PRO/CON DEBATE

Treatment of hyperphosphatemia: the dangers of aiming for normal PTH levels

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Abstract

Secondary hyperparathyroidism is part of the complex of chronic kidney disease-associated mineral and bone disorders (CKD-MBD) and is linked with high bone turnover, ectopic calcification, and increased cardiovascular mortality. Therefore, measures for CKD-MBD aim at lowering PTH levels, but there is no general consensus on optimal PTH target values. This manuscript is part of a pros and cons debate for keeping PTH levels within the normal range in children with CKD, focusing on the cons. We conclude that a modest increase in PTH most likely represents an appropriate adaptive response to declining kidney function in patients with CKD stages 2–5D, due to phosphaturic effects and increasing bone resistance. There is no evidence for strictly keeping PTH levels within the normal range in CKD patients with respect to bone health and cardiovascular outcome. In addition, the potentially adverse effects of PTH-lowering measures, such as active vitamin D and calcimimetics, must be taken into account. We suggest that PTH values of 1–2 times the upper normal limit (ULN) may be acceptable in children with CKD stage 2–3, and that PTH levels of 1.7–5 times UNL may be optimal in patients with CKD stage 4–5D. However, standard care of CKD-MBD in children relies on a combination of different measures in which the observation of PTH levels is only a small part of, and trends in PTH levels rather than absolute target values should determine treatment decisions in patients with CKD as recommended by the 2017 KDIGO guidelines.

Keywords Parathyroid hormone · Target range · Children · Chronic kidney disease · Phosphate · Calcification · Bone turnover
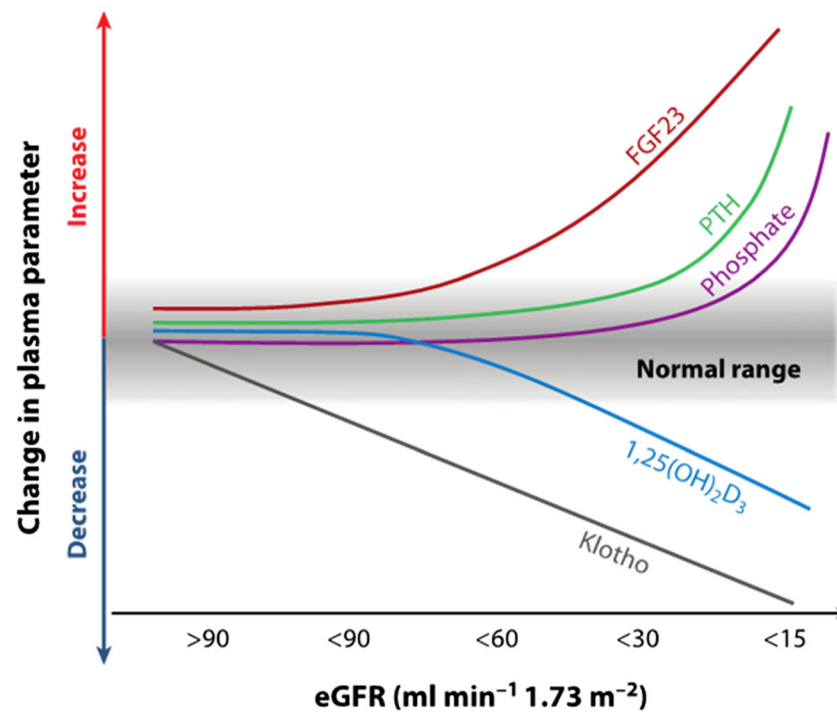
Introduction

Secondary hyperparathyroidism (SHPT) is part of the complex chronic kidney disease-associated mineral and bone disorders (CKD-MBD) [1]. In early CKD, high plasma fibroblast growth factor 23 (FGF23) is the earliest detectable abnormality in mineral metabolism (Fig. 1) [2, 3]. FGF23 serum levels start to rise as early as CKD stage 2, most likely due to elevated phosphate load, in order to keep serum phosphate levels within the normal range by decreasing renal phosphate reabsorption and inhibiting renal synthesis of active vitamin D,

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which in turn reduces phosphate reabsorption from the gut. In addition, low levels of Klotho—the co-receptor for FGF23—may partially induce FGF23 resistance, resulting in a compensatory increase in FGF23 serum levels to maintain phosphate homeostasis. However, as renal function further declines calcitriol deficiency results in hypocalcemia which stimulates, together with an increasing phosphate load, the synthesis of parathyroid hormone (PTH) by the parathyroid gland [2]. Increased PTH stimulates phosphaturia, renal 1α-hydroxylase, and calcium resorption from the bone [4]. Indeed, elevated PTH levels are present in about 50% of pediatric CKD patients with an estimated glomerular filtration rate (eGFR) < 50 ml/min/1.73m^2 [3]. This allows the body to counterbalance calcitriol deficiency-induced hypocalcemia and to keep serum phosphate levels within the normal range despite advanced CKD until the system decompensates and severe complications of CKD-MBD occur, i.e., renal osteodystrophy including bone pain, fractures, rickets, leg deformities, and growth failure, as well as ectopic calcification. Severe SHPT is associated with high bone turnover, ectopic calcification, anemia, left ventricular hypertrophy, and

Fig. 1 Proposed time profile of changes in blood phosphate, calcium, Klotho, and hormones relevant to mineral metabolism in chronic kidney disease (CKD). The decrease in Klotho protein in the kidney and blood is an early event in CKD and is sustainably and progressively reduced along with the decline of renal function. Low Klotho may partially induce fibroblast growth factor 23 (FGF23) resistance, resulting in an initial compensatory increase in FGF23 serum levels to maintain phosphate homeostasis. Elevated FGF23 decreases vitamin D levels and is followed by elevation of parathyroid hormone (PTH). Hyperphosphatemia is a relatively late event in advanced CKD; normal range is shown in gray. The scale is not meant to be truly proportionate; e.g., the elevation of FGF23 is massive in CKD compared with the elevation of PTH. The *X*-axis represents decline in renal function from stage 1 to 5 of CKD based on estimated glomerular filtration rate (eGFR). Reproduced with permission from Hu et al. [2]

increased mortality [5–11]. However, recommended CKD stage-dependent PTH target range values differ widely (Table 1) [12–16]. The European Dialysis Working Group of the ESPN recommend that PTH levels should be maintained within normal limits in children with GFR > 29 ml/min/ 1.73m^2, and within 2–3 times the upper normal limit (UNL) in CKD stages 4–5D [14]. By contrast, the US-based K/DOQI guidelines recommend a target range of 3–5 times the UNL in CKD stage 5 [12]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a PTH target range of 2–9 times the UNL in CKD stage 5D, but the higher end of the range is rarely deemed acceptable in pediatric bone care [13]. However, most importantly is the acknowledgment that none of these recommendations have been validated in a large pediatric CKD cohort study/investigation. Most recently, data from the International Pediateric Dialysis Network (IPPN) has suggested that an optimal PTH target range of 1.7–3 times UNL in pediatric peritoneal dialysis patients is associated with lower CKD-MBD complications, such as growth failure [15]. This manuscript is based on the pros and cons debate held at the 51st Annual Scientific Meeting of the European Society for Paediatric Nephrology in Antalya

Table 1 Recommended PTH target range according to CKD stage

Reference	CKD stage	GFR (ml/min/1.73m^2)	iPTH (fold UNL)
K/DOQI [12]	2	60–89	1×
	3	30–59	1×
	4	15–29	1–2×
	5	< 15, dialysis	3–5×
KDIGO [13]	5	< 15, dialysis	2–9×
ESPN [14]	2	60–89	1×
	3	30–59	1×
	4	15–29	2–3×
	5	< 15, dialysis	2–3×
IPPN [15]	5	Peritoneal dialysis	1.7–3×
Present article	2	60–89	1–2×
	3	30–59	1–2×
	4	15–29	1.7–5×
	5	< 15, dialysis	1.7–5×

CKD, chronic kidney disease; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; K/DOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease: Improving Global Outcomes; ESPN, European Society for Paediatric Nephrology; IPPN, International Pediatric Dialysis Network

in 2018 on the question of whether normal PTH levels should be aimed for in children with CKD, focusing on the cons.

Elevated PTH levels represent an appropriate body response in CKD

In children with CKD, plasma PTH levels start to rise as early as CKD stage 2 in order to keep serum phosphate levels within the normal range and to counterbalance FGF23-induced calcitriol deficiency and hypocalcemia [3, 17]. This seems to be an important compensatory mechanism since hypocalcemia is associated with poor bone mineralization [18, 19]. Even more importantly, phosphate is a vascular toxin [20]. There is a wealth of evidence coming from in vitro and clinical studies, showing that increased phosphate is associated with ectopic (vascular) calcification and mortality. In vitro studies showed that when exposed to high phosphate conditions, vessels develop apoptosis, vascular smooth-muscle cells convert to bone-like cells, and thus vessels develop extensive calcification [21]. In children on dialysis, elevated serum phosphate levels are associated with increased vessel wall thickness, arterial stiffness, and vascular calcification [8, 9, 22–25]. Elevated phosphate is associated with increased mortality in dialysis patients and with cardiovascular changes even in pre-dialysis CKD [26, 27]. This data suggests that maintaining serum phosphate levels within the normal range is important to reduce cardiovascular risk and mortality. Therefore, moderately elevated PTH levels may be required to keep a balanced mineral metabolism despite progressive CKD. This mechanism may start as early as in CKD stage 2. Thus, elevated PTH in CKD patients may be primarily interpreted as an appropriate body response in order to survive, i.e., avoid phosphate toxicity, calcitriol deficiency, and symptomatic hypocalcemia.

PTH and bone metabolism

Maintenance of calcium homeostasis and bone remodeling is an important function of PTH. Both PTH pulses and sustained elevations in PTH stimulate calcium release from the bone. PTH elicits its bone anabolic and catabolic effects by stimulating both bone formation and resorption [28]. Adequate bone remodeling is a prerequisite for skeletal development and for attaining peak bone mass. PTH acts via PTH type 1 receptor (PTH1R) expressed in osteoblasts and osteocytes, and increases osteoanabolic Wnt signaling, e.g., via repression of the osteocytic sclerostin. However, severe SHPT may result in high bone turnover and overt renal osteodystrophy including demineralization of bone.

Interpretation of plasma PTH levels in CKD

High phosphate intake, low calcium intake, and/or vitamin D deficiency may cause SHPT even in patients with CKD stage 2–3. In addition, inadequate dialysis efficacy may result in low phosphate removal and thus promote SHPT as well. Therefore, we recommend considering these things first if a patient presents with elevated PTH levels. In addition, serum concentration of PTH generally overestimates biological activity, at least in patients with advanced CKD, due to: i) post-translational modification (oxidation) of PTH, since oxidized PTH is inactive, ii) PTH resistance in target tissue due to accumulation of inhibiting C-terminal fragments, which were shown to have a prolonged half-life in advanced CKD, and iii) end-organ hyporesponsiveness to PTH [28–32]. There is an increasing evidence that CKD impacts on PTH signaling by competitive inhibition between (1-84) PTH and its fragments, PTH1R downregulation, PTH1R dysfunction, e.g., due to FGF23-stimulated soluble Klotho which prevents binding of intact PTH to PTHR, and by inhibitory or competing down-regulation signals, including sclerostin, osteoprotegerin, and inflammation [28]. This experimental data is supported by clinical studies in patients with end-stage CKD (ESKD), demonstrating that peripheral arterial disease, i.e., vascular stiffness, is associated with a more pronounced osteoblast resistance to PTH. In patients presenting with peripheral arterial disease, weaker correlation coefficients (slopes) between serum PTH and osteoblast surface were noted when compared with patients lacking vascular stiffness [33]. Therefore, PTH hyporesponsiveness in advanced CKD may explain why low bone turnover disease may be present in patients with PTH levels far above the upper normal limit, and the association between low bone turnover disease and vascular disease. Consequently, "normal" PTH levels cannot be called normal in the light of PTH resistance in advanced CKD.

PTH and growth

Although severe skeletal deformities can contribute to growth retardation, the relationship between longitudinal growth and serum PTH is unclear. Of course, growth is usually completely arrested when SHPT results in severe destruction of the metaphyseal bone architecture [12]. However, in a prospective randomized trial comparing daily or intermittent calcitriol for treatment of SHPT in pre-dialysis patients, a positive association between mean PTH levels and annual change in height SD score (SDS) was observed [34]. In a retrospective study in prepubertal children on long-term dialysis, no association between PTH levels and change in height SDS per year was noted [35]. The IPPN offers the most up-to-date information pertaining to the association between PTH and growth in a large cohort of children on peritoneal dialysis. The annual prospective change in standardized height of this patient

cohort tended to correlate inversely with time-integrated mean PTH levels: patients with mean PTH levels > 500 pg/ml (i.e., > 9 times UNL) showed a significant loss in height SDS compared with children with lower PTH levels (−0.28 versus −0.05 SDS per year; *p* < 0.05) [6]. Thus, dialyzed children with normal or up to 9 times UNL elevated PTH levels retain the potential for normal growth, whereas patients with high PTH levels (> 500 pg/ml) are at an increased risk of growth failure.

PTH and bone histology

Although PTH is widely used for monitoring CKD-MBD, it is not a true marker of bone turnover. This is due to the fact that PTH is neither involved in the process of, nor is a direct product of, bone resorption or formation. Additionally, PTH levels have proved unreliable in independently predicting bone turnover, partly due to skeletal resistance to PTH and accumulation of long C-terminal fragments, as well as PTH assay variability as outlined above. Low bone turnover is generally associated with low or low-normal PTH levels in children as well as in adults with CKD [7, 18, 19, 36]. However, low bone turnover is rarely seen in children on dialysis nowadays (approx. 4%) [18]. In addition, low bone turnover may coincide with elevated levels of PTH and high bone turnover with low PTH levels [37]. There are several pediatric bone biopsy studies designed for correctly identifying bone turnover category by using PTH or a combination of biochemical parameters which showed highly variable PTH thresholds, as recently summarized by Lalayiannis et al. [38]. This is reflected by current guidelines for children which differ markedly with respect to the recommended PTH target levels ranging from 2–3 times UNL in the European guideline, to 2–9 times UNL in the KDIGO guideline. Taken together, cohort studies in children showed that only at extremes is PTH able to predict the bone turnover status with acceptable sensitivity and specifity.

PTH and ectopic calcification

In general, elevated PTH levels are thought to be associated with cardiovascular calcification in patients with ESKD [8–10, 23]. However, in one retrospective study evaluating the presence of coronary artery calcification in young adults with childhood-onset ESKD, high PTH levels (> 4 times UNL) were associated with an increased calcification score in combination with increased inflammation (elevated C-reactive protein) only [9]. This concept is further supported by recent ex vivo studies using vessels from children with CKD stage 5, with and without dialysis, demonstrating that calcifying conditions such as high phosphate and calcium promote vascular "inflammaging," i.e., premature aging and inflammation [39]. In a cohort of 85 children who had received dialysis for at least 6 months, only a weak association between intact PTH serum levels and the degree of coronary artery calcification could be observed (*r* = 0.39; *p* = 0.03) [21]. Indeed, half of the patients presenting with PTH levels above 5 times UNL showed no coronary artery calcification at all. Important to note, in the same cohort, carotid intima-media thickness was associated with both PTH levels and vitamin D dosage. Thus, factors other than elevated PTH, such as inflammation and vitamin D medication, may be also important for the development of ectopic calcification in children with ESKD [40].

PTH and patient mortality

In adult dialysis patients, normal or slightly elevated (1–3 times UNL)—as well as very elevated PTH levels (> 5 times UNL)—were associated with increased mortality when compared with patients presenting with PTH levels between 3 and 5 times UNL [10]. Recently, the association of a CKD-MBD phenotype and risk of death was prospectively investigated in a cohort of 26,221 adult dialysis patients [41]. High PTH levels (> 5 times UNL) as well as low PTH levels (< 3 times UNL) were associated with increased risk of death and the composite endpoint of death or cardiovascular hospitalization. It is important to note that this association was much more pronounced in patients also showing high serum calcium and/or phosphate levels. The highest risk was noted in patients with high calcium and PTH (> 5 times UNL). Data from the IPPN registry indicates that PTH levels above 800 pg/ml (> 13 times ILN) are associated with increased mortality (hazard ratio 2.4, *p* < 0.05) in children on peritoneal dialysis (personal communication, Franz Schaefer). In addition, youth (< 6 years), defined syndrome, hypoalbuminemia (< 25 g/l), serum bicarbonate < 20 mM, and fluid overload (> 4%), were also independently associated with increased mortality in this cohort.

Taken together, studies in dialysis patients point to a U-shaped association between PTH levels and patient outcome (mortality, ectopic calcification). Modest increases in PTH (3–5 times UNL) are associated with a better outcome compared with normal or excessive PTH. Additional alterations of mineral metabolism, e.g., hyperphosphatemia and hypercalcemia also contribute to increased mortality in dialysis patients. Thus, "normal" PTH may be harmful in these patients.

Cardiovascular outcome of PTH decreasing measures (active vitamin D, calcimimetics)

There is no doubt that treatment with active vitamin D and/or calcimimetics improves bone health in patients with high bone turnover [42]. However, the currently available data on cardiovascular outcome is discouraging. Two trials, PRIMO and

OPERA, demonstrated a significantly increased risk of hypercalcemia in adult patients with CKD stages 3–5 and PTH levels of 50–300 pg/ml (1–5 times UNL) treated with paricalcitol, compared with a placebo in the absence of beneficial effects on surrogate cardiac endpoints [43, 44]. The EVOLVE trial could not prove the beneficial effects of cinacalcet on patients with CKD stage 5D and SHPT (> 5 times UNL) with respect to the primary endpoint cardiovascular outcome, but demonstrated an increased risk of hypocalcemia [45].

Potential adverse clinical consequences of reducing PTH values to the normal range by use of active vitamin D or calcimimetics

Both treatment for SHPT with active vitamin D and calcimimetics may result in over-suppression of bone remodeling, i.e., low bone turnover disease in patients with advanced CKD, as outlined above. In addition, active vitamin D further stimulates FGF23 in a vicious circle which may promote the development of left ventricular hypertrophy in CKD patients [46]. Furthermore, active vitamin D is known to increase phosphate and calcium (re)absorption in the kidney and from the gut, which may promote ectopic vascular calcification [47]. The use of calcimimetics may cause clinically relevant hypocalcemia resulting in impaired bone mineralization and may cause arrhythmia [48]. Thus, both medications have, at least theoretically, long-term consequence for increased cardiovascular morbidity, especially when aiming for normal PTH levels.

Conclusions

Moderate increases in PTH most likely represent an appropriate adaptive response to declining kidney function in patients with CKD stages 3–5 and perhaps also in CKD stage 2, due to phosphaturic and calcitriol stimulating effects, and increasing bone resistance in advanced CKD. There is no hard evidence for strictly keeping PTH levels within the normal range in CKD patients with respect to bone health (mineralization, turnover, growth), cardiovascular outcome and patient survival. In addition, the potentially adverse effects of PTH-lowering measures, such as active vitamin D and calcimimetics, must be taken into account. In other words, it may even be dangerous to aim for normal PTH levels in patients with advanced CKD. Unfortunately, there is no precise CKD stage-dependent PTH level at which the positive effects of PTH (phosphaturia and stimulation of renal 1α-hydroxylase for prevention/amelioration of hyperphosphatemia and hypocalcemia) are offset by its negative effects (high bone turnover and associated cardiovascular

damage). However, based on the available data, we suggest that normal or modest elevated PTH (up to 2 times UNL) may be acceptable in children with early CKD (stages 2–3), provided that measures for treatment of CKD-MBD, including adequate phosphate and calcium intake and vitamin D supplementation in vitamin D-deficient patients, are undertaken. We also suggest that PTH levels of 1.7–5 UNL in patients with advanced CKD (CKD stages 4–5D) may be optimal, and that higher levels should be avoided. Finally, it must be taken into account that the standard care of CKD-MBD in children relies on a combination of different measures in which the observation of PTH levels is only a small part, and it may be wiser to use trends in PTH levels rather than absolute target values to determine treatment decisions in patients with CKD, as recommended by the 2017 KDIGO guidelines [42].

Research recommendations

- In a large cohort of pediatric patients with CKD stages 3–5D, do assessments of bone histomorphometry and cardiovascular status and correlate these results with various PTH target ranges.
- Establish a readily available assay quantifying PTH1R signaling tone or sensitivity to PTH and use this test to asses PTH target-organ sensitivity in pediatric patients with advanced CKD. This may help to identify individual PTH target ranges in CKD patients.
- Assess the sensitivity and specifity of specific biomarkers (or a panel of biomarkers) for bone and cardiovascular health by use of the gold standard bone biopsy and non-invasive measures of cardiovascular status (e.g., carotid intima-media thickness, central pulse wave velocity, cardiac ultrasound for assessment of left ventricular mass, and skin microvascular blood flow).

Compliance with ethical standards

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