PTH Receptors and Skeletal Resistance to PTH Action

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Introduction

Chronic kidney disease (CKD) is an important global health problem, involving about 10% of the population worldwide and entailing high cardiovascular and mortality risks [1, 2]. CKD-mineral and bone disorder (CKD-MBD) is one of the many complications associated with CKD and represents a *systemic* disorder manifested by either one or a combination of: (a) abnormalities of calcium (Ca), phosphate (P), parathyroid hormone (PTH), or vitamin D metabolism; (b) abnormalities in bone turnover, mineralization, volume, linear growth, or strength (formerly known as renal osteodystrophy); and (c) vascular or other soft tissue calcifications [3–5]. Consequently, renal osteodystrophy is currently considered one measure of the skeletal component of CKD-MBD, which is quantifiable by bone histomorphometry, and recent knowledge indicates bone to be an endocrine organ at the heart of metabolic and cardiovascular complications of CKD [6].

Increased PTH levels [classically referred to as secondary hyperparathyroidism (SHPT)] are an integral component of the CKD-MBD syndrome and if they remain uncontrolled, they will worsen the laboratory abnormalities of CKD-MBD (e.g., calcium and phosphate levels), the bone structure (high-turnover bone disease), and cardiovascular parameters (e.g., vascular calcification)

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A. Covic et al. (eds.), *Parathyroid Glands in Chronic Kidney Disease*,
https://doi.org/10.1007/978-3-030-43769-5_4

[7–9]. Moreover, PTH has also classically been considered a "uremic toxin" [10] since the effect of PTH appears not to be limited to bone [11, 12]. Indeed SHPT has been claimed to contribute to many "off-target" extraskeletal clinical manifestations frequently present in CKD [11, 12]. For instance, PTH produces an increase in cytosolic "intracellular calcium" in many different cell types [13, 14] and this may be a common pathway that explains the relationship of PTH with many other systemic effects such as cognitive decline, cachexia, peripheral neuropathy, increasing osmotic fragility of erythrocytes, abnormalities of the immune system, muscular dysfunction and wasting, decreased testosterone and increased prolactin serum levels, carbohydrate intolerance and lipid abnormalities, renin-angiotensin-aldosterone system stimulation, myocardial dysfunction, and cardiac hypertrophy and fibrosis [11, 12, 15–17]. The improvement of some of these deleterious outcomes (e.g., left ventricular hypertrophy) following parathyroidectomy (PTX) supports the hypothesis of a causal link with PTH, although evidence of a direct role is still lacking [12, 18]. The above-mentioned toxic effects of PTH may explain the association of SHPT with CKD progression and atheromatous and non-atheromatous cardiovascular disease, as well as with all-cause and/or cardiovascular morbidity and mortality [19–23].

SHPT is classically considered a common, serious, and progressive complication of CKD. In the United States, the estimated prevalence of SHPT in CKD patients ranges from 2 to nearly 5 million individuals, with 30–50% of dialysis patients being affected with SHPT [24]. However, very low or relatively low PTH levels (which are associated with adynamic bone disease) are also considered an important contributory factor to the high morbidity and mortality in CKD patients [20, 25]. An increased risk of fractures and cardiovascular calcifications have been related to low PTH levels and is attributable to the inability of bone to buffer an excess of Ca and P loading [26]. Therefore, it is not surprising that associations between mortality and PTH are recognized to be complex, except at both extremes (high and low) of serum PTH levels [27]. Similarly, cohort studies have clearly indicated that only extreme levels are able to predict with acceptable sensitivity/specificity the bone turnover status [from adynamic bone disease (low-turnover) to osteitis fibrosa (high-turnover bone disease) [4, 28]. Although PTH is a crucial determinant of bone remodeling [12], in uremic conditions it does not offer information on bone properties and strength, similarly to most bone markers [12, 29, 30]. Beyond the CKD population, investigations of cohorts of primarily cardiology patients have confirmed the independent association between high PTH levels, cardiovascular events, and mortality (including sudden cardiac death) [31–33].

Pathophysiology of Secondary Hyperparathyroidism

It is well known that progressive loss of kidney function leads to an increased P load (retention) [34, 35], increased fibroblast growth factor 23 (FGF23) and decreased α-klotho [36–38], and decreased synthesis and increased catabolism

of calcitriol (1,25-dihydroxyvitamin D; active vitamin D), among many other metabolic derangements [15, 39]. All these factors, extensively reviewed elsewhere [15, 40, 41], involve various closely interacting mechanisms, including the down-regulation of Ca-sensing, vitamin D, and FGF23 receptors, and contribute in increasing the synthesis and secretion of PTH by the parathyroid glands as well as the proliferation (polyclonal and/or monoclonal) of parathyroid cells. It is well known that hyperplasia of the parathyroid glands starts to develop during the very early stages of CKD [11, 15, 42, 43].

Although it is currently known that P can both directly and indirectly induce SHPT in patients with CKD [44–46], it is widely accepted that Ca is the most important regulator of parathyroid gland function [12]. In order to correct *hypocalcemia*, rapid release of stored PTH is necessary, with increased synthesis and, eventually, parathyroid cell proliferation if required to produce the necessary amount of PTH to correct Ca. Thus, most of the previously mentioned mechanisms (e.g., P retention, decreased calcitriol production) share in common the capability to lead to secondary multifactorial hypocalcemia and hence induce SHPT. In the parathyroid cell, the transmembrane Ca-sensing receptor (CaSR), the complex FGFR1-klotho receptor complex, and the nuclear parathyroid vitamin D receptor (VDR) are down-regulated, resulting in increased PTH synthesis and secretion as well as parathyroid cell proliferation [47, 48]. It is beyond the scope of this review to analyze the complex interrelationships among all these pathophysiologic factors leading to SHPT. Rather, the focus will be on analysis of the importance of skeletal resistance to the action of PTH in the pathogenesis of SHPT and, on the other hand, the development of adynamic bone disease, since this remains greatly underappreciated by the nephrology community.

Skeletal Resistance to PTH Action

"Skeletal" resistance to the action of PTH in CKD (also known as calcemic resistance to PTH or PTH resistance) is an old concept [49], recently recognized as "hyporesponsiveness" to PTH [27, 50]. In fact, both bone and renal responses to the action of PTH are progressively impaired in CKD [27] and the term "hyporesponsiveness" may be more appropriate because the response to PTH is blunted but not completely absent [27].

A decreased calcemic response to PTH was first described by J. M. Evanson in 1966 [49] when he reported the calcemic response to an infusion of crude parathyroid *extract* (1 U/kg/h over 10 h) to be significantly lower in 12 hypocalcemic patients with CKD than in normal subjects or patients with primary hyperparathyroidism [49]. He postulated that vitamin D is necessary for the action of PTH on bone, since a decreased calcemic response was also observed in hypocalcemic patients with steatorrhea or rickets [49]. Subsequently, Massry et al. observed that the calcemic response to a parathyroid *extract* (2 IU/kg over 8 h) in thyroparathyroidectomized (T-PTX) dogs, before and after the induction of uremia by bilateral

ureteral ligation (BUL) or by bilateral nephrectomy, was markedly impaired, but that the impairment was more severe one day after nephrectomy [51]. They also observed that the calcemic response after 2 or 3 days of BUL was similar to that seen at one day after nephrectomy and that calcitriol partially restored the calcemic response to PTH [51]. The authors concluded that a deficiency of calcitriol was at least partly responsible for the skeletal resistance to the calcemic action of PTH in the presence of uremia and that uremia, per se, could also have contributed to this phenomenon. In addition, it was observed that the calcemic response to PTH was lower in *patients* with moderate and advanced CKD (including hemodialysis and renal transplant patients) than in normal healthy subjects [52]. This reduced calcemic response was not related to the initial levels of serum Ca, P, or PTH and was not reversed by hemodialysis [52].

Llach et al. also noted a decreased calcemic response to *endogenous* PTH and an altered divalent ion metabolism in *patients* with early CKD [53, 54]. For instance, they described delayed recovery from ethylene diamine tetra-acetic acid (EDTA)-induced hypocalcemia in these patients as compared with normal subjects, despite higher serum PTH levels in the CKD group [53]. Such observations indicated that the impaired calcemic response to PTH appears early in the course of CKD and that a direct consequence is a continuous requirement for a greater concentration of circulating PTH in order to maintain a normal Ca homeostasis in affected patients. Ever since the study by Albright et al. [55] it has been hypothesized that P retention and reciprocal blood Ca lowering in CKD patients might cause parathyroid hyperplasia and renal osteitis fibrosa. With the formulation of the "trade-off" hypothesis by Bricker and Slatopolsky [34, 56–58], the reduction in the level of serum Ca in CKD was considered to be the main driver of increased synthesis and secretion of PTH, as well as parathyroid hyperplasia. However, the presence of skeletal resistance to PTH in CKD provides a usually forgotten additional mechanism in the pathogenesis of hypocalcemia and SHPT in CKD [15, 59, 60]. The appearance of skeletal resistance to the action of PTH *early* in the course of renal failure would induce hypocalcemia, which in turn would stimulate the parathyroid glands, resulting in continuously increased secretion of the hormone and hyperplasia. At the other extreme, the *late* appearance of detectable hypocalcemia in advanced stages of CKD [61] clearly represents the final failure of PTH to restore Ca levels to normal, and the maximal clinical expression of hyporesponsiveness to PTH.

Factors Linked to Impaired Calcemic Response to PTH (See Table 1)

Decreased Levels of Calcitriol

Since the earliest work in this field it was considered that vitamin D appears to be necessary for the proper action of PTH on bone [49]. Later, it was demonstrated that the administration of calcitriol restored, at least partially, the blunted

calcemic response to PTH in experimental animals (rats and dogs) [51, 62, 63] leading to the conclusion that this impaired calcemic response to PTH is related to the decreased calcitriol levels observed in early CKD. Also, in *patients* with early CKD, daily administration of 0.5 μg of calcitriol for 6 weeks improved the calcemic response to PTH [54]. Finally, studies in experimental animals also exhibited complete correction of the calcemic response to PTH after the administration of calcitriol [$1,25(OH)_2D_3$] together with $24,25(OH)_2D_3$ [64]. Consequently, although an adequate mechanistic explanation for these observations is still lacking, it seems clear that reduced serum vitamin D levels play a role in the impaired calcemic response to PTH, and that vitamin D could enhance the action of PTH on bone. However, other investigators did not confirm this beneficial effect of calcitriol on the calcemic response to PTH [62, 65]. There is also no scientific evidence demonstrating that the correction of native vitamin D deficiency (25OHD < 15 ng/ml), which is often the case in CKD, by restoring serum 25OHD levels, would improve the calcemic response to PTH.

Phosphate Retention

It is also well known that P retention significantly decreases the calcemic response to PTH in CKD [63, 66]. Somerville and Kaye reinfused urine into T-PTX rats, inducing *acute* uremia in the presence of normal kidneys, and observed that the calcemic response to PTH after 5 h of PTH extract infusion was clearly blunted. Removal of P by treating urine with zirconium oxide completely restored the calcemic response to PTH [66]. Moreover, other groups of T-PTX rats given PTH extract were infused with an electrolyte solution containing varying amounts of P up to a maximum similar to the amount that a urine-infused rat would receive. A highly significant inverse relationship was found between the dose of P infused with the electrolyte solution and the measured calcemic response to PTH [66]. Since P and calcitriol are also closely interrelated (P inhibits the synthesis of calcitriol), it could not be excluded that at least some of these observations might be mediated indirectly by inhibition of calcitriol. Thus, using a different model, Rodriguez et al. [63] demonstrated that rats with CKD fed with a low-P diet exhibited an improvement in the calcemic response during a constant 48-h infusion of 1–34 rat PTH with an ALZET® pump; moreover, rats with either moderate or advanced CKD had an impaired calcemic response to PTH and low levels of calcitriol. The low-P diet enhanced the calcemic response to PTH in both groups of rats, but only those with moderate CKD had a significant increment in calcitriol levels. Thus, with moderate CKD, P restriction improved the calcemic response to PTH, and this effect could be due to higher levels of calcitriol. However, in advanced CKD, the calcemic response to PTH improved with P restriction *independently* of calcitriol. As a matter of fact, we observed that the negative effect of P retention on the calcemic response to PTH may be far superior to the effect of calcitriol deficiency in rats with CKD [67, 68] (See Fig. 1).

Improvement of the calcemic response to a standardized infusion of PTH after P restriction has also been demonstrated in *patients* with mild CKD [69]. Interestingly, in rats with normal renal function that received a high-P diet, the calcemic response to PTH was reduced in the absence of any change in serum P levels; this indicates that the diet itself was responsible for the reduction in response. This is an issue that should be taken into consideration currently, given the lack of a clear recommendation on whether dietary P restriction should be applied in CKD stages 2–3. The intrinsic mechanism that leads to a P-induced decrease in the calcemic response to PTH is not completely known but, in addition to the effect of P on calcitriol levels, the ambient P concentration in bone may affect the amount of exchangeable Ca that can be mobilized by PTH [62, 70].

All of the above experiments were done before the discovery of FGF23, and to date the possibility that high FGF23 (which may act on osteoblasts) may reduce the calcemic effect of PTH on bone has not been excluded. It could be that high FGF23 either directly or indirectly (via calcitriol suppression, Dkk1 stimulation or sclerostin) interferes with PTH-mediated Ca efflux from bone. Moreover, multiple binding sites for Ca^{2+} and PO_4^{3-} ions have been described at the CaSR [71]. While Ca^{2+} ions stabilize its active state, PO_4^{3-} ions reinforce the *inactive* conformation of the CaSR, thus contributing to increased PTH secretion [71]. A similar inactivating effect of P on the bone CaSR could also be involved in such reduced calcemic response to PTH in CKD.

Although both P restriction and calcitriol supplementation *improve* the calcemic response to PTH, they do not seem to completely restore it, either alone or together. Conversely, in PTX dogs or rats [63, 65, 72], the removal of circulating PTH corrects the calcemic response to PTH despite the presence of hyperphosphatemia and low calcitriol levels.

Down-Regulation of PTH Receptors

The aforementioned findings suggested that high levels of endogenous PTH levels in PTX uremic animals could have desensitized the skeleton to the administration of exogenous PTH [65, 73]. The role of down-regulation of PTH bone receptors by high PTH levels was established after the observation that the removal of PTH seemed to restore the responsiveness to its receptors. Likewise, it was described in isolated perfused bones from uremic dogs with acute or chronic renal failure that the release of cyclic adenosine monophosphate (cAMP) was blunted in response to PTH, whereas it was restored by T-PTX [74, 75]. Although PTX corrected the calcemic response to PTH in experimental uremia, we noted that holding PTH levels in the normal range in rats with CKD fed with a low-P diet did *not* correct the calcemic response to PTH [72]. Thus, uremic rats with normal PTH levels, achieved with partial PTX, still showed a 50% decrease in the calcemic response to PTH as compared with normal rats [72]. This is consistent with clinical studies showing that subtotal PTX resulted in almost normal PTH levels but did not

enhance the calcemic response to PTH [52]. Similarly, PTX improved the calcemic response to PTH not only in animals with CKD but also in sham-operated rats [72]. Therefore, PTH-induced down-regulation of PTH receptors appeared not to be the sole explanation for the decrease in the calcemic response to PTH in CKD. It was hypothesized that the significant improvement in the calcemic response to PTH after PTX could be due to a phenomenon of hypersensitization following hormone depletion, as described for other hormonal systems, among other potential explanations affecting the exchangeable Ca pool in bone described elsewhere [72, 76].

All of these findings do not exclude down-regulation of PTH receptors as a potential cause of the decreased calcemic response to PTH [77]. Thus, the cloning of a ubiquitous PTH receptor (PTHR) gene—a common receptor for both PTH and PTH-related peptide (PTHrP) [78, 79]—has allowed demonstration that the PTH1R (PTHR-1) is not only widely distributed in tissues [80] but also down-regulated in uremic kidneys, epiphyseal cartilage growth plates, and osteoblasts, at least at the transcription level [81–84]. Human data are less consistent, with some investigators demonstrating decreased expression [85] while others have recently reported increased expression [86]. Methodological issues and variation in the characteristics of the studied populations may explain this apparent discrepancy [27].

The finding of down-regulation of the PTH1R mRNA in bone tissue and not in the liver or heart suggested that PTH1R expression is regulated in a cell-specific manner regardless of the uremic state [87]. It is likely, however, that factors other than the increased PTH levels down-regulate this receptor [82, 87]. Thus, Ureña et al. showed the expression of PTH1R mRNA to be decreased in kidneys from both rats with CKD and rats with CKD that were subjected to PTX [87]. Since PTX did not restore the expression of PTH1R mRNA, elevation of PTH levels would not be necessary to induce its down-regulation in CKD. Their data also demonstrated that neither an increase in plasma PTH and P nor a decrease in plasma Ca is important in renal PTH1R down-regulation during CKD, and that it is also unlikely that an increase in the locally produced renal PTHrP could down-regulate its own receptor. However, other authors observed *increased* expression of PTH1R mRNA after PTX, but controls were not available [83].

Although the mechanisms responsible for the putative desensitization or down-regulation of PTH1R in CKD remain very poorly defined, several studies have implicated several uremic factors and C-terminal PTH fragments (see below). The available information on PTH1R regulation is very limited and even contradictory, and beyond the scope of this review [88–91].

Uremia

Importantly, in experimental rats with CKD we observed a significant decrease in the calcemic response to a 48-h rat 1–34 PTH infusion despite the presence

of normal serum Ca, P, calcitriol, and PTH levels. This finding suggests that factors intrinsic to uremia may, per se, impair the calcemic response to PTH [72]. These data were subsequently confirmed in a different model when Berdud et al. [92] observed that maintenance of *normal* PTH levels in uremic PTX rats by constant infusion of PTH did not correct the impaired calcemic response to PTH.

The presence of unknown uremic factors, beyond P, that are potentially responsible for the decreased calcemic response to PTH in CKD had already been postulated previously [52]. Similarly, Wills and Jenkins had also shown that serum from uremic patients inhibited PTH-induced bone resorption in an in vitro model, whereas serum obtained after dialysis did not [93]. Low molecular weight inhibitors of osteoblast mitogenesis in uremic plasma were described [94], and subsequent experimental studies pointed towards different uremic toxins [95] triggering oxidative stress, such as indoxyl sulfate (IS) and *p*-cresyl sulfate (PCS) [96, 97] and/or inflammatory bioactive oxidized low-density lipoproteins [98]. Increased oxidative stress and low-degree inflammation are common conditions in CKD, and thus they may be not only causal but also common pathways (e.g., P retention or calcitriol deficiency is also associated with oxidative stress and inflammation) linking CKD and PTH hyporesponsiveness [27]. In vitro studies [99] have shown that the uremic toxin IS inhibits not only osteoblast but also osteoclast differentiation and function, and that these effects are enhanced in the presence of high P concentrations. In vivo studies [100] have also shown that the administration of the oral charcoal adsorbent AST-120 prevented low-turnover bone in uremic rats. Nii-Kono et al. [96] further showed that IS induces a state of PTH resistance, consisting in a reduction of PTH-induced cAMP and PTHR gene expression, and decreases the viability of osteoblasts maintained in culture. These authors also demonstrated that free radical production in osteoblasts increases in relation to the concentration of IS added [96]. Furthermore, their results suggested that IS is taken up by osteoblasts via the organic anion transporter-3, augmenting oxidative stress to impair osteoblast function and down-regulate PTH1R expression [96]. On the other hand, contradictory results have recently been reported by Barreto et al. [101], who showed a *positive* association of serum IS with osteoblast surface and bone formation rate in 49 CKD stage 2–3 patients (36 ± 17 ml/min/1.73 m^2); however, this study may have been largely underpowered to address this question. Although the temporal sequence is unknown, it is possible that early accumulation of uremic toxins induces skeletal PTH hyporesponsiveness and therefore contributes to the initial adaptive increase in PTH (initial biochemical SHPT) in order to normalize the important serum Ca (and P) levels. At a certain point, the progressive increase in serum PTH levels could then override the described direct inhibitory effects of IS on bone turnover [39]. Finally, uremic toxins may also stimulate PTH secretion indirectly by decreasing calcitriol synthesis and binding to DNA vitamin D response elements [102, 103], inducing resistance to the inhibitory action of calcitriol.

PTH Abnormal Metabolism and Fragments in CKD

An increased rate of PTH secretion is primarily responsible for high plasma levels of PTH in CKD. However, evidence demonstrates that the kidneys play an important role in the degradation of PTH and that, in patients with CKD, the metabolic clearance of PTH, like that of other peptide hormones, is reduced.

PTH is a hormone actively secreted mainly by chief cells of the parathyroid gland as a single-chain polypeptide containing 84 amino acids (1–84 PTH) [104, 105]. The physiological role of the increased number of parathyroid oxyphil cells in CKD or the chief-to-oxyphil transdifferentiation is still largely unknown [106, 107]. As mentioned previously, PTH increases serum Ca by activation of the PTH1R, which is mainly present in bone and kidney but is also found in a variety of tissues not regarded as classic PTH targets. This explains the widespread effects of PTH and illustrates why PTH is considered to be a clinically relevant uremic toxin, at least in patients with advanced CKD [11].

The amino-terminal extreme of PTH is required for activation of adenyl-cyclase. The PTH1R, coupled to G-proteins, is activated equivalently by 1–84 PTH, amino-terminal PTH, and PTHrP.

PTH is physiologically released in episodic secretory bursts that are superimposed on a basal, tonic mode of secretion [108], and this pulsatile secretion may determine the balance between its catabolic and anabolic effects on the skeleton [109, 110]. Such pulsatility has been detected in both normal subjects and patients with CKD [108, 111]. Despite the pulsatile character of PTH release, intact PTH levels were found to be continuously maintained within the normal range in a control group and in CKD patients with normal parathyroid function whereas in CKD patients with SHPT, PTH changes were restricted within a level of hyperparathyroidism [111].

Secreted 1–84 PTH is degraded rapidly (half-life of approximately 2–4 min) to amino-terminal and carboxy-terminal fragments [112]. The amino-terminal residues bind to the PTH1R, activate cellular responses, and mimic all the Ca-regulating actions of PTH in animals [113]. The carboxy-terminal fragment of PTH seems to be essential for hormone processing (efficient transport across the endoplasmic reticulum) and secretion [114]. Although 1–84 PTH is the main source of secreted PTH, it is also known that the gland can secrete carboxy-terminal fragments and that the relative secretion of these fragments increases or decreases in the presence of hypercalcemia or hypocalcemia, respectively [115, 116]. Studies have shown that preferential secretion of carboxy-terminal fragments may not occur in primary hyperparathyroidism as it does in other hypercalcemic states [117], and that some subpopulations of parathyroid cells from hyperplastic or adenomatous glands can secrete in vitro more amino-terminal fragments than 1–84 PTH [118].

Because of the shorter half-lives of both 1–84 PTH and amino-terminal fragments, the carboxy-terminal fragments become the predominating PTH peptide in the circulation. The parent peptide is rapidly degraded in the peripheral

tissues, particularly in the kidneys and the liver [11, 112, 119]. The liver has great capacity to degrade the peptide, but it may not play an important role in the degradation of fragments [120]. By contrast, the kidney can extract and degrade the complete molecule and its fragments [121], at least partially via the action of cathepsin D [122]. Thus, impairment of renal function causes accumulation of carboxy-terminal fragments, and although amino-terminal fragments are also produced by cleavage of 1–84 PTH (i.e., by Kupffer cells), they are rapidly degraded, unlike the corresponding carboxy-terminal fragments [11].

As mentioned above, carboxy-terminal fragments are mainly catabolized in the kidney, and the degradation process involves solely glomerular filtration and tubular reabsorption, whereas the amino-terminal fragment undergoes both tubular reabsorption and peritubular uptake, like 1–84 PTH [112]. These pathways of PTH metabolism are altered in the presence of CKD, and renal excretion of PTH and its fragments (mainly carboxy-terminal) is decreased [112, 123]. Therefore, such alterations in PTH metabolism also partially account for the elevated PTH levels observed in CKD.

Although PTH measurement with the current immunoradiometric (IRMA) and immunochemiluminescence assays directed to the so-called *intact* PTH (the most widely implemented worldwide) has significantly improved clinical management, several fragments still affect the measurement and interpretation of these second-generation *intact* PTH assays. Thus, it is now well known that there are non-(1–84)-PTH truncated fragments in the circulation (such as 7–84 PTH) which, in addition to 1–84 PTH, are measured by most IRMA intact PTH assays, giving erroneously high PTH values [27, 124, 125]. This fact is especially important now that many different (automated and non-automated) *non-standardized* intact PTH kits are available on the market, using different antibodies and without a common calibrator [11, 27, 126–129]. Consequently, there is wide variability among commercially available intact PTH assays [128]. Third-generation assays (measuring the so-called "whole" or "bioactive" PTH) seem to detect only the biologically active 1–84 PTH molecule because the detection antibody is more specific for the first four amino acids at the amino-terminal end [130, 131]. While these new-generation "whole PTH" assays do not interact with 7–84 PTH fragments, they seem to measure, in addition to 1–84 PTH, a post-translational form called amino-PTH [132]. In any case, "intact" and "whole" PTH assays appear to be of similar clinical value for the diagnosis of SHPT and the follow-up of CKD-MBD, and "whole"/"bio-intact" PTH measurement is not yet fully recommended in any guideline [4].

The recent description of *non-active* oxidized-PTH adds complexity to the clinical interpretation of PTH values [112, 133–136], and it has recently been debated whether the increased mortality risk associated with PTH might actually reflect an oxidative stress-related mortality [19, 112, 135]. Whereas it is widely accepted that PTH measurement (especially *trends*) is an appropriate marker of *parathyroid* activity, PTH is only indirectly and weakly associated with bone dynamics [137]. Therefore, over the last decade there has been increased controversy over the validity of PTH as a surrogate marker of CKD-MBD and/or bone turnover

[137, 138], as well as for the definition of optimal PTH targets in both non-dialysis and dialysis CKD patients [4, 139].

Furthermore, regarding the importance of these abnormalities in the metabolism of PTH for the calcemic response to PTH, it has been reported that, in PTX rats fed a calcium-deficient diet, 7–84 PTH was not only biologically inactive but also had *antagonistic* effects on the PTHR in kidney and bone [130]. In these animals, plasma Ca was increased 2 h after 1–84 PTH treatment, while 7–84 PTH had no effect. However, when 1–84 PTH and 7–84 PTH were given simultaneously in a 1:1 molar ratio, the calcemic response to 1–84 PTH was decreased by 94%. Moreover, the administration of 1–84 PTH increased the renal fractional excretion of P in normal rats. However, when 1–84 PTH and 7–84 PTH were given simultaneously, the 7–84 PTH decreased the phosphaturic response by 50.2%. Finally, in surgically excised parathyroid glands from six uremic patients, the authors found that 44.1% of the total intracellular PTH was the non-PTH (1–84), most likely PTH 7–84. They concluded that in patients with CKD, the presence of high circulating levels of non-1–84 PTH fragments detected by the "intact" assay and the antagonistic effects of 7–84 PTH on the biological activity of 1–84 PTH explain the need for higher levels of "intact" PTH to prevent adynamic bone disease and provide a novel mechanism for skeletal resistance to PTH in uremia [130].

In addition to the "classic" PTH1R, it is currently accepted that a carboxy-terminal PTHR (PTH4R or PTHR-C) may mediate these different actions [140–142]. Increasing evidence indicates that the C-terminal PTH fragments, by binding and competing with 1–84 PTH for the PTH1R or by binding to the PTHR-C, exert these different/opposite biological effects as compared to 1–84 PTH [11, 27, 130, 141, 143–145]. Actually, it has been shown that the effects of 7–84 PTH on 1–84 PTH secretion and on plasma Ca levels are not associated with changes in PTH, PTH1R, CaSR, and PTHrP gene expression in rat parathyroid glands [145], and it has been hypothesized that PTH 7–84 regulates PTH secretion via an autocrine/paracrine regulatory mechanism [145]. The biological significance of this system may relate to the fact that during hypercalcemia the PTHR-C may help to maintain normal bone formation when the carboxy-terminal fragments exceed those of 1–84 PTH. Therefore, it has been postulated that the ratio of 1–84 PTH (or amino-terminal PTH) to carboxy-terminal PTH, which would be equivalent to the opposite effects of PTH1R/PTHR-C receptor activation, may be important in understanding not only the changes in the parathyroid gland but also the bone activity observed in CKD patients [11]. Moreover, the increased production of large carboxy-terminal PTH fragments by parathyroid glands during hypercalcemia, mentioned earlier, may help to restore Ca by inhibition of bone resorption [11, 115]. This relative increase in C-terminal fragments has been demonstrated in hemodialysis patients exposed to low and high Ca concentrations in the dialysis bath [116].

Other PTH receptors (PTH2R and PTH3R) have also been described but their effects in humans and in CKD are largely unknown [12, 146, 147]. PTH2R is not expressed in renal tubules and bone and is not activated by PTHrP. Like PTH1R,

PTH2R responds to PTH with generation of cAMP and an increase in intracellular calcium.

Additional information on PTH metabolism and signaling, both in health and in CKD and including classic and non-classic target organs for PTH, may be found in recent review papers [11, 27].

Downstream Competing Signals, Local or Systemic Factors

It is possible that the downstream effects of PTH may be offset by associated competing and/or inhibitory endocrine or paracrine signals, mediated by, for example, FGF23, klotho, calcitonin, osteoprotegerin, bone morphogenetic proteins, Wnt antagonists, and insulin-like growth factors, in addition to local environmental factors (i.e., inflammation, cytokines, oxidative stress, acid-base disturbances, and Ca, P, magnesium, and aluminum concentrations) [27, 39].

Thus, a recent study demonstrated that a recombinant human *klotho* protein interacted with human PTH1R to inhibit the binding of human PTH in *renal* tubular cells. It also inhibited the PTH-induced 1-α-hydroxylase expression by tubular cells both in vitro and in vivo [148]. These results suggest that free klotho mediates the FGF23-induced inhibition of calcitriol synthesis [148], and it has been hypothesized that as long as PTH underlies basal production of calcitriol, free klotho mediates, at least in part, the decrease in calcitriol levels in response to FGF23 by impairing PTH signaling [148].

The role of endogenous *calcitonin* production by thyroid C cells in the pathogenesis of SHPT—in general, in the protection against hypercalcemia, and in the decreased calcemic response to PTH in CKD—has also been analyzed [149–154]. It has been shown that in the absence of calcitonin, the calcemic response to PTH increased in rats regardless of whether they had CKD or not. In the presence of SHPT and hypercalcemia, calcitonin was an important modifier of the calcemic response to PTH, especially in animals with CKD [149, 151].

There is scarce information about a potential role of *osteoprotegerin* (OPG, a potent osteoclast activation inhibitor) in the CKD-MBD complex. Since skeletal resistance to PTH appears as an anti-calcemic effect against exogenous PTH load in the physiological aspect, and as the discrepancy between serum PTH level and bone turnover in the morphological aspect, OPG has been postulated to be a common pathogenic mediator of both high- and low-bone turnover diseases [155, 156]. Thus, the high circulating OPG levels found in CKD [156] may promote skeletal resistance to PTH through suppression of osteo*clasto*genesis [155, 157].

Importantly, *Wnt antagonists* such as *sclerostin*, the product of the SOST gene and mainly produced by osteocytes, was originally believed to be a non-classic BMP antagonist [158]. Sclerostin has now been identified as a soluble inhibitor of the Wnt signaling pathway via binding to LRP5/6 receptors [159, 160], and hence it may lead to decreased bone formation by inhibiting osteo*blasto*genesis (in contrast to OPG). Sclerostin may also play a role in the mediation of systemic and local factors such as calcitriol, PTH, glucocorticoids, and tumor necrosis

factor-α [161]. Circulating sclerostin levels increase with age and with declining renal function [161–163] and are also increased in diabetic patients independently of gender and age [164]. Levels decrease rapidly after renal transplantation [165, 166]. Nevertheless, it remains a matter of debate to what extent circulating sclerostin levels reflect bone expression and affect local signaling, since discrepant findings have been described [167]. Increased osteocytic sclerostin expression has indeed been observed in early-stage CKD despite still normal serum PTH levels [168], and the increase persists in dialysis patients, although to a lesser extent, despite elevated PTH levels [169].

Sclerostin and the related Dickkopf-1 (Dkk1) or secreted frizzled-related protein 4 (sFRP4) have been postulated to be potentially important mediators of the development of adynamic bone disease [12, 39, 97, 170] and/or skeletal resistance to the action of PTH [39, 97, 170]. A new paradigm is evolving and it has been proposed that early inhibition of the osteocyte Wnt pathway with an increase in the expression of sclerostin and other inhibitors of the Wnt/β catenin signaling pathway may be the initial stage of renal osteodystrophy and may explain observations of a relatively high and increasing prevalence of adynamic bone disease [101, 171–173]. It has even been hypothesized that in early CKD stages, low bone turnover prevails, with adynamic bone disease being the predominant form [39, 97]. With the progression of CKD to more advanced stages and increasing circulating levels of PTH, the steadily increasing activation of the PTH1R eventually overcomes the skeletal resistance to PTH and osteitis fibrosa ensues, if left untreated [12, 39]. Whether FGF23 and α-klotho play a direct role in this postulated transition from low- to high-turnover bone disease or participate only indirectly via regulating PTH secretion remains to be seen [39], but osteocyte dysfunction has been shown to be altered early in the course of CKD [39]. Of note, the use of an anti-sclerostin antibody in a CKD rat model of progressive renal osteodystrophy was shown to increase trabecular bone volume/total volume and trabecular mineralization surface in animals with low, but not high, PTH [174]. Similarly, bone properties (bone volume, cortical geometry, and biomechanical properties) improved only when PTH levels were low [174]. Whether high sclerostin levels are the cause or the consequence of PTH hyporesponsiveness in CKD remains to be clarified [166].

It also has to be taken into account that other factors such as racial and sex differences [175–177], the higher age and increased prevalence of diabetes among the CKD population, and overzealous PTH control (e.g., normalization of PTH in non-dialysis CKD patients) may influence the evaluation of PTH hyporesponsiveness [144].

Clinical Implications of Skeletal Resistance to the Action of PTH

Skeletal resistance to PTH was initially suggested as a mechanism of PTH hypersecretion in CKD. Interest in this background abnormality has been resuscitated by the effective, potentially excessive suppression of PTH by different therapies (i.e., Ca-based P binders, vitamin D, calcimimetics) and the increasing prevalence

of adynamic bone disease and its associated risks (including vascular calcification and fractures) [9, 27, 60, 97, 170, 178]. As mentioned previously, skeletal resistance to PTH is currently recognized as "hyporesponsiveness" to PTH or "relative hypoparathyroidism" in terms of its relation to bone turnover [27, 39, 60, 97]. London et al., analyzing the presence of a bone–vascular axis and/or bone–vascular cross-talk [179], had already shown an inverse association between vascular calcification and lower serum PTH, low osteoclast numbers and smaller osteoblastic surfaces, and smaller or absent double tetracycline labeling surfaces, although also with high percentages of aluminum-stained surfaces [180]. In a recent cross-sectional study, these authors also found peripheral artery disease to be associated with significant reductions in the skeletal anabolic response to PTH, as demonstrated by weaker correlation coefficients (slopes) between serum PTH and double-labelled surfaces or osteoblast surfaces in patients with peripheral artery disease [181].

Additional evidence that PTH hyporesponsiveness is an important factor in the development of SHPT and/or adynamic bone disease derives from clinical studies demonstrating that a high level of circulating PTH is necessary to maintain normal bone remodeling [182–184]. Consequently, for instance in dialysis patients, current guidelines [4, 185] suggest that treatment should be modified to keep PTH levels higher than twice the upper limit of normal (better in conjunction with evaluation of bone-specific alkaline phosphatase) to avoid a low bone turnover. Also, "predialysis patients" with CKD need higher levels of PTH to maintain a normal osteoblastic surface [183], a fact that suggests that maintenance dialysis may enhance the skeletal response to PTH. However, reversibility by dialysis is not a uniform observation [52]. Finally, the presence of this multifactorial complex hyporesponsiveness to PTH may also explain the absence of clear associations between circulating PTH levels and outcomes in CKD patients (usually U-, J-, or inverted J-shaped, and overall rather weak) as opposed to the linear associations observed in primary hyperparathyroidism [27].

Conclusion

According to the previously described experimental observations demonstrating the presence of a decreased calcemic response using a PTH infusion, either with extracts in CKD patients or with synthetic PTH in different experimental models, hyporesponsiveness to PTH is just as much an integral component of CKD-MBD as are elevated circulating PTH levels [27]. Clear differences in the calcemic response to PTH among CKD and normal subjects or animals cannot just be explained by the presence of distinct inactive or antagonistic PTH fragments, since all individuals and experimental animals received the same PTH compound (usually from the same batch) at a constant rate [67, 72]. Phosphate retention, calcitriol deficiency, sclerostin, and other uremic factors may play a role by desensitizing and/or down-regulating the PTHR or downstream signaling.

Although skeletal resistance to PTH was initially suggested as a mechanism of PTH hypersecretion in CKD, "hyporesponsiveness" to PTH has also been associated with the increasing prevalence of low-turnover bone disease, which is explained by, among other factors, an increasing number of elderly and diabetic patients with CKD and treatment overshooting. Therefore, hyporesponsiveness to PTH should be taken into account when treating SHPT in CKD patients and it is important to avoid the normalization of PTH levels in these patients [139, 185]; on the other hand, progressively increasing PTH levels may indicate a change from an adaptive to a maladaptive clinical situation that requires therapeutic decisions (See Fig. 2).

Defining an optimal PTH target may be challenging but accomplishable at the population level, but it may be very difficult at the individual patient level [27]. Whether it is best to wait for onset of severe SHPT before starting antiparathyroid treatment, as suggested by the recent KDIGO guidelines [4], or to avoid complete normalization of PTH levels, as suggested by others [139], remains to be determined. Probably one single PTH recommendation does not fit all CKD patients, and nephrologists will be drawn towards a more personalized and individual management by the need to take into account other factors such as age, diabetic status, presence of metabolic syndrome, fracture risk, vascular calcification, and other biochemical markers, as well as recently identified factors that require further investigation (uremic toxins, FGF23/klotho, Wnt/β-catenin, type 2 activin A receptor pathways, etc.). Interestingly, recent evidence has indicated that osteocytes are crucial cellular targets of PTH, and the concept of "osteocytic osteolysis" has been proposed as a mechanism through which PTH rapidly increases blood calcium levels [186]. One attractive mechanism through which PTH signaling in osteocytes influences skeletal remodeling is by coordinated transcriptional regulation of paracrine mediators, including SOST [myocyte enhancer factors (MEF2)] and receptor activator of NF-κB ligand (RANKL) [186]. Beyond SOST and RANKL, PTH/PTHrP signaling in osteocytes may directly influence the way osteocytes remodel their perilacunar environment to influence bone homeostasis in a cell-autonomous manner [186].

In the meantime, despite its limitations [187], no other biomarker or therapeutic strategy has been proven to be superior to PTH, and efforts seem mandatory to improve diagnosis. More frequent monitoring, enabling PTH trends to be captured, seems the appropriate way to proceed [27] until better new molecular targets and treatments become available that demonstrate proven efficacy in clinical practice [137, 188].

Finally, resistance to the biological action of several other hormones, such as insulin, calcitriol, growth hormone, and FGF23, is also a well-known feature of CKD [189–192], as is decreased expression of several other receptors (i.e. VDR, CaSR, FGFR/klotho) [15, 72, 193–201]. As a matter of fact, uremia may thus be considered a disease which extensively affects different types of receptor (uremia as a "receptor disease") [137]. Additional studies at cellular and molecular levels are needed to establish preventive and therapeutic modalities which may be of value beyond their significance for hyporesponsiveness to PTH.

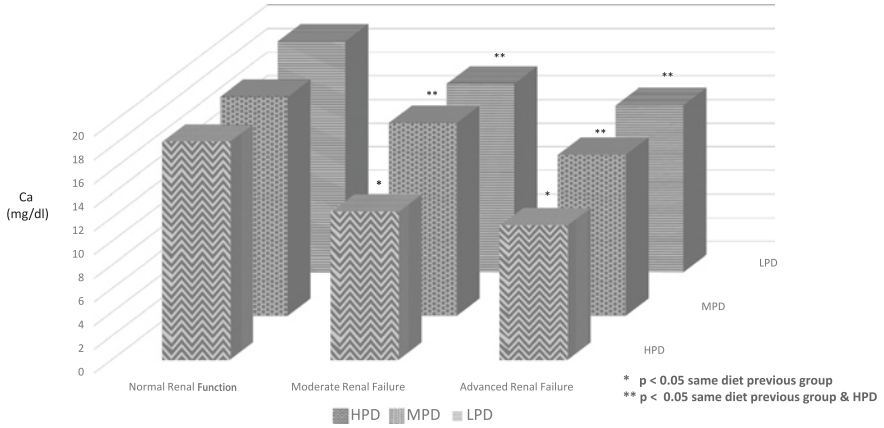

Fig. 1 Calcemic response after a 48 h PTH infusion in rats, according to different degrees of renal function (normal, moderate and advanced renal failure) and dietary phosphate (HPD: high phosphorus diet; MPD: moderate phosphorus diet; LPD: low phosphorus diet). During the PTH infusion, rats received a calcium-free-low phosphorus diet. The magnitude of the calcemic response to PTH inversely depends on the degree of renal failure and the content of phosphorus in the diet. The term "calcemic response" to PTH, "skeletal response" to PTH or "end-organ resistance" to PTH evolved to "hyporesponsiveness" to PTH (see text) Adapted from Ref. [68]

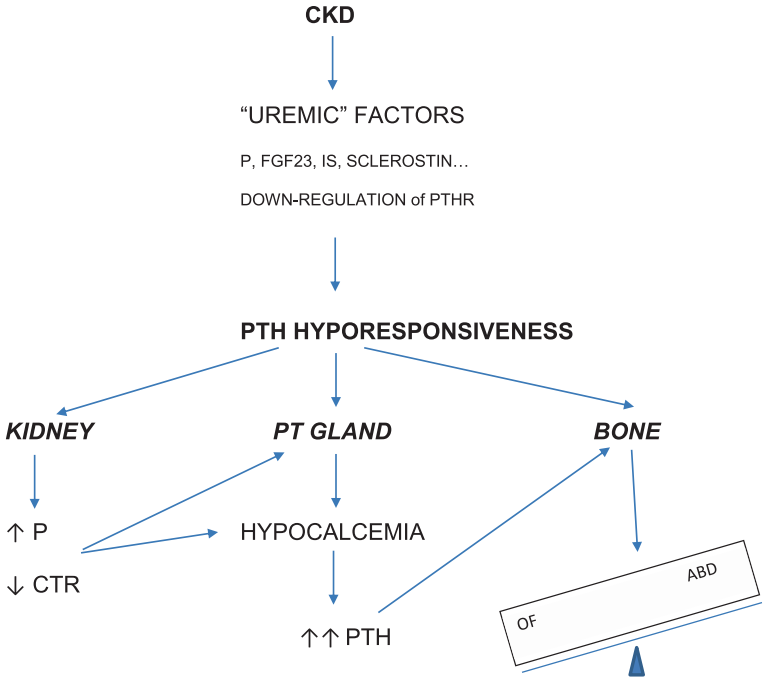

Fig. 2 Causes and consequences of parathyroid hormone (PTH) hyporesponsiveness in chronic kidney disease (CKD). P = Phosphate; FGF-23 = Fibroblast Growth Factor 23; IS = indoxyl-sulfate; PTHR = PTH receptor; PT = parathyroid; CTR = calcitriol; OF = Osteitis fibrosa; ABD = Adynamic bone disease

Table 1 Factors associated with skeletal resistance to PTH action (hyporesponsiveness to PTH)

Decreased levels of calcitriol
Phosphate retention and hyperphosphatemia
Down-regulation of PTH receptors
Uremia
PTH abnormal metabolism and PTH fragments
FGF23/klotho
Calcitonin
Osteoprotegerin
Wnt antagonists: sclerostin…
RANKL
Other: race, sex, aging, diabetes

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