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CKJ REVIEW

# Novel insights into parathyroid hormone: report of The Parathyroid Day in Chronic Kidney Disease

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## ABSTRACT

Chronic kidney disease (CKD) is often associated with a mineral and bone disorder globally described as CKD-Mineral and Bone Disease (MBD), including renal osteodystrophy, the latter ranging from high bone turnover, as in case of secondary hyperparathyroidism (SHPT), to low bone turnover. The present article summarizes the important subjects that were covered during 'The Parathyroid Day in Chronic Kidney Disease' CME course organized in Paris in September 2017. It includes the latest insights on parathyroid gland growth, parathyroid hormone (PTH) synthesis, secretion and regulation by the calcium-sensing receptor, vitamin D receptor and fibroblast growth factor 23 (FGF23)–Klotho axis, as well as on parathyroid glands imaging. The skeletal action of PTH in early CKD stages to the steadily increasing activation of the often downregulated PTH receptor type 1 has been critically reviewed, emphasizing that therapeutic strategies to decrease PTH levels at these stages might not be recommended. The effects of PTH on the central nervous system, in particular cognitive functions, and on the cardiovascular system are revised, and the reliability and exchangeability of second- and third-generation PTH immunoassays discussed. The article also reviews the different circulating biomarkers used for the diagnosis and monitoring of CKD-MBD, including PTH and alkaline phosphatases isoforms. Moreover, it presents an update on the control of SHPT by vitamin D compounds, old and new calcimimetics, and parathyroidectomy. Finally, it covers the latest insights on the persistence and *de novo* occurrence of SHPT in renal transplant recipients.


**Keywords:** calcium, CKD, hyperparathyroidism, phosphataemia, vitamin D

## INTRODUCTION

Chronic kidney disease (CKD) is often associated with a mineral and bone disorder globally described as CKD-Mineral and Bone Disease (MBD), including renal osteodystrophy (ROD), the latter ranging from high-turnover bone diseases such as in secondary hyperparathyroidism (SHPT), with its extreme and severe manifestation osteitis fibrosa, to low-turnover bone diseases such as osteomalacia and adynamic bone disease. Serum parathyroid hormone (PTH) is a recognized marker of bone remodelling in patients with ROD. However, identification of N-terminal truncated PTH fragments, oxidized PTH and new forms of PTH, which interfere with PTH assays and may be responsible for the great variability of PTH values in CKD, gave rise to the wide range of the PTH targets suggested by Kidney Disease: Improving Global Outcomes (KDIGO) [1]. Despite the fact that its importance in CKD has been recognized for decades, insight on PTH measurement, clinical relevance and modes of action still evolve. To provide an update on these most recent developments the ERA-EDTA working group on CKD-MBD organized 'The Parathyroid Day in Chronic Kidney Disease'. This was a continuous medical education (CME) course organized in Paris in September 2017. In this report, we provide a summary of key aspects with special focus on important novel insights, preceded by a brief review of established knowledge in a historical perspective.

## PARATHYROID GLANDS IN CKD—ANATOMY, HISTOLOGY, PHYSIOLOGY AND MOLECULAR BIOLOGY IN CKD

Most frequently, humans have four parathyroid glands. They are variably located on the back of the upper and lower poles of the thyroid gland. However, ~20% of people have five parathyroid glands, and a few have even six glands, often in ectopic locations. The identification of aberrant parathyroid glands by imaging methods and during neck exploration in case of surgical parathyroidectomy (PTX) often proves extremely difficult. The parathyroid tissue is composed of two main secretory cell types, namely chief cells and oxyphil cells. The synthesis and secretion of PTH are regulated by numerous factors. Besides calcium, which is the most important regulator, calcitriol, phosphate, fibroblast growth factor 23 (FGF23), α-Klotho, PTH itself and PTH-related peptide (PTHrP), as well as their respective receptors, all participate in this process [2]. Additional modulation occurs at the posttranscriptional level via mRNA stabilizing protein AU rich binding factor 1 [3] and differential expression of miRNAs [4]. The physiological control of PTH synthesis and secretion is progressively lost with the progression of CKD, as a consequence of changes in the circulating levels and/or parathyroid tissue expression of these regulators, and also disturbances of hepatic and renal PTH catabolism. In parallel with a chronic stimulation of PTH secretion the parathyroid tissue undergoes an increase in parathyroid cell proliferation (hyperplasia), also due to the above PTH changes in regulators and the recently discovered mechanistic target of rapamycin complex 1 pathway activation [5]. Although a higher apoptosis rate occurs concomitantly, this is unable to compensate for the excessive cell growth [6]. The combined result is the well-known SHPT of CKD. Although initially the hyperplasia is of polyclonal nature and considered to be reversible its growth pattern generally changes from polyclonal to monoclonal or multiclonal proliferation when the SHPT becomes severe [7]. On light microscopy examination, it is characterized by nodular transformation of the parathyroid gland, suggesting the presence of one or several benign tumours. The clonal proliferation is due to loss of tumour growth inhibitory genes and/or gain of tumour growth promoter genes, as reflected by chromosomal gains and losses using comparative genomic hybridization and genome-wide molecular allelotyping techniques [8]. Clinically, clonal parathyroid cell growth probably induces a state of relative resistance to PTH-lowering treatments. Moreover, such benign tumours do not regress after renal transplantation despite the restoration of near normal or at least greatly improved kidney function and give rise to so-called persistent hyperparathyroidism as discussed below.

### CaSR AND PTH RECEPTOR IN CKD

The extracellular calcium-sensing receptor (CaSR) was first described in the parathyroid gland [9]. It is a 121-kDa protein that plays a crucial role in Ca homeostasis, in particular via a tight control of the extracellular ionized calcium concentration. It belongs to class C of the G-protein-coupled membrane-bound receptor superfamily. At the cell surface, the CaSR is present constitutively in a dimeric configuration. This homodimerized

configuration is crucial for its normal function. Recent studies have shown that the CaSR is also expressed in the cardiovascular system but our understanding of its physiological functions in this system remains incomplete [10]. Inactivating CaSR mutations lead to familial hypocalciuric hypercalcaemia or neonatal severe hyperparathyroidism and activating mutations to autosomal dominant hypocalcaemia. In CKD, decreased parathyroid CaSR expression participates in the pathogenesis of SHPT [11]. Several factors are probably involved in this decrease, including uremic toxins. Calcimimetics have been demonstrated to be particularly useful in controlling PTH hypersecretion and concomitantly reducing serum calcium and phosphate levels in dialysis patients. Recent findings also point to the role of CaSR allosteric coactivators as inhibitors of the development of vascular calcification not only by correcting PTH hypersecretion, but also by directly modulating vascular CaSR activity [12].

PTH binds to PTH/PTHrP receptor type 1 (PTH1R), which is expressed in numerous tissues including kidney and bone and activates several intracellular second messengers [13]. Activation of PTH1R reduces serum phosphate by decreasing its renal reabsorption. It also increases calcitriol production by its stimulatory effect on renal 25-hydroxy vitamin D (25OHD)–1$\alpha$-hydroxylase activity. PTH1R is highly expressed the primary target organs for PTH, kidney and bone, and at relatively lower levels in the vasculature [14]. In addition to PTH1R, a second G protein-coupled PTH receptor, PTH2R, of uncertain physiological significance has been identified [15]. Finally, a receptor with specificity for the C-terminal region of PTH (C-PTHR) has been identified, but not yet fully characterized, in osteoblasts and osteocytes [16]. Available evidence suggests that it acts antagonistically to the PTH/PTH1R system. End-organ hyporesponsiveness to PTH, formally referred to as PTH resistance, has long been recognized in CKD. It is attributed, at least partially, to downregulation or desensitization of PTH1R [17]. Factors such as phosphate, indoxyl sulphate and paracresyl sulphate accumulation may play a role in this phenomenon [18]. Hyporesponsiveness to the skeletal action of PTH in early CKD stages could explain observations of a relatively high prevalence of low bone turnover disease, predominantly adynamic bone disease. An early inhibition of the Wnt pathway with an increase in the expression of sclerosis and other inhibitors of Wnt signalling may be involved. With the progression of CKD to more advanced stages and more severe SHPT, the steadily increasing activation of PTH1R eventually overcomes the skeletal resistance to the action of PTH, and osteitis fibrosa or mixed ROD ensue, if left untreated.

## KLOTHO–FGF23–PTH AXIS IN CKD

The physiological role of FGF23, in particular its effect on renal phosphate handling, and its associations with dismal outcomes in CKD is well established and beyond the scope of this report [19].

In parathyroid glands, FGF23 downregulates PTH secretion, principally through the classic Klotho-dependent pathway of mitogen-activated protein kinases (MAPK) activation, or secondarily through the less-explored phospholipase C gamma (PLC$\gamma$)-dependent activation of the nuclear factor of activated T-cells (NFAT) cascade [20]. In fact, recent data suggest that in addition to CaSR and vitamin D receptor activation, the FGF23–Klotho endocrine axis suppresses PTH secretion. In parathyroid tissue, FGF23 binds to the cell membrane-located FGF receptor–Klotho complex to elicit activation of the MAPK-pathway, but it can also act in absence of Klotho via a phosphoinositide-specific PLC$\gamma$-dependent activation of the NFAT pathway.

Available evidence suggests that a positive phosphate balance occurs even in still normo-phosphataemic CKD patients, secondary to reduced glomerular filtration rate (GFR). These events are thought to trigger both PTH and FGF23 increments to counterbalance phosphate overload [21]. FGF23 resistance, resulting from progressively reduced Klotho expression in kidney and parathyroid gland tissue with the progression of CKD, further enhances FGF23 synthesis and increased circulating FGF23 levels [19, 21].

SHPT is a common consequence of CKD. Initially, this condition may seem counterintuitive, considering that FGF23 inhibits PTH secretion. Currently, the most reasonable explanation for SHPT in CKD patients is resistance of parathyroid tissue to the action of FGF23, particularly in cases with extremely high FGF23 levels. This hypothesis is supported by reduced Klotho and FGF receptor expression observed in surgically resected human hyperplastic parathyroid glands [22].

## PTH, CNS AND COGNITIVE FUNCTIONS

In addition to their roles in the periphery, it has been shown that many hormones, which include insulin, leptin, thyroid hormone, sex steroid hormones, glucocorticoids and osteocalcin, can also influence the central nervous system (CNS), regulate brain development, modulate cognitive functions and strongly influence the central regulation of whole-body energy balance [23–31]. Importantly, increasing evidence suggests that changes in their circulating levels may contribute to age-related cognitive decline, as well as to the development of neurodegenerative diseases [32, 33]. While the impact of the hormones on brain functions, both in normal and ageing conditions, is undeniable, the influence of many of them on brain cognitive functions still remains to be explored. A better understanding of the influence of hormonal homeostasis in brain metabolic and cognitive activities may open up new roads for therapeutic intervention to ameliorate disease-related cognitive impairments, and reverse/prevent age-related memory decline.

Interestingly, numerous studies have reported that the age-induced increase in PTH levels is associated with higher risk of cognitive decline and incident dementia [34, 35]. Moreover, observational studies have described impaired cognitive functions such as memory and attention tasks in patients with primary hyperparathyroidism (PHPT) in the presence or even absence of hypercalcaemia. These disturbances can be significantly improved after surgical intervention normalizing PTH levels [36–38]. SHPT, which is generally characterized by high serum PTH levels with normal to low calcium levels as occurs in CKD, is also associated with cognitive impairment, followed by the same postoperative improvement [37, 39–41]. However, little is known about the mechanisms linking PTH and cognition impairments, both in HPT and in ageing populations.

Several hypotheses have been proposed to explain the association between high PTH levels and cognitive deficits. Impaired cognition in primary HPT has been traditionally attributed to hypercalcaemia [42]. High serum calcium levels have been associated with faster decline in cognitive function, neuronal signalling disruption or atrophy in hippocampus and Alzheimer's disease, frontal-subcortical dementia. Furthermore, PTH also promotes the conversion of vitamin D to its active form (1, 25-dihydroxy vitamin D), which an emerging body of evidence suggests may be neuroprotective. However, based on the fact that PTH crosses the blood–brain barrier [43–45] and that PTH receptors (Figure 1) are highly expressed in human and rodent brains [14, 46–48], it is legitimate to ask whether PTH signalling may also exert direct actions on the CNS. Further neuropsychological investigations of cognitive functions in patients with PHPT or age-related dementia, which include confounding factors such as altered serum calcium, phosphate

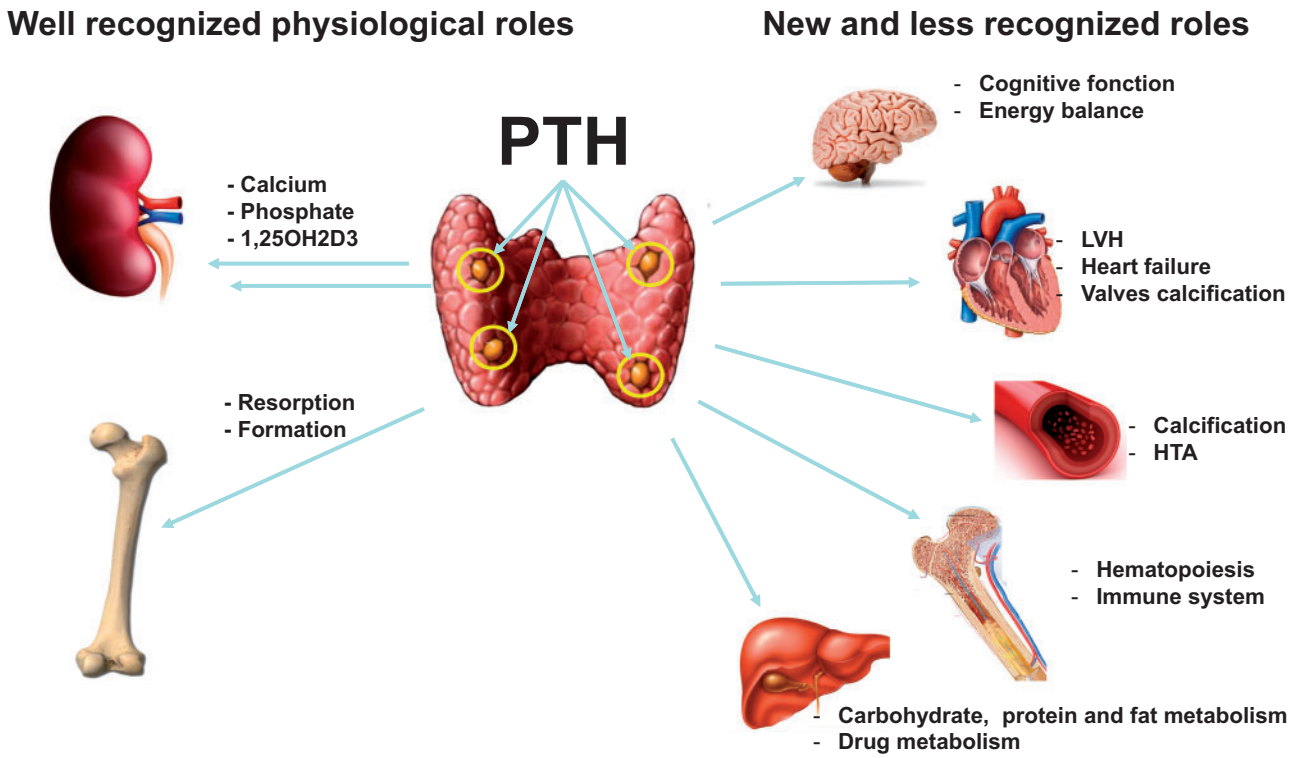


**FIGURE 1:** A possible role of PTH signalling in the brain. PTH is a major regulator of the calcium/phosphate balance in the body through its actions on bone and kidney. PTH can bind and activate at least two receptors that belong to the G protein-coupled receptor family, PTH1R and PTH2R; however, its principal functions are associated with the first one. Importantly, these receptors are expressed in the CNS and may also bind paracrine ligands such as PTHrP for PTH1R and Tip 39 for the PTH2R. These findings and the observation that patients with PHPT and SHPT often have memory loss and loss of appetite suggest a direct effect of PTH on the CNS.

and vitamin D sterol levels and the examination of a possible direct role of PTH in the CNS, are clearly warranted.

## PTH MEASUREMENT IN CKD PATIENTS

PTH measurement is very important for the follow-up of patients with CKD, in particular more advanced CKD. PTH determination represents the paradigm of quality in laboratory medicine as many variables in the pre-, intra- and post-analytical phases strongly affect the value of the clinical information. PTH circulates as a 1-84 amino acids bioactive peptide, but its analytical determination is difficult because of the presence, in the circulation, of N-terminal truncated fragments [called non-(1-84) PTH] that tend to accumulate in CKD patients [49]. These fragments also have a longer half-life compared with the 1-84 PTH. Basically, two types of assays are present on the market: second-generation (or 'intact' PTH: PTH2) and third-generation assays (PTH3). PTH2 recognize the non-(1-84) PTH fragments whereas PTH3 assays do not (Figure 2). PTH determination lacks standardization, despite an International World Health Organization Standard (IS 95/646) being available. Also, no reference method is available yet for PTH measurement. Hence, results provided by the different assays are very different, especially in CKD patients [50]. Since the fragments cross-react differently with the antibodies used in PTH2 assays, a full standardization of PTH will only be possible with PTH3 assays. It has been shown, however, that mathematical factors could help to improve comparability of PTH results [51], but this is not consistent over time and is a lower quality solution. Another problem with PTH is the reference range (RR). Indeed, healthy subjects selected for RR establishment need to be free of SHPT and PHPT [52]. Hence, 25OHD, calcium and creatinine measurements need to be performed prior to enrolment. Unfortunately, most manufacturers have not performed such determinations when establishing the RR, rendering those inaccurate. For instance, up to 18% of PTH values are not comprised within the RR we correctly established with the Roche PTH2 assay and the manufacturer's RR, and most of these cases actually presented 25OHD values far greater than 30 ng/mL. The KDIGO target range for patients with dialysis-dependent CKD (2–9× upper limit of normal) will also be differently classified, according to a correctly established RR. Manufacturers' RR and our own studies have shown that using a correctly established RR improves patient classification according to KDIGO guidelines [53]. Besides these issues, PTH can be oxidized on its two methionine amino acids, on Positions 8 and 18. It has been shown that oxidized PTH is biologically inactive. PTH2 and PTH3 assays recognize both oxidized (ox-PTH) and non-oxidized PTH (n-oxPTH). Measurement of n-oxPTH alone needs a pretest capture of ox-PTH by a specific antibody and subsequent measurement of PTH by a PTH2 assay. Since important oxidative stress is present in CKD patients, it has been hypothesized that PTH2 and PTH3 assays do not accurately measure bioactive PTH, but mostly oxidized, inactive PTH. It has indeed been shown that n-oxPTH may reflect more precisely the true hormone status and not the risk of mortality. The increased mortality risk associated with PTH might be reflecting an oxidative stress-related mortality [54] as recently observed by Seiler-Mussler *et al.* [55] These findings must however be confirmed by further studies.

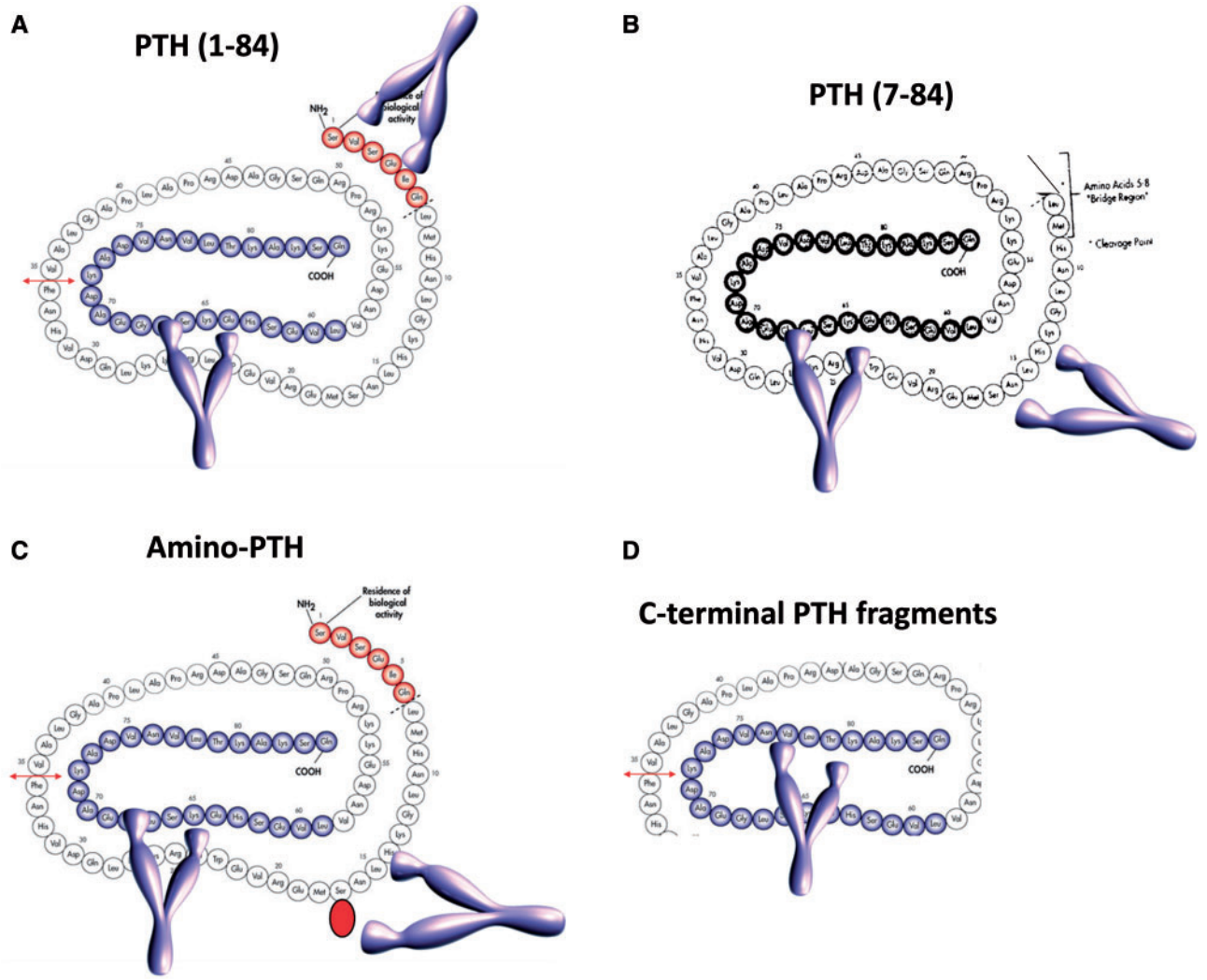


**FIGURE 2:** PTH measurements. PTH circulates as a bioactive 1-84 peptide (**A**), together with large N-truncated fragments called non-(1-84) PTH (**B**) and truncated fragments (**D**). A form called amino-PTH corresponds to a 1-84 PTH containing a phosphorylated serine in Position 17 (**C**). 'Intact' PTH assays recognize the bioactive peptide, but also the non-(1-84) PTH. Third-generation PTH assays use an antibody targeted against the first four amino acids of PTH and recognizes the bioactive peptide, but not the non-(1-84) PTH. PTH can be oxidized on the methionine in Positions 8 and 18 and both third- and second-generation PTH assays recognize it. To measure the non-oxidized PTH, a pretreatment of the sample with an antibody targeted against the oxidized PTH is needed, before determination with a second-generation PTH assay.

## BONE METABOLIC MARKERS IN CKD PATIENTS

Bone markers reflect the activities of bone cells. They are divided into two subgroups; humoral factors derived from bone cells, and factors associated with type-I collagen metabolism. Of the bone cell-derived factors, those secreted by osteoclasts are regarded as bone resorption markers, and those originating from osteoblasts are regarded as bone formation markers, except for under-carboxylated osteocalcin, which also reflects vitamin K status.

Bone remodelling is the lifelong process by which mature bone is removed and new bone is formed; it is also the mechanism allowing skeletal growth, bone reshaping and the replacement of injured bone following fractures and micro-damages. Bone remodelling is also crucial for the regulation of circulating calcium and phosphate levels. Dialysis patients display extremely high risk of hip fracture [56–58]. Nevertheless, modern clinical studies repeatedly demonstrated that PTH levels show only a limited association with hip fracture risk [56, 57, 59, 60].

Bone markers roughly and noninvasively estimate activities of bone cells and the degree of bone remodelling. The significance of bone markers may be close to that of PTH action on bone, since PTH is the most crucial determinant of bone remodelling frequency. In fact, PTH itself is regarded as one of the most reliable bone turnover markers in dialysis patients. However, bone metabolism is no longer considered identical to bone cell metabolism in modern bone biology. Bone extracellular material metabolism can be independent from bone cell metabolism, and recent studies revealed that bone material properties, i.e. bone biochemical characteristics rather than bone remodelling frequency, are the critical determinant of bone strength in uraemic condition [61, 62]. Most of the bone markers including PTH do not give information about these features, nor does bone histology examination. Although bone histomorphological analysis is the only way to establish a histological diagnosis, this is also the only information such a bone biopsy can provide. Moreover, estimating bone histology by the level of circulating bone markers remains of limited accuracy.

Total serum alkaline phosphatase (tAP) level showed tight associations with hip fracture risk as well as mortality in dialysis patients [63]. Its level may not totally represent bone remodelling because serum PTH level showed no relation to it. However, this assumption should be taken with caution because the lack of correlation between tAP and PTH may be due to the inaccuracies of PTH determination as above described. Arterial 'osteonization', commonly called Mönckeberg-type vascular calcification, in which vascular smooth muscle cells display osteoblast-lineage like phenotype, is frequently observed among dialysis patients. Since serum AP level represents the number of osteoblasts and osteoblast-like cells, it may reflect, at least partially, the development of this disease condition.

## DELETERIOUS EFFECTS OF PTH ON THE HEART

PTH—among others—is a prototypic factor linking bone disease to cardiovascular disease, since PTH affects not only this physiological target organ, but also exhibits major 'off-target' effects in the cardiovascular system. Noteworthy, numerous cohort studies reported significant and independent associations between serum PTH levels and adverse outcomes including mortality [64]. It is important to mention that the association between PTH and outcome is not linear but J-shaped, suggesting an 'optimal PTH' range for these specific outcomes, which could be ~150–300 pg/mL in dialysis patients [65]. Not only end-stage renal disease (ESRD) patients but also cohorts of primarily cardiology patients confirm the independent association between PTH and clinical outcome [66].

Left ventricular hypertrophy (LVH) is among the major contributing factors to morbidity and mortality in CKD and ESRD patients. LVH is driven by several factors among which PTH is a prominent one. A causal link between the two may exist by the stimulatory actions of PTH upon the renin–angiotensin–aldosterone system (RAAS) leading to increased levels of angiotensin II and aldosterone, which in turn cause LV remodelling and arterial hypertension [67]. Data from a meta-analysis of PTX effects upon LVH support the hypothesis of a causal link between PTH and LVH since LVH regressed in most patients with PHPT after surgery [68]. Underlying mechanisms may be (i) PTH-induced specific vascular pathology such as endothelial dysfunction and atherosclerosis; or (ii) direct detrimental myocardial effects by PTH that could lead to increased myocardial susceptibility to ischaemia or an increased risk for heart failure of non-ischaemic origin. However, proof of a causal role for PTH in cardiovascular disease is still lacking. Actually, lowering of PTH might in parallel induce lowering of other factors (i.e. FGF23), which are by themselves propelling cardiovascular morbidity and mortality [69]. Some experimental research data even point towards protection by PTH: application of PTH in rodent myocardial infarction models led to reduction in infarction size and improved cardiac function parameters [70]. Better recruitment of stem cells via PTH-induced mobilization might serve as an explanation for these remarkable observations [71].

## CONTROL OF SHPT BY OLD AND NEW VITAMIN D COMPOUNDS

True deficiency, or relative insufficiency, of 25OHD is highly prevalent among patients with CKD or ESRD and is a critical component in the pathogenesis of SHPT. Accordingly, current guidelines suggest that in the setting of CKD G3a–G5D, 25OHD levels might be measured, and repeated testing depending on baseline values and therapeutic interventions. They also suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population [1, 72].

Whereas nutritional vitamin D replacement may restore 25OHD concentration to near, or even above 'normal', the real target of treating vitamin D insufficiency is and will remain the successful treatment of SHPT, which is largely unaffected by nutritional vitamin D.

Ranged against that is softer evidence for the usefulness of using vitamin D to treat 'renal bone disease' which has been clinical custom and practice now for nearly six decades. The practice has been in the main to use high doses of synthetic vitamin D compounds, not naturally occurring ones. It is disappointingly true to say that even in 2018 there is paucity of evidence concerning the clinical benefits of vitamin D supplementation to treat vitamin D insufficiency in patients with Stages 3b–5 CKD [73].

While there are a number of studies that report the impact of vitamin D supplementation on serum vitamin D concentrations and some variable evidence of serum PTH concentration suppression, there has been much less focus on hard endpoint analysis (e.g. fractures, hospitalizations and overall mortality). In 2018, with the practice pattern changes of widespread clinical use of vitamin D and widespread supplementation of cholecalciferol or ergocalciferol by patients, it is now next to impossible to run a placebo-controlled trial over a decent period of time to explore relevant clinical outcomes. In this challenging situation, we need to ask what it is we are trying to achieve here for our patients, and how best to balance potential benefits with potential harm [74].

Extended-release calcifediol (ERC) 30 μg capsules were recently approved by the United States Food and Drug Administration for the treatment of SHPT in adults with Stages 3–4 CKD and vitamin D insufficiency (serum total 25OHD <75 nmol/L) [75]. Calcifediol is 25-hydroxyvitamin D3, a prohormone of the active calcitriol (1, 25-dihydroxyvitamin D3). ERC capsules have a lipophilic fill, which gradually releases calcifediol, corrects vitamin D insufficiency and increases serum calcitriol, and thereby suppresses production of PTH in CKD patients without perturbing normal vitamin D and mineral metabolism. Randomized clinical trials (RCTs) have demonstrated that non-modified nutritional vitamin D is ineffective for treating SHPT (when used in conventional doses, up to the equivalent of around 4000 IU/day) whereas vitamin D receptor activators can very easily and significantly correct elevated PTH concentrations, but with increased risk of hypercalcaemia and hyperphosphataemia [74]. ERC offers healthcare professionals a new treatment option that has been demonstrated in RCTs to be safe and effective for controlling SHPT without meaningfully increasing serum concentrations of calcium or phosphorus [75, 76].

## OLD AND NEW CALCIMIMETICS

Calcimimetics are established treatments for SHPT. They increase the sensitivity of CaSR leading to the decrease of the set-point for systemic calcium homeostasis. This enables a decrease in plasma PTH levels, and consequently of calcium levels. Cinacalcet was the first calcimimetic approved for clinical use and effectively reduces PTH and improves biochemical control of mineral and bone disorders in dialysis patients [77]. Three randomized controlled trials analysed the effects of treatment with cinacalcet on vascular calcification, bone histology and cardiovascular mortality and morbidity [78–80].

The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial [81] was a RCT enrolling 3883 haemodialysis patients with moderate to severe SHPT assigned to receive cinacalcet or placebo. All patients could simultaneously receive conventional treatment including phosphate binders and vitamin D sterols. The primary composite endpoint was time until death, myocardial infarction, hospitalization for unstable angina, heart failure or a peripheral vascular event. Regrettably, this large RCT could not demonstrate improvement of hard outcomes with cinacalcet based on intention-to-treat analysis. However, the interpretation of a negative study outcome has been considered inconclusive rather than definitive, due to significant cross-over of placebo-treated cases to the active treatment arm.

Etelcalcetide is a new, second-generation calcimimetic administered intravenously. Its pharmacokinetic profile allows thrice-weekly dosing at the time of haemodialysis. It was recently approved in Europe. A double-bind, double-dummy active RCT was conducted comparing intravenous etelcalcetide with oral placebo versus oral cinacalcet with intravenous placebo in 683 haemodialysis patients with PTH higher than 500 pg/mL [82]. The primary efficacy endpoint was non-inferiority of etelcalcetide at achieving more than a 30% reduction from baseline in mean pre-dialysis PTH concentration. Secondary endpoints included superiority in achieving biochemical endpoints (>50% and >30% reduction in PTH) and self-reported nausea or vomiting. Etelcalcetide was not inferior to cinacalcet in reducing PTH concentration and also met superiority criteria. The proportion of patients who achieved a greater than 30% and 50% PTH reduction was greater for etelcalcetide compared with cinacalcet treatment [83]. Hypocalcaemia was more frequent in the etelcalcetide group. Etelcalcetide did not prove to have fewer gastrointestinal symptoms despite intravenous administration. Overall safety and tolerability between etelcalcetide and cinacalcet were similar. Etelcalcetide treatment yielded more pronounced reduction in FGF23 levels than cinacalcet. Of note, in the EVOLVE trial (using oral cinacalcet) a 30% reduction of FGF23 levels was associated with significant reduction of primary composite endpoint, heart failure and death [69]. This promising finding of calcimimetics raises the possibility of a more pronounced impact in cardiovascular outcomes, mediated by FGF23 reductions.

## IS THERE ANY INDICATION LEFT FOR PTX IN 2018?

The 2017 update of the KDIGO guideline indicates the need for PTX 'in patients with CKD G3a–G5D with severe SHPT who fail to respond to medical or pharmacological therapy'. The strength of this recommendation, unchanged from the previous edition, is graded 2B ('we suggest' with 'moderate evidence') [1, 72]. Thus, PTX continues to be the last therapeutic step to control SHPT in CKD. Since in recent years the number of drugs available for SHPT increased, the need for PTX should progressively decrease. Indeed, data from the dialysis outcomes and practice patterns study [84] demonstrated that from 1996 to 2008 there has been a decrease in PTX rates, accompanied by an increased prescription of vitamin D and cinacalcet. Notably, this change of therapeutic strategy was associated with increasing PTH values in Europe, Australia-New Zealand and North America, but not in Japan (where PTH values were stable and the proportion of patients at target increased). However, a more recent study from the United States Renal Data System registry, which included a huge number of PTX cases (32 971) recorded between 2002 and 2011, showed that the rates of PTX have not declined in recent years. It is interesting to notice, in this study, that the nadir was reached in 2005, concomitant with cinacalcet commercialization, but then increased and remained stable at roughly 5/1000 dialysis patients by 2006 [85].

Thus, new more powerful drugs do not seem to reduce the incidence rate of PTX for biochemical control of SHPT. Unfortunately, available data indicate that after PTX, the biochemical control of SHPT sometimes does not improve [86] or might even worsen in the medium-long term, due to a high prevalence of low PTH values [87]. Hyperparathyroidism after PTX is of concern because of the assumed risk of low turnover bone, even though bone biopsies before and after PTX are rarely performed. A very recent prospective study, which included only 19 patients, demonstrated that 1 year after PTX almost all patients developed adynamic bone disease, and this was associated with a significant increment of coronary calcium content [88]. This negative finding is partly compensated by another recent study, showing lower hip fracture rates in patients who received PTX as compared with a control group [89]. Finally, Ishani *et al.* [90] reported increased hospitalization rates in the 30 days and 1-year periods following PTX, which would contribute to discourage this surgery. However, in contrast to these findings, the vast majority of observational studies evaluating hard clinical outcomes in the medium-long term after PTX indicate improvement as compared with control cases. A large recent observational study [91] including 4428 PTX cases and 4428 propensity-score matched controls from a Japanese registry showed a statistically significantly lower all-cause and cardiovascular mortality in the PTX group, in the 12 months following surgery. Despite the use of adequate methodology to adjust for confounding, selection bias can never be excluded in observational data analysis, which would favour the outcome for those allowed for surgery. The need for a prospective randomized trial persists for the optimal treatment of SHPT [92].

## PREOPERATIVE PARATHYROID IMAGING

Whatever the surgical procedure performed, that is, subtotal PTX or total PTX with auto-transplantation, identification by the surgeon of all parathyroid glands is required, as outlined above. In one recent series, 12.8% of patients had fewer than four parathyroid glands identified at surgery and this was associated with the risk of persistent SHPT [93]. This is consistent with a large retrospective analysis showing that in ~10% of operated patients, serum PTH levels at 1 month remained elevated (≥897 pg/mL) [86]. Difficulty in identifying all parathyroid glands is also associated with a higher risk of surgical complications, such as bleeding, haematoma, infection and injury to the recurrent laryngeal nerve [94].

Ultrasound is a useful and widely used preoperative imaging technique. However, even in experienced hands, ultrasound has limitations, mainly due to its inability to detect ectopic parathyroid glands, such as retro-tracheal, retro-oesophageal or mediastinal glands [95].

99mTc-sestamibi scintigraphy has higher sensitivity at detecting ectopic parathyroid glands than ultrasound [96, 97]. Moreover, hybrid gamma cameras now allow delineating the precise anatomical position of ectopic glands by fusing three-dimensional 99mTc-sestamibi images with computerized tomography (CT) cross-sectional images (single photon emission computerized tomography (SPECT)/CT) [98]. In the neck area, various protocols have been proposed to differentiate parathyroid lesions from the thyroid gland. The highest sensitivity is

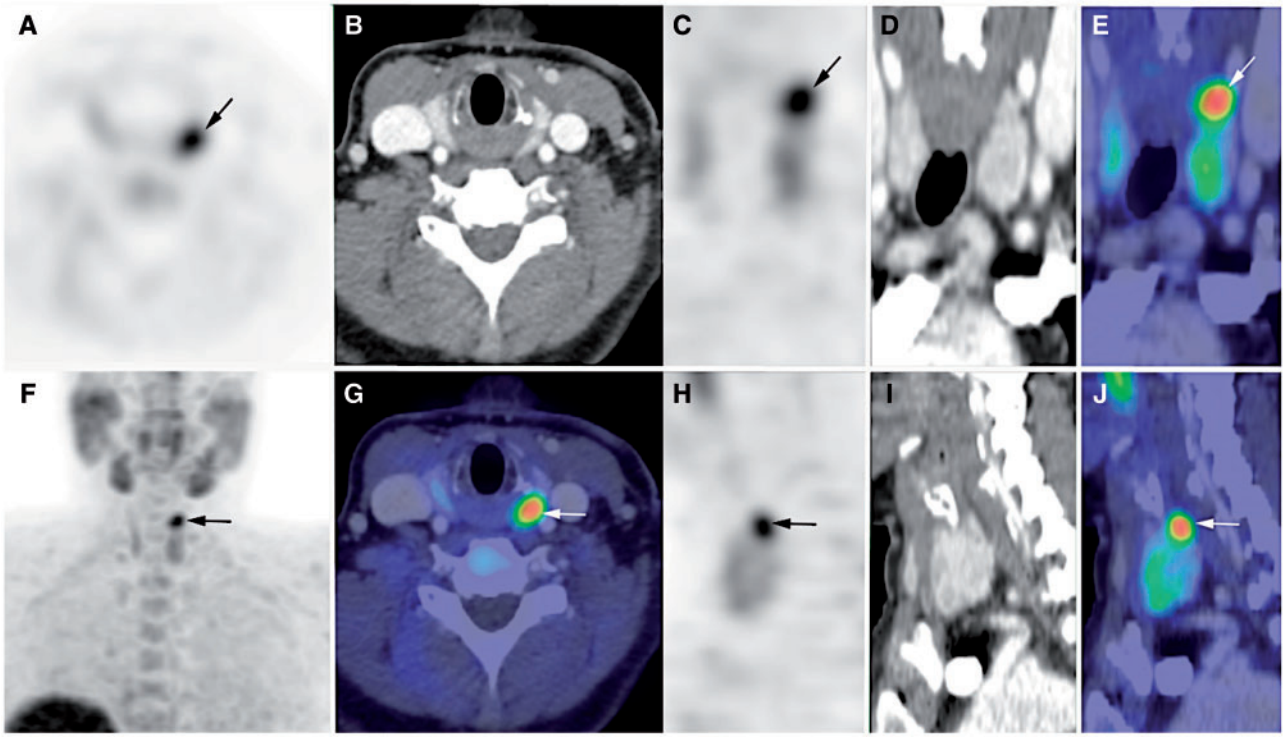


**FIGURE 3:** $^{18}$F-fluorocholine PET/CT of parathyroid glands. $^{18}$F-fluorocholine PET/CT (contrast-enhanced CT) in a patient with PHPT and doubtful results on 99mTc-sestamibi scintigraphy. PET, CT and PET/CT images are displayed in axial (**A**, **B** and **G**), coronal (**C**, **D** and **E**) and sagittal (**H**, **I** and **J**) views, as well as PET maximum-intensity projection **(F)**. Choline-avid hyperfunctioning parathyroid gland is seen at upper pole of left thyroid lobe (arrow). Neck ultrasound confirmed presence of hypoechoic 10 × 5 × 12 mm nodule behind left upper pole of thyroid. Adapted from Hindié *et al.* [102].

obtained through dual-tracer imaging using 99mTc-sestamibi + 123-iodine, with image subtraction [98, 99].

Besides depicting ectopic and supernumerary glands, 99mTc-sestamibi scanning can offer functional information in SHPT and tertiary hyperparathyroidism that can be helpful to select the remnant parathyroid tissue with the least autonomy, thus reducing the risk of recurrence [96, 100, 101].

Recurrent SHPT can be due to hyperplasia of remnant tissue after subtotally resected parathyroid gland or autograft, a supernumerary parathyroid gland, or both [102]. Reoperation for persistent or recurrent SHPT generally is a difficult procedure with a higher risk of complications than initial surgery. A combination of imaging techniques (ultrasound, 99mTc-sestamibi/iodine-123 subtraction, CT, magnetic resonance imaging (MRI)) is necessary to localize the offending lesion with enough certainty.

The clinical utility of radiopharmaceuticals labelled with isotopes and used in positron-emitting tomography (PET), such as the amino acid $^{11}$C-methionine or the lipid tracer $^{18}$F-fluorocholine, is also being investigated [103, 104]. Large series comparing $^{18}$F-fluorocholine PET/CT (or PET/MR) with state-of-the-art 99mTc-sestamibi/iodine-123 subtraction scintigraphy in SHPT are warranted (Figure 3).

## PERSISTENT HYPERPARATHYROIDISM AFTER RENAL TRANSPLANTATION

Successful kidney transplantation corrects the metabolic abnormalities responsible for SHPT. PTH levels show a biphasic decline after successful renal transplantation: an initial rapid drop (by ~50%) during the first 3–6 months, attributed to a reduction of the parathyroid functional mass, followed by a more gradual decline. The long lifespan of parathyroid cells (approximately 20 years) contributes to the very slow involution of the hyperplastic parathyroid glands after renal transplantation [105]. Parathyroid hyporesponsiveness (resistance), conversely, rapidly wanes after renal transplantation, parallel to the recovery of renal function, giving rise to the frequently encountered hypophosphataemia after kidney transplantation [13].

There is wide variation in the reported prevalence of post-transplant HPT, ranging between 10% and 66%. This huge variation may be explained at least partly by differences in diagnostic criteria, differences in study era and differences in interval since transplantation. A long dialysis vintage and severe SHPT at the time of transplantation reflected by high levels of PTH, calcium, phosphorus, and/or tAP or need for calcimimetic therapy confer an increased risk for persistent HPT [105]. After transplantation, suboptimal graft function, immunosuppressive drug therapy, metabolic acidosis, hyperphosphatoninism and low vitamin D levels may also increase PTH secretion and contribute to post-transplant HPT [105].

It should be emphasized that post-transplant HPT is the composite of truly persistent HPT and *de novo* SHPT. Estimating the relative contribution of these two components to high PTH levels observed in the individual patient may prove difficult. In general, persistent HPT prevails in the early post-transplant period while *de novo* SHPT will become more prominent as kidney transplant function declines. While persistent HPT by definition is maladaptive and may contribute to specific post-transplant complications such as hypercalcaemia [106], hypophosphataemia [107, 108], (cortical) bone loss [109], fractures [110, 111] and nephrocalcinosis [112], *de novo* SHPT may be appropriate to the declining transplant function. Consequently, patients with a

(predominant) persistent HPT phenotype may be hypothesized to benefit most from PTH suppressive therapy. Calcimimetics, nutritional and active vitamin D (analogues) and PTX may all be considered in these patients. Calcimimetics effectively controlled hypercalcaemia in patients with post-transplant HPT but, opposite to PTX [113] and paricalcitol [114], failed to demonstrate a beneficial impact on bone mineral density [115]. Bone biomarkers [116], imaging techniques and ultimately bone histomorphometry [117] may help identifying patients that will benefit most from PTH-lowering therapy.

## CONCLUSIONS AND PERSPECTIVES

A broad range of aspects related to PTH biology and pathology in CKD was covered during the PTH day, where many different specialties gathered. As outlined above, exciting, and even more important, highly clinically relevant new insights about PTH biology, its measurement, classical and off-target effects, continuously emerge from ongoing basic and clinical research, even today. Recent data suggest that the skeletal action of PTH in early CKD stages to the steadily increasing activation of PTH1R may be a key one, and the therapeutic strategies to decrease PTH levels at these stages might not be recommended. Of high relevance to patients with advanced CKD stages, complicated by SHPT, ongoing efforts to improve and fine-tune treatment, indeed broadened the therapeutic armamentarium. This is exemplified by the discovery, and subsequent targeting by drugs, of the CaSR, which are now developed into the recently released second-generation calcimimetics. Insights into the regulatory role of the FGF23 and Klotho on PTH release may also eventually be applied in clinical practice, as pharmaco-interventions on this recently discovered integrated system are at their dawn. Even the first available medical treatment for SHPT, vitamin D therapy, is about to undergo a revival, as the kinetic profile of a metabolic form of vitamin D for oral use has been modified by ERC, with promising preliminary efficacy and safety. For a long time, surgical treatment has been a more or less definite solution for unremitting SHPT. A major drawback of both subtotal PTX and total PTX with autotransplantation has been, besides early surgical complications, the difficulty in estimating the amount of parathyroid tissue to remove, frequently leading to persistent HPT or iatrogenic HPT inducing adynamic bone disease. During the PTH day the most recent imaging and functional techniques, combining the use of dedicated tracers and high-resolution imaging, were summarized. These techniques hold promise to future better 'dosing' of surgical treatment of SHPT.

In addition to the advances above, patient-tailored approaches may eventually become feasible. This may in the future be achieved by deciphering in an individual patient to what extent SHPT contributes not only to bone disease, but also to cardiac dysfunction and even cognitive function, as recent data suggests a role for PTH in these morbidities, which highly impact on quality of life.

All in all, the comprehensive update on PTH in CKD as presented in Paris, September 2017 during the ERA-EDTA CKD-MBD Working Group meeting, reinforced the importance of this hormonal system, revived interest and holds promise to further improvements in care for our patients.

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## CONFLICT OF INTEREST STATEMENT

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