
PTH Ineffective PTH is ineffective when the PTHR1–signaling protein complex is defective (as in the different forms of PHP, discussed below) or in CKD in which the calcium-elevating action of PTH is impaired.

Typically, hypophosphatemia is more severe than hypocalcemia in vitamin D deficiency states because the increased PTH levels, although only partly effective in elevating blood calcium, are readily capable of promoting urinary phosphate excretion.

PHP, on the other hand, has a pathophysiology that is different from the other disorders of ineffective PTH action. PHP resembles hypoparathyroidism (in which PTH synthesis is deficient) and is manifested by hypocalcemia and hyperphosphatemia yet elevated PTH levels. The cause of the disorder is defective PTH-dependent activation of the stimulatory G protein complex or the downstream effector protein kinase A, resulting in failure of PTH to increase intracellular cyclic AMP or to respond to elevated cyclic AMP levels (see below).

CKD Improved medical management of CKD allows many patients to survive for decades and, hence, provides time enough to develop features of renal osteodystrophy, which must be controlled to avoid additional morbidity. Impaired production of $1,25(\text{OH})_2\text{D}$ is a principal factor that causes calcium deficiency, secondary hyperparathyroidism, and bone disease; hyperphosphatemia, which lowers further blood calcium levels, typically occurs only in the later stages of the disease. Low levels of $1,25(\text{OH})_2\text{D}$ due to increased FGF23 production in bone (and possibly other tissues) are critical in the development of hypocalcemia. It is notable that FGF23 levels are often dramatically elevated in end-stage kidney disease (ESKD). The uremic state also causes impairment of intestinal absorption by mechanisms other than defects in vitamin D metabolism.

Nonetheless, treatment with supraphysiologic amounts of vitamin D or calcitriol can correct impaired calcium absorption. Increased FGF23 levels are seen already during the early CKD stages and have been reported to correlate with kidney disease progression, increased mortality, and left ventricular hypertrophy. Strategies