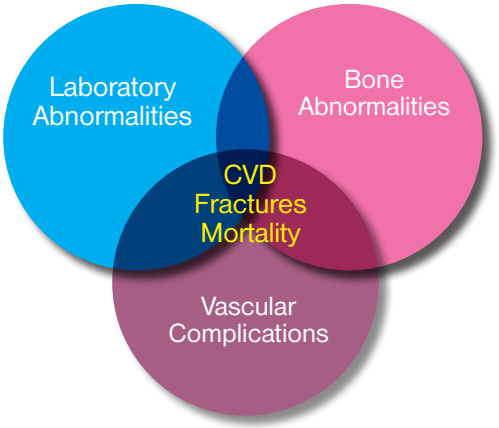
Background

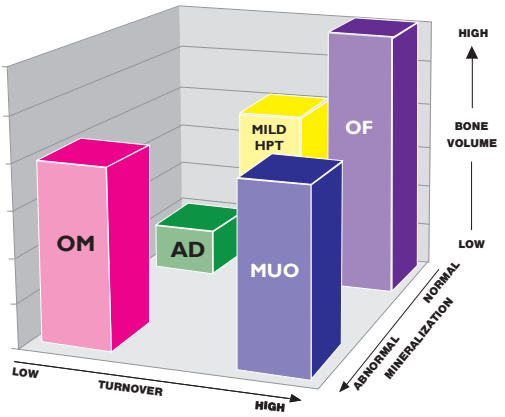
Chronic kidney disease (CKD) affects 14.5% of the U.S. population[1] with a host of biochemical and clinical abnormalities, including chronic kidney disease-mineral and bone disorder (CKD-MBD) and renal osteodystrophy (ROD).[2] CKD-MBD refers to the clinical syndrome encompassing mineral, bone, and vascular calcification abnormalities that develop as complications of CKD, whereas ROD is currently used to describe the bone pathology of CKD according to these parameters found on biopsy: bone turnover, mineralization, and volume.[2] Figures 1 and 2 depict the diagnostic spectrum of CKD-MBD and ROD, respectively.

Figure 1. Chronic kidney disease-mineral and bone disorder (CKD-MBD)[3]



Adapted from Moe SM, et al. *Advances in Chronic Kidney Dis.* 2007

Figure 2. Renal osteodystrophy[2]



Adapted from: Moe SM, et al. *Kidney Int.* 2006

AD = adynamic bone disease; Mild HPT = Mild hyperparathyroid-related disease; MUO = mixed uremic osteodystrophy; OF = osteitis fibrosa or advanced hyperparathyroid-related disease; OM = osteomalacia.

The gold standard for diagnosing bone disease in CKD is bone biopsy, but this is not feasible for the majority of patients. Without a biopsy, however, the clinician should evaluate trends in biochemical markers in order to help guide treatment, but only as part of an integrated and comprehensive assessment. Clinical practice guidelines recommend that, in patients with CKD stage 5D, either serum parathyroid hormone (PTH) or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover.[4] The biochemical abnormalities of CKD-MBD may begin in CKD stage 3, but the rate and severity of these changes are highly variable among patients. For this reason, it is strongly recommended that monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase begin at CKD stage 3, and in children at CKD stage 2.[4]

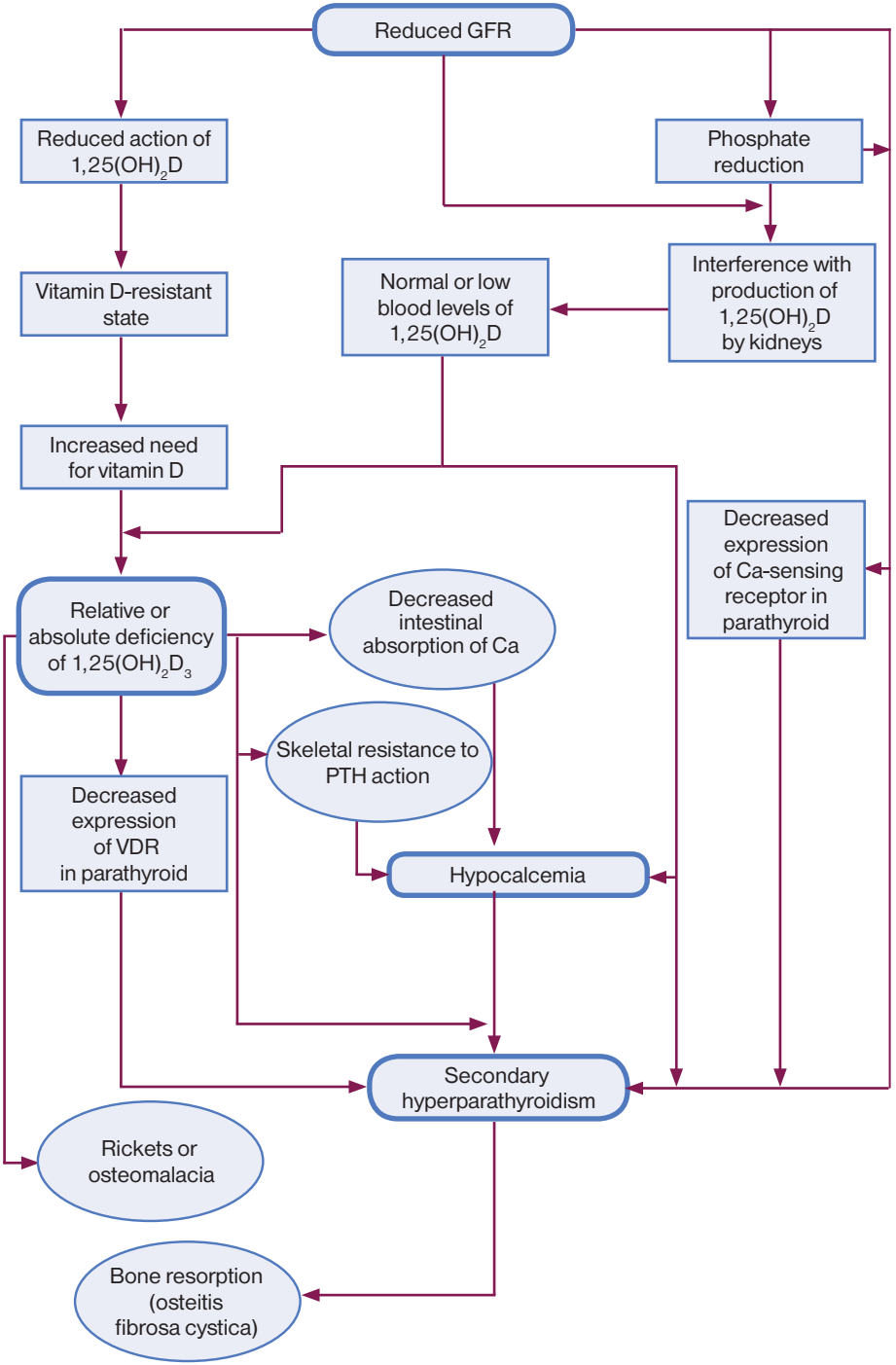
The Role of PTH in Secondary Hyperparathyroidism (secondary HPT)

Secondary HPT manifests as one of two types of renal osteodystrophy: either a high turnover state known as osteitis fibrosa, or, in combination with low bone turnover, known as mixed uremic osteodystrophy. The burden of disease caused by osteitis fibrosa and mixed disease includes: marrow fibrosis that can exacerbate the anemia of CKD; abnormal bone mineralization; bone pain; myopathy and muscle weakness; spontaneous tendon rupture; pruritis; fractures; and vascular calcification.[5]

The development of secondary HPT results from many factors, including deficiency of calcitriol, retention of phosphorus, a decrease in the activation of the calcium-sensing receptor (CaR) in the parathyroid gland, and skeletal resistance to the calcemic effect of PTH. As kidney function declines, so does phosphorus excretion, thus causing plasma phosphorus levels to rise while plasma calcium and calcitriol levels decrease. A reduction in calcitriol also contributes to a reduction in intestinal calcium absorption. All of these factors contribute to the development of hypocalcemia, which is the impetus for an increased production of PTH.[5] More recently, fibroblast growth factor-23 (FGF-23), which increases early in the course of CKD possibly as a consequence of phosphorus retention, has been found to suppress calcitriol synthesis, in turn leading to increased PTH.[6] Figure 3 is a schematic depiction of the pathogenesis of secondary HPT.

Aside from the negative skeletal effects of secondary HPT, soft tissue calcification can occur in other body tissues, including the skin and subcutaneous tissue, cornea and conjunctiva, muscle, lung, gastrointestinal tract, and cardiovascular system. Calcification of cardiac tissue can affect the myocardium, the conduction system, and valves, and thus may cause adverse cardiovascular events.[8] Calcification of the aortic and/or mitral valve is quite common in adults receiving maintenance hemodialysis, with a prevalence of 2.5-5.0-fold greater as compared with non-hemodialysis patients with suspected and documented coronary artery disease.[9] Cardiac calcification may also cause myocardial fibrosis and left ventricular dysfunction, which can culminate in heart failure, or when it involves the electrical conduction system, cardiac arrhythmias may result.[8] Left ventricular hypertrophy has been identified as an independent risk factor for morbidity and mortality in the dialysis population.[10,11] Secondary HPT has also been implicated in causing severe pruritis which has been shown to improve after parathyroidectomy.[12]

Figure 3. Pathogenesis of abnormalities in mineral metabolism and bone disease in CKD[7]



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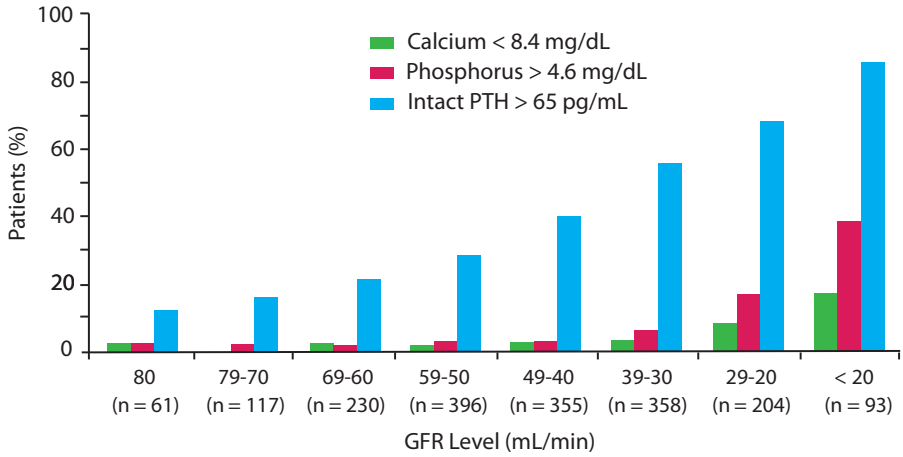
Based upon estimations of the prevalence of secondary HPT in the United States, and the cost of treating CKD comorbidities, Joy et al had calculated back in 2007 that between 2.0 and 4.7 million people with CKD had elevated PTH levels and were candidates for treatments that would cost between $52 billion and $122 billion dollars per year.[13-16] With the prevalence of CKD at 14.5% of the population, these numbers have likely increased.

Although secondary HPT is an important complication of CKD with significant burdens on health and financial resources, it remains under-recognized and under-diagnosed at earlier stages of CKD.[13] Because it is more often detected in advanced CKD, severe secondary HPT may be resistant to dietary/dialytic/pharmacological therapy and may persist following transplantation.[17] See Figure 4 for the prevalence of secondary HPT with decreasing glomerular filtration rate (GFR).

Figure 4. Prevalence of abnormal serium calcium, phosphorus, and intact PTH by GFR[16]



Adapted from: Levin A, et al. *Kidney Int.* 2007

Evaluating and Monitoring PTH Levels

Severe secondary 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 2 or greater than 9 times the upper normal limit of the assay). Progressive increases of PTH should be avoided and marked changes in PTH levels should trigger a response to avoid a future result outside the range.[17] Monitoring trends is important for the detection and treatment of CKD-MBD.[4]

Establishing narrow target ranges for serum intact PTH is difficult because: 1) studies demonstrate that the median intact PTH increases and the range widens with progressive CKD; 2) there are methodological problems with the measurement of PTH because assays differ in their measurement of accumulating PTH fragments and there is inter-assay and biological variability (see the section "Overview of PTH Assays"); and 3) the predictive value of PTH for underlying bone histology is poor when PTH values are between approximately 2 and 9 times the upper normal laboratory range according to the assay used.[17]

In CKD stage 5D, it is suggested that PTH be maintained at approximately 2 to 9 times the upper normal limit for the particular assay. If PTH changes markedly in either direction within this range, a response is warranted to avoid progression to levels outside this range. This PTH range corresponds to approximately 130-600 pg/mL (depending on the assay).[4]

Clinicians should be aware that certain populations, such as blacks with CKD, have higher PTH levels.[18-20] Bone turnover is also lower in blacks across a wide range of PTH values as compared to whites, thus suggesting PTH resistance in the black population.[18] This finding is especially important in light of associations between low bone volume and cardiovascular calcification in CKD stage 5D patients.[21]

In patients with CKD stage 5D, it is reasonable to base the frequency of PTH monitoring on the presence and magnitude of abnormalities and rate of progression of CKD. Reasonable monitoring intervals: at least every 3 to 6 months with the goal to maintain PTH at approximately 2 to 9 times the upper normal limit for the particular assay. If PTH changes markedly in either direction within this range, a response is warranted to avoid progression to levels outside the range.[4]

Overview of PTH Assays

PTH is an 84 amino acid peptide that is cleaved both within the parathyroid gland and after secretion into the N-terminal, C-terminal, and mid-region fragments. There has been a progression of increasingly sensitive assays developed over the past few decades to measure PTH (Figure 5), but it was the second generation assay, or "intact PTH" assay that improved the detection of full-length (active) PTH molecules. For this reason, it is the type of assay most widely used today. Recent data, however, demonstrates that the intact assay also detects "N-truncated" fragments (such as 7-84 PTH) that have been shown to exert effects opposite to those of 1-84.[22] And unfortunately, assay kits from different manufacturers measure varying types and amounts of these circulating fragments, leading to inconsistent results.[17]

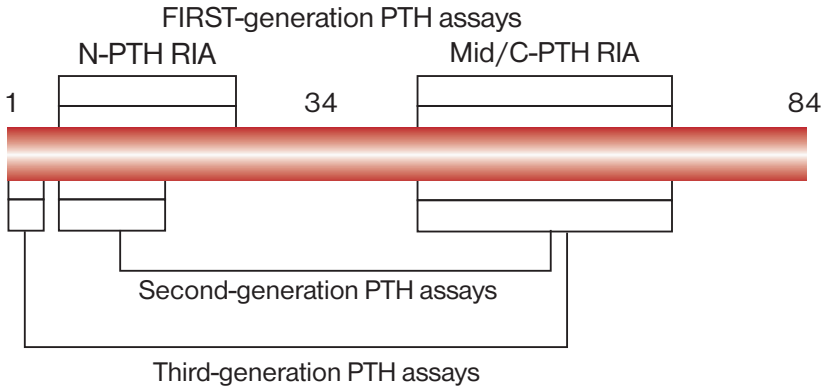
The previously recommended target PTH levels of 150-300 pg/mL were arrived at between the late 1980s to the 1990s using the Nichols Allegro Intact PTH assay, which was the reference for PTH measurement until early 2006. But since then, inter-method variability has been shown to produce significantly different concentrations. In addition, most assays have been calibrated against synthetic 1-84 PTH from different sources.[22] Addressing the need for 1-84 PTH standardization, The World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) recently reported a preparation of recombinant human 1-84 PTH to serve as the international standard, known as 95/646.[23] But even with a new standard, PTH concentrations will vary and it is recommended 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 appropriate interpretation of biochemical data.[17]

The use of correction factors to overcome the inter-method variability of PTH measurement is not the ultimate solution, but may be considered as a pragmatic approach to minimize the problem. It does not take into account the variable proportions of 1-84 PTH versus PTH fragments and the various cross-reactions for 7-84 PTH from one second-generation assay to another.[22]

Table 1. Proposed correcting factors for PTH measurements. Division of measured PTH value by the indicated correction factor results in a PTH value roughly equivalent to a value that would be measured by the Nichols Allegro™ Intact PTH assay.[22]

Assay Kit	Correction Factor
Bayer PTH Advia Centaur™	No Correction
Access Intact PTH™ (Beckman Coulter)	No Correction
Roche Elecsys™ PTH	No Correction
Schering CisBio™ ELSA	No Correction
Scantibodies Total Intact PTH	No Correction
Architect™ PTH (Abbott)	1.3
Beckman Coulter PTH IRMA	1.2
DiaSorin Intact PTH IRMA	0.55
LIAISON N-tact PTH	0.90
Scantibodies Ca-PTH IRMA (the only third-generation assay)	0.55
DPC Immulite 2000™, serum	No Correction
DPC Immulite 2000™, plasma	1.25

Figure 5. PTH assays. The figure shows the entire parathyroid hormone molecule, composed of 84 amino acids.[24]



Moe SM, Sprague SM. Chapter 52: Mineral bone disorder in chronic kidney disease. In: *Brenner and Rector's The Kidney*, 8th ed. WB Saunders Company. Philadelphia, PA, 2007

Mid/C-PTH = mid/carboxyl-terminus of parathyroid hormone; N-PTH = amino-terminus of parathyroid hormone; PTH = parathyroid hormone; RIA = radioimmunoassay

Several commercial assays provide results that are numerically quite similar to those observed using the Nichols Allegro Intact PTH assay, as reported by Souberbielle et al. These include the Bayer PTH Advia Centaur™, Scantibodies Total Intact PTH, and Roche Elecsys™ iPTH.[22] For several other assays, a correction factor can be applied to compare the values from each assay with those determined by the Nichols Allegro Intact PTH assay. It should be noted, however, that a reference range of values that corresponds with normal bone pathology has not been determined for any of the PTH assays currently available as was done in the past with the Nichols Allegro Intact PTH assay.[22]

The following clinical factors that influence PTH results must also be considered, especially those for which the clinician does have some control: 1) **uncontrollable intra-individual biological variation** reflects each person's unique biochemical makeup, homeostatic set point, and presence of disease[25]; 2) **uncontrollable pre-analytic variation** caused by variations in body mass index; age; race; calcium, phosphorus, and vitamin D status[26]; dialysis history (number of months or years on dialysis)[27]; glomerular filtration rate; and stage of CKD[26]; and 3) **controllable pre-analytic variation** of samples achieved by consistency in exclusively obtaining either serum or plasma specimens; maintaining proper temperature during storage and shipping; adhering to recommended time intervals between storage and analysis; adhering to recommended time limits between freezing and analysis; adhering to proper procedures for collecting, processing, shipping, and storing samples as described by the test manufacturer[26,28]; preventing sample hemolysis and/or contamination by standardizing collection procedures; and implementing quality assurance programs.[29,30]

Summary

Despite the limitations discussed, PTH is still considered a useful indicator in managing secondary HPT. Encouragingly, experts suggest that it will be possible to improve the comparability of PTH results because the new international standard 95/646 for PTH (1-84) is available for calibration, and because improvements in mass spectrometry could lead to the development of a reference measurement procedure for PTH.[31] While these measures are being refined, experts agree on interim strategies to reduce error in clinical classification:

- When formulating a diagnosis, the clinician should use an integrated and comprehensive assessment that includes sufficient laboratory data to recognize trends over time rather than isolated data points. In patients with CKD stages 3-5D, it is recommended that decisions be based on trends rather than a single laboratory value, taking into account all available CKD-MBD assessments.[4]
- Consider that all types of bone turnover can be found in a broad range of PTH levels[26,32], so it is crucial to closely monitor trends in alkaline phosphatase, calcium, phosphorus, and vitamin D, and assess patients accordingly.[7,17]
- Obtain all lab information regarding the PTH assay and related standards for specimen collection, handling, and shipping. Remain up to date with any changes in these procedures and create a standardized lab protocol and quality assurance program for your facility. Correction of some measurement kits can be considered, though a common standard is not yet available.[22] Be aware that "systematic" unidirectional trends observed in the majority of patients in a single center should prompt suspicion that the central laboratory may have changed the assay.[17]
- Test PTH at similar times during the day and week to reduce the influence of diurnal variations, and in order to decrease inter-assay variability, the same assay should be used for monitoring changes over time.[4]
- Control pre-analytic variation of samples by:
    - Maintaining consistency by exclusively obtaining either serum or plasma specimens, depending upon assay specifications[26,31]
    - Maintaining proper temperature during storage and shipping[26]
    - Adhering to the recommended time limits between sample collection, freezing, and analysis[26]
    - Adhering to proper procedures for collecting, processing, shipping, and storing samples as described by test manufacturer[26,28]
    - Preventing sample hemolysis and/or contamination by standardizing collection procedures and implementing quality assurance programs to achieve proficiency[29,30]
- Evaluate the role of malnutrition in relative PTH deficiency[5]
- Use assay-specific targets for CKD patients[33]
- Investigate known specific assay interferences (eg, high doses of biotin for the treatment of diabetic peripheral neuropathy can interfere with immunoassays that use streptavidin-biotin interactions)[34]

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