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Abstract or Article Brief (if supplied by editors):
As a 'Therapy in Practice' article, we would like this to provide a succinct, up-to-date clinically orientated guide to the optimum management of secondary hyperparathyroidism in patients with chronic kidney disease. The review should include an appropriate background to the development of SHPT. It should focus primarily on pharmacological treatments but as appropriate, non-pharmacological approaches (dietary, surgical) may be discussed to fully place pharmacological therapy in context.

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Takeaway messages from the article

- SHPT is associated with adverse outcomes in CKD and dialysis patients
- Optimum PTH level is unclear in pre-dialysis CKD and the recommended range is wide for dialysis patients.
- Management of SHPT is largely pharmacological focussing on lowering PTH
- PTH lowering treatment has not shown improved cardiovascular risk, fractures and mortality.

Abstract

Secondary hyperparathyroidism (SHPT) is a common complication of CKD and is part of the chronic kidney disease-mineral bone disorder (CKD-MBD). SHPT is associated with increased risk of fracture and mortality, thus SHPT control is recommended as kidney function declines. Effective SHPT management becomes more difficult once skeletal and cardiovascular adverse effects associated with severe SHPT have become established. However, interventional studies to lower parathyroid hormone (PTH) have so far shown inconsistent results in improving patient-centred outcomes such as mortality, cardiovascular events and fracture. Pharmacological treatment effect on PTH level is also inconsistent between pre-dialysis CKD and dialysis patients which adds to the complexity of SHPT management. This review aims to give an overview on the pathophysiology, pharmacological and non-pharmacological treatment for SHPT in CKD including some of the limitations of current therapeutic options.

1. Introduction

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD), affecting almost all CKD patients by the time they reach end stage renal disease requiring dialysis. Biochemical (calcium, phosphate, parathyroid hormone [PTH] and vitamin D) and bone abnormalities (renal osteodystrophy) complicating advanced CKD and dialysis are associated with significant morbidity and mortality (1-6), probably due to greater risk of fracture and extra-skeletal calcification leading to cardiovascular disease (7-9). Severe SHPT in dialysis patients is associated with up to 20% increased mortality (4, 5) and dialysis patients also have up to four fold increase in fracture incidence compared to non-dialysis patients (10) due to impaired bone quality (11, 12). Vascular calcification is highly prevalent in CKD and is only weakly related to traditional risk factors of cardiovascular disease in the general population such as hypertension and hyperlipidaemia (13). In 2006, this triad of biochemical abnormalities in mineral metabolism, vascular calcification and renal osteodystrophy was described as chronic kidney disease-mineral bone disorder (CKD-MBD) by the Kidney Disease: Improving Global Outcomes (KDIGO) group (14).

Interventional studies to lower PTH have so far shown inconsistent results in improving patient-centred outcomes such as mortality, cardiovascular events and fracture (15, 16). Furthermore, the healthcare cost associated with uncontrolled SHPT treatment have been estimated at an additional USD$5600 per patient annually (17). This review aims to give an overview on the pathophysiology, pharmacological and non-pharmacological treatment for SHPT in CKD including some of the limitations of current therapeutic options.

2. Pathophysiology of SHPT in CKD

High serum phosphate can directly increase PTH secretion by parathyroid gland (18) but SHPT onset in CKD often precedes high serum phosphate. Fibroblast growth factor-23 (FGF-23) is a phosphaturic hormone which is released through an as yet uncertain mechanism by osteocytes and osteoblasts. FGF-23 levels start to rise in early CKD stage 2 while serum phosphate, calcium and PTH are still within the normal range and bone mineral metabolism is considered to be normal (19, 20). FGF-23 maintains normal serum phosphate via two main mechanisms. Firstly, by binding to its co-receptor, klotho, in the distal tubule in the kidney (21) which down-regulates the sodium-phosphate co-transporter in the proximal tubule resulting in reduced phosphate reabsorption and thereby, promotes phosphaturia (22). Secondly, FGF-23 affects the vitamin D pathway by inhibiting 1α-hydroxylase activity in the kidney (22). At the same time, it increases the activity of 24-hydroxylase which metabolises 1,25-dihydroxy and 25-hydroxyvitamin D (23). The net effect is a reduction in total 1,25-dihydroxyvitamin D level which reduces calcium and phosphate absorption from the gut (see Figure 1). Serum phosphate level is maintained in the normal range until the phosphaturic effect of FGF-23 is blunted due to declining nephron number with progressive CKD.

The effect of high FGF-23 on vitamin D metabolism is detected by two other receptors on parathyroid gland, namely calcium sensing receptor (CaSR) and vitamin D receptor (VDR). Hypocalcaemia due to low 1,25-dihydroxyvitamin D is detected by CaSR leading to increased PTH gene expression and PTH release in order to restore normal serum calcium. Similarly, reduced 1,25-dihydroxyvitamin D levels are sensed by VDR, also stimulating PTH release. Persistent stimulation of parathyroid gland in CKD leads to diffuse (polyclonal) hyperplasia which transforms into nodular (monoclonal) hyperplasia (24). These monoclonal parathyroid cells have reduced expression of CaSR and VDR (25); thus, they have reduced sensitivity to the change in serum calcium and 1,25-dihydroxyvitamin D levels. PTH release becomes autonomous which often results in hypercalcaemia and is termed tertiary hyperparathyroidism.

Elevated levels of FGF-23, often a 1000-fold higher than in healthy individuals, are found in dialysis patients. Experimental study in rats with normal kidney function or early CKD showed that high circulating FGF-23 lowers PTH secretion. However, there is downregulation of Klotho-FGFR1c receptor complex in parathyroid gland of rats with advanced CKD. Therefore, high level of FGF-23 failed to decrease PTH level (26).

3. Management of SHPT in CKD

An approach to managing SHPT is summarised in Figure 2. It is important to follow the trend in the rise/fall of PTH rather than the absolute value when deciding on treatment at any level of CKD. This is because PTH level is influenced by serum calcium, vitamin D level and circadian rhythm (27). Furthermore, variation in sample stability, accuracy of assay calibration, standardisation and antibody specificity contribute to the variability between assays (28, 29). The frequently used assays are the second generation assays, so called ‘intact’ PTH (iPTH), which measure both the whole PTH (1-84) and PTH (7-84) molecules. The third generation ‘whole’ PTH assays, which only measure PTH (1-84) molecule, are available but is not currently recommended for routine clinical use. The ratio of PTH (1-84)/ PTH (7-84) has been assessed in the context of discriminating renal osteodystrophy subtypes, for which the findings have been inconsistent (30-33). There is limited evidence for its role in predicting clinical outcomes such as mortality and cardiovascular events (34-36).

The KDIGO CKD-MBD guideline recommends keeping the PTH level 2-9 times the upper limit of normal for the assay in dialysis patients (37) based on a number of bone biopsy studies which demonstrated that PTH poorly predicts underlying bone turnover within this range (38-40).Whilst a very low or very high PTH levels can predict low-turnover and high-turnover bone disease, PTH remains a poor marker of underlying bone histomorphometry within the target range. Alkaline phosphatase (ALP) may improve the sensitivity of PTH in predicting high/low bone turnover (41, 42) and mortality in dialysis patients (43, 44). The guideline also recommended simultaneous measurement of total ALP although no clear management target was set. The optimum PTH level is unknown for pre-dialysis CKD patients but

consistently rising levels above the upper limit of normal should prompt an assessment of bone mineral parameters.

Hyperphosphataemia is usually found in CKD stage 5 or on dialysis; it worsens SHPT and is associated with increased morbidity and mortality (3, 4, 6, 45-47). An observational study in haemodialysis patients by Streja et al showed that the lowest mortality was associated with concurrently controlled PTH and phosphate levels (2).

3.1 Dietary phosphate restriction

Dietary phosphate restriction has been shown to reduce 24-hour urinary phosphate excretion resulting from reduction of dietary phosphate absorption (48). Two studies have compared strict dietary phosphate restriction (500-900mg of phosphate daily) against normal or high phosphate diet (1500-2500mg of phosphate daily). Firstly, a study by Burnett et al in healthy subjects showed that dietary phosphate restriction reduced urinary phosphate excretion, lowered serum phosphate and FGF-23 although PTH level was unchanged (49). In contrast, a pilot study by Isakova et al in normophosphataemic CKD stage 3-4 showed that dietary phosphate restriction reduced urinary phosphate excretion but serum phosphate, PTH and FGF-23 remained unchanged (48). Unchanged PTH level in both studies may be due to the short period of intervention and longer period may be required in CKD to show the true overall effect on phosphate balance, PTH and FGF-23 control. However, there is no interventional study to show that phosphate restriction improves clinical outcomes and it is widely accepted that dietary phosphate restriction is unlikely to be sustained and extreme protein restriction to lower dietary phosphate can also be harmful (50).

3.2 Pharmacological

3.2.1 Phosphate binders

The main aim for using phosphate binders is to lower intestinal absorption of phosphate by binding with dietary phosphate in the gut; thus lowering serum phosphate which may indirectly attenuate worsening SHPT. Specific instruction and adherence on taking it before or with meals is crucial for its effectiveness. There is little doubt that all types of phosphate binders are effective in lowering serum phosphate in dialysis patients when compared to placebo as shown in the systematic review carried out by Navaneethan et al (51). PTH reduction has also been observed with the use of phosphate binders in dialysis patients in some studies (52-55).

The KDIGO CKD-MBD guideline recommends using phosphate binders only in hyperphosphataemic pre-dialysis CKD (37). This is because the optimum PTH level and the benefit of using phosphate binders in moderate CKD who are normophosphataemic to control SHPT remain unclear. Block et al randomised 148 patients with CKD stage 3-4 who had serum phosphate in the upper normal range (mean 4.2 mg/dl) to calcium acetate, lanthanum carbonate, sevelamer carbonate

and placebo. Results showed that all the phosphate binders modestly reduced serum phosphate despite significant reduction in urinary phosphate when compared to placebo (56). PTH level was unchanged in the treated group but worsened in the placebo group whereas FGF-23 level was unchanged in both groups. The treated group had an improvement in their bone mineral density but there was worsening of coronary artery calcification when compared to placebo which raises the question on safety of using phosphate binders in moderate CKD patients. In contrast, another study found that the progression of vascular calcification in patients randomised to low phosphate diet were similar to those on calcium-based phosphate binder (57). Thus, treating SHPT in pre-dialysis CKD remains controversial.

Calcium-based binders (acetate and carbonate) are cheap and in current practice, modest dose of calcium (<1.5 g of elemental calcium daily) is widely accepted. However, there have been concerns regarding calcium loading and the risk of extra-skeletal calcification. This led to the development of non-calcium based binders, namely sevelamer (hydrochloride and carbonate) and lanthanum (carbonate). These non-calcium-based phosphate binders have not shown superior phosphate or PTH reduction compared to calcium-based phosphate binders in head-to-head studies (51, 58, 59) but the studies have also focussed on 3 other outcomes; incidence of hypercalcaemia, mortality (60) and progression of vascular calcification (52, 53, 56, 61-63). Three systematic reviews have been published by Navaneethan et al (51) and Jamal et al (64, 65) with different conclusions on whether there is a survival benefit when using non-calcium-based compared to calcium-based phosphate binders. It is unlikely that a sufficiently large study will be done to resolve this question.

Aluminium-based phosphate binder is inexpensive and effective. Concerns regarding aluminium toxicity led to almost complete discontinuation of its use in 1980s although the primary source of aluminium exposure at the time came from dialysis fluid rather than aluminium-based binder (66). Reverse osmosis and stringent testing of dialysis water have almost completely removed aluminium in current practice. Thus, 6-14% of dialysis patients in Australia, New Zealand, Germany, Italy and Spain use this binder, whereas its use in the UK is minimal (2%) and often short term (67). Regular monitoring of serum aluminium is required.

A recently published phase 3 clinical trial of PA21 compound (sucroferric oxyhydroxide) showed comparable efficacy to sevelamer in dialysis patients and PTH was reduced in both groups but more so with PA21 (68). Its use has been approved in the United States and Europe in 2014. Small clinical trials of SBR759 iron-based compound have also shown its safety and efficacy in phosphate lowering but its effect on PTH was inconsistent (69-71).

3.2.2 Vitamin D

Vitamin D deficiency is highly prevalent in CKD, haemodialysis and peritoneal dialysis patients (72-74) and is associated with increased mortality (75, 76). The KDIGO CKD-MBD guideline suggests that the level is measured in CKD stages 3-5

and dialysis; and replaced if deficiency or insufficiency is detected (37). It is a weak recommendation given the lack of conclusive evidence on patient level outcome from randomised controlled trials (RCTs) although a number of large observational studies showed a survival benefit associated with vitamin D treatment in CKD and dialysis patients (46, 77-82). The dose of vitamin D that should be used is also unclear in the guideline, so the dose in our treatment algorithm (Figure 2) is based on our local guideline.

Vitamin D replacement in CKD patients can cause increased gut absorption of calcium and phosphate (83, 84). Given the importance of lowering serum phosphate to control SHPT and the risk of vascular calcification with hypercalcaemia, vitamin D replacement may seem counter-productive. However, not all vitamin D trials have shown significant hypercalcaemia and hyperphosphataemia as one would expect (85-87), nonetheless, the development of hypercalcaemia requires vitamin D dose reduction or cessation.

The broad term of vitamin D has caused a lot of confusion in terms of investigations and treatment. The 25-hydroxyvitamin D level is the metabolite routinely measured in clinical practice whilst 1,25-dihydroxyvitamin D is often measured in research setting only. Treatment options for vitamin D deficiency comes in several forms; either as vitamin D2 or D3, or in its native form or analogs. Vitamin D receptor activator or agonist (VDRA) describes the vitamin D compounds which directly activate VDR. VDR are polymorphic and most VDRAs are non-selective (calcitriol, alfacalcidol, and doxercalciferol) but the selective VDRA (paricalcitol) has the theoretical advantage of targeting the VDR on parathyroid gland with minimal effect on VDR elsewhere such as in the gut and bone. Table 1 lists the commonly used vitamin D preparations.

3.2.2.1 Native vitamin D

It was previously thought that CKD and dialysis patients should only be given alfacalcidol (1-alpha hydroxyvitamin D3) or doxercalciferol (1-alpha hydroxyvitamin D2) which will then undergo 25-hydroxylation in the liver to form the active 1,25-dihydroxyvitamin D. However, other sites in the body, such as skin, lymph nodes and macrophages, also have 1α-hydroxylation activity (88, 89). To confirm this, several studies have shown that native vitamin D3 (cholecalciferol) supplementation improves 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 levels in dialysis patients (85-87). PTH level was significantly reduced by 20-35% from baseline in two studies although there was no placebo group for comparison (85, 86). One RCT on 42 haemodialysis patients over 15 weeks did not show significant change in PTH with cholecalciferol compared to placebo (87) whereas a more recent RCT on 43 haemodialysis patients by Delanaye et al showed statistically significant reduction in PTH with cholecalciferol whilst PTH was increased in the placebo group over a one-year period (90). An RCT using ergocalciferol (native vitamin D2) or placebo over 12 weeks in 105 dialysis patients did not show any difference in PTH level between the groups (91). The difference in PTH lowering effect from these 3 RCTs using native vitamin D in dialysis patients may be due to the different study duration but it is worth noting that there were no significant changes in serum calcium and phosphate.

Despite the beneficial effect of native vitamin D replacement in controlling SHPT in dialysis patients, the effect in pre-dialysis CKD is inconsistent. In a study of elderly women, where over half had CKD stage 3, calcium (1.2g elemental calcium) and 800IU cholecalciferol supplementation resulted in >30% decrease in PTH compared to placebo (92). However, this study cannot differentiate the individual effect from either calcium or vitamin D supplementation. Two small RCTs in pre-dialysis CKD using cholecalciferol did not show significant reduction in PTH compared to placebo but both studies had short intervention and follow up periods (93, 94). Two observational studies assessing ergocalciferol in CKD stages 3-4 consistently showed significant PTH reduction by up to 20% in CKD stage 3 but not in the more advanced CKD stage 4 (95, 96).

3.2.2.2 Non-selective VDRA

The active 1,25-dihydroxyvitamin D3, calcitriol, is a non-selective VDRA. A retrospective study showed that oral calcitriol significantly lowered PTH in pre-dialysis CKD but at the expense of higher risk of hypercalcaemia compared to non-users (82). In the 1990s, intravenous (IV) calcitriol was recommended as an alternative to oral calcitriol in dialysis patients with SHPT. Thrice weekly IV calcitriol on haemodialysis significantly lowered PTH but majority of patients also developed hypercalcaemia (97).

Vitamin D analogs are non-selective synthetic VDRA of vitamin D3 (alfacalcidol) or vitamin D2 (doxercalciferol). A study using alfacalcidol in 176 mild-moderate CKD for 2 years showed attenuation of PTH rise compared to placebo, but with increased incidence of hypercalcaemia which was likely to be dose-dependent as it resolved with dose reduction (98). In contrast, two other studies using alfacalcidol in pre-dialysis CKD showed a significant PTH reduction from baseline by 15-50% but no hypercalcaemia (99, 100). A number of small studies assessed different preparations and dosing schedules of alfacalcidol in dialysis patients (101-103) but none compared it with placebo. These studies consistently showed that alfacalcidol is equally effective in reducing PTH across all forms (oral or IV) and dosing schedule (intermittent or daily). Doxercalciferol showed >40% PTH reduction from baseline with no significant change in serum calcium or phosphate in CKD (104) and dialysis patients (105). In contrast, another 2 studies in dialysis patients showed similar PTH reduction but with elevation of serum calcium and phosphate with doxercalciferol (106, 107).

3.2.2.3 Selective VDRA

Paricalcitol, a selective synthetic VDRA, is effective in lowering PTH in CKD (108, 109) and dialysis patients (110-112). Both RCTs in CKD stages 3-4 by Coyne et al (108) and the PRIMO study (109) showed that 85-90% of paricalcitol-treated group achieved >30% PTH reduction compared to only around 15% in the placebo group achieving the same endpoint. However, there was a significantly higher incidence of hypercalcaemia when compared to placebo in the PRIMO study but no difference

was found in the Coyne et al study. This difference may be due to the different dosing regimens but it is hard to compare because only one study reported the average dose used throughout the study (108).

A small head-to-head study in 66 dialysis patients demonstrated that paricalcitol was as effective as calcitriol in reducing PTH and had similar safety profile (111). An earlier direct comparison study using their respective IV forms, which also included a dose adjustment protocol, showed that paricalcitol may achieve quicker PTH reduction with less sustained hypercalcaemia compared to calcitriol (112). Furthermore, an observational study on 38,000 dialysis patients showed a survival advantage associated with paricalcitol use compared to calcitriol (113). Despite these favourable evidence for using paricalcitol, it is uncertain whether it is cost effective compared to non-selective VDRA which are much cheaper. An investigator-led randomised crossover trial comparing IV paricalcitol with alfacalcidol over a 16-week period in dialysis patients demonstrated equal effectiveness in PTH reduction whilst maintaining calcium and phosphate in the desired range for dialysis population (114).

The IMPACT SHPT (Improved Management of iPTH with Paricalcitol-centred Therapy versus Cinacalcet Therapy with Low-dose Vitamin D in Haemodialysis Patients with Secondary Hyperparathyroidism) study was an open label study comparing paricalcitol to calcimimetic (cinacalcet) plus low dose vitamin D in 268 dialysis patients over a 28-week period. The mean baseline iPTH in this study was around 500 pg/mL and the primary efficacy end point was the proportion of patients achieving iPTH value of 150-300 pg/mL from week 21 onwards. A greater proportion of patients achieved the primary end point in paricalcitol group compared to cinacalcet group (115, 116). However, FGF-23 level was increased significantly with paricalcitol which was likely due to the significant increase in serum phosphate. Around 8-17% of patients on paricalcitol developed hypercalcaemia whilst 14-26% of patients on cinacalcet developed hypocalcaemia. This study highlights the difficulty in reducing PTH with VDRA at the expense of rising serum phosphate and FGF-23, and furthermore, paricalcitol still causes significant rise in serum phosphate despite being a selective VDRA.

3.2.3 Calcimimetics

Calcimimetics increase the sensitivity of CaSR in parathyroid glands to extra cellular calcium concentrations, leading to a reduction in circulating PTH concentrations within 1–2 hours after dosing. In the UK, cinacalcet is not part of routine treatment for SHPT largely due to cost (117). The National Institute of Health and Care Excellence (NICE) guideline recommends its use in patients with uncontrolled SHPT (iPTH >800pg/ml) refractory to standard therapy with normal or high adjusted serum calcium or in whom the risk of surgical parathyroidectomy outweighs the benefit (118).

Phase 3 clinical study of cinacalcet in dialysis patients demonstrated its effectiveness in PTH reduction, safety and tolerability (119). Vitamin D is often used

to counteract hypocalcaemia related to cinacalcet. Thus, the combination use of native vitamin D or its analogs with cinacalcet allows calcium, phosphate and PTH target levels to be achieved simultaneously and greater PTH reduction has been observed using this combination therapy compared to either agent alone (120, 121). The OPTIMA study was an open label study which used an algorithm-based adjustment of VDRAs during the dose titration of cinacalcet in patients with moderate to severe SHPT (iPTH 300 – 800 pg/ml). The analysis suggested that VDRAs can be used in conjunction with cinacalcet in order to achieve greater PTH reduction but there is a trade-off with respect to higher serum phosphate and calcium relating to VDRA use (122). In addition to PTH reduction, the combination therapy also attenuated vascular calcification in moderate to severe SHPT as shown in the ADVANCE study (123).

A pooled analysis of phase 3 clinical trials data suggested benefit of using cinacalcet on a number of important end points including parathyroidectomy rates, fracture, cardiovascular hospitalisation and quality of life (15). This led to the design of EVOLVE (Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events) trial, an ambitious RCT aimed at a primary composite end point comprising of time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular events (16). 3883 haemodialysis patients with moderate to severe SHPT (median iPTH of 693 pg/ml) were randomised to cinacalcet or placebo while continuing conventional therapy including phosphate binders and vitamin D analogs as required. After a follow up of up to 63 months, the unadjusted intention-to-treat analysis showed a non-significant 7% reduction in primary outcome measure (i.e. a negative study). However, in the prespecified subgroup analysis, a 30% reduction in primary outcome was found in the older (≥ 65 years) patients who also had more cardiovascular co-morbidities (124). Secondary end points analysis showed no difference in fracture rate but parathyroidectomy rate was half in the intervention group compared to that in the control group. Despite significantly higher adverse events of hypocalcaemia in the cinacalcet group, it did not seem to have adverse impact on fractures or cardiovascular mortality.

Gastrointestinal symptoms such as nausea and vomiting are known side effects of oral cinacalcet which may be overcome by IV calcimimetics. IV velcalcetide or AMG416 is currently in phase 3 clinical trial in haemodialysis patients with SHPT. It is a novel, long-acting selective peptide agonist of the CaSR which has been well tolerated and has shown rapid and sustained PTH reduction after a single dose in haemodialysis patients (125).

3.3 Surgical

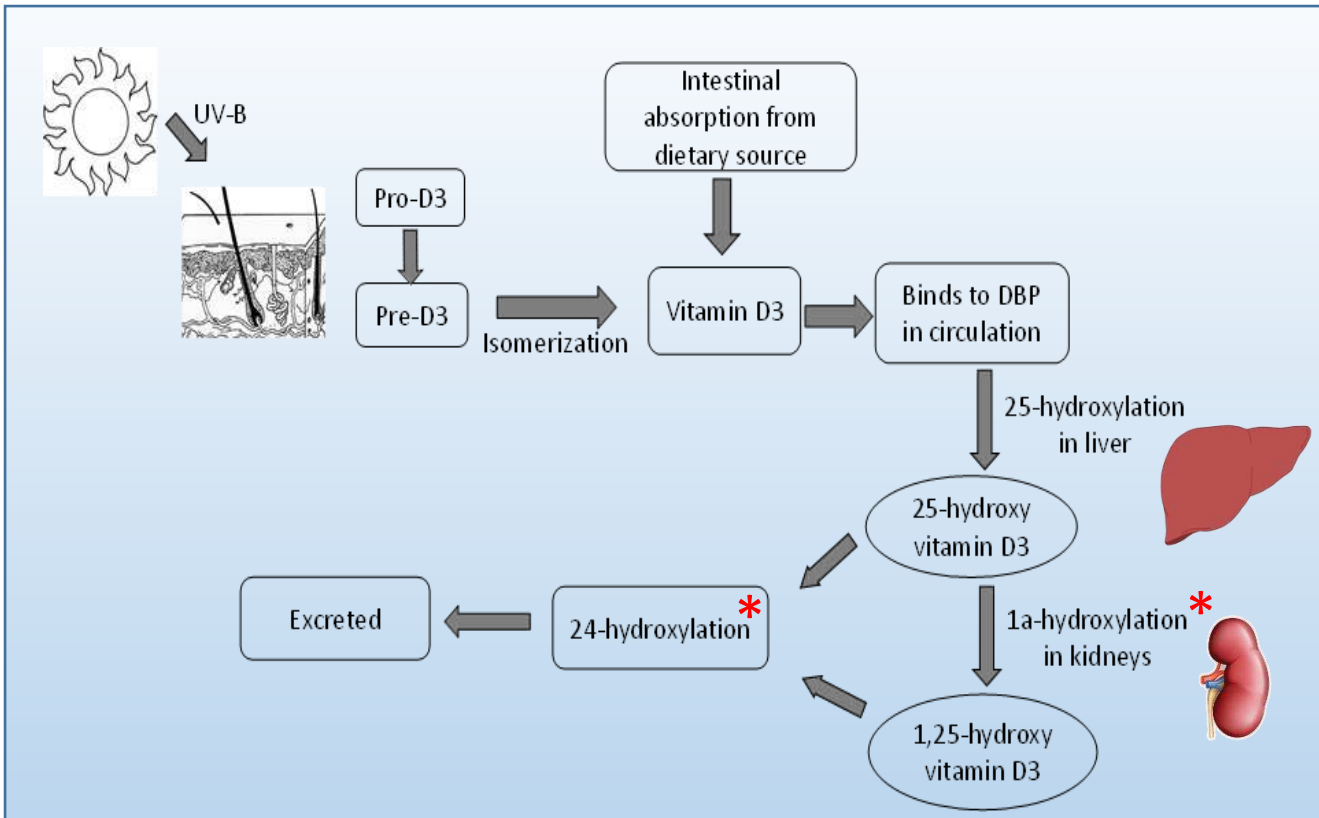
Parathyroidectomy is considered for patients with uncontrolled SHPT when pharmacological treatment options have been exhausted. Evidence of potential survival benefit after parathyroidectomy came from retrospective studies (77, 126, 127) but one retrospective study suggested that patients with persistently very low PTH levels post-parathyroidectomy had a higher 5-year mortality (128). Furthermore, there is concern relating to bone turnover as parathyroidectomy is likely to turn high

turnover bone disease to adynamic bone disease (129) which is also associated with worse vascular calcification (130). An improvement of around 10% in bone mineral density (BMD) at 6 months after parathyroidectomy was reported (131) but another study found only modest improvement in BMD at 5 years after parathyroidectomy although no patient suffered any fractures during the follow up period (132). An RCT to compare the benefit of parathyroidectomy versus pharmacological treatment in uncontrolled SHPT is unlikely to ever be carried out and with increasing age and co-morbidities amongst dialysis patients, surgical parathyroidectomy is becoming rare. Parathyroidectomy may be largely replaced by pharmacological treatment in the future if the cost of calcimimetics is reduced.

4. Summary

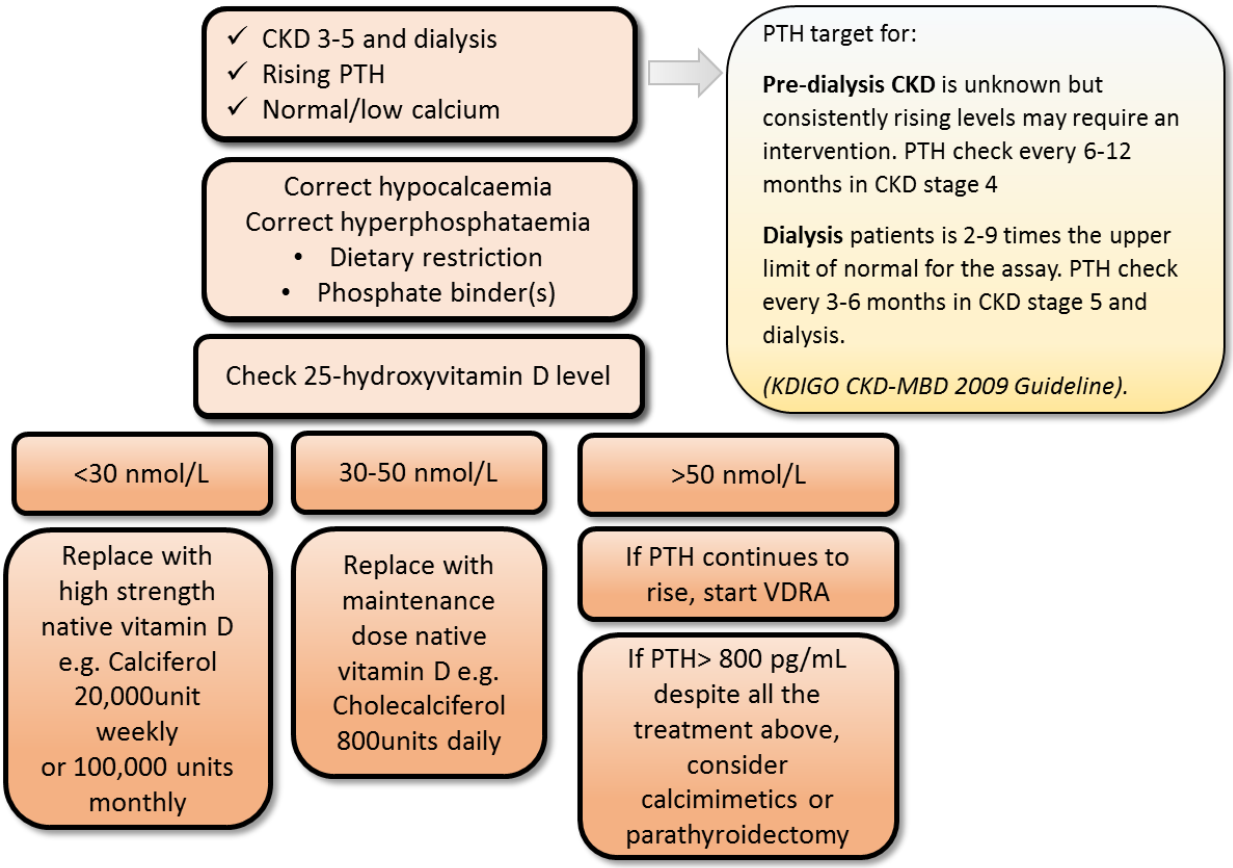
SHPT is associated with adverse outcomes in CKD and dialysis patients, thus there is a recommendation to control SHPT as renal function declines. Effective SHPT management becomes more difficult once skeletal and cardiovascular adverse effects associated with severe SHPT are established. Interventional strategies largely comprise of dietary phosphate restriction and pharmacotherapy although it remains very difficult to extrapolate biochemical end point to meaningful patient-centred outcomes. Management of SHPT in pre-dialysis CKD remains inconclusive, partly because optimum target PTH level is still unknown and there is such heterogeneity in PTH level and CKD stages between clinical trials. The wide PTH range in dialysis patients as recommended by the KDIGO CKD-MBD guideline is sensible given that PTH is a poor marker of bone turnover and quality. Future studies in controlling SHPT requires multiple pharmacological and non-pharmacological approach reflecting real clinical practice, inclusion of patient-centred outcomes, and better assessment of bone and vascular calcification which are also part of CKD-MBD.

Figure 1: Normal vitamin D metabolism and steps that are affected by high FGF-23 in CKD.



Vitamin D3 is made in the skin when 7-dehydrocholesterol (also known as pro-D3) is converted to pre-D3 when the skin is exposed to sunlight ultraviolet B-ray. Pre-D3 forms isomers which then binds to vitamin D binding protein (DBP) which is present in the circulation. Vitamin D3 is also available from dietary source where it enters the circulation via the intestine and binds with DBP. Vitamin D then goes through hydroxylation in the liver to make 25-hydroxyvitamin D (calcidiol). The final hydroxylation occurs in proximal tubule of the kidney to produce the active form 1,25-hydroxyvitamin D (calcitriol). The 1,25-dihydroxyvitamin D increases intestinal calcium and phosphate absorption and promotes bone mineralization. It also has functions in the regulation of immune system. Vitamin D is removed from the body via 24-hydoxylation of calcidiol or calcitriol which are principally excreted in the bile. Its water soluble metabolites can also be excreted in the urine. * indicates the steps that are affected by high FGF-23 in CKD.

Figure 2: Treatment algorithm for secondary hyperparathyroidism (SHPT) in pre-dialysis CKD and dialysis patients.



Abbreviations: chronic kidney disease, CKD; parathyroid hormone, PTH; vitamin D receptor activator, VDRA.

Table 1: The commonly used vitamin D in CKD and dialysis patients for controlling SHPT.

Vitamin D	**PTH reduction**	**Hypercalcaemia**	**Note**
Cholecalciferol (25-hydroxyvitamin D3)	Conflicting in CKD (93, 94) Yes in dialysis (85-87, 90)	No	Requires 1α-hydroxylation in extra-renal sites
Ergocalciferol (25-hydroxyvitamin D2)	Conflicting in CKD (95, 96) No in dialysis (91)	No	Requires 1α-hydroxylation in extra-renal sites
Calcitriol (1,25-dihydroxyvitamin D3)	Yes in CKD (82) Yes in dialysis (97)	Yes	Non-selective VDRA
Alfacalcidol (1-alpha hydroxyvitamin D3)	Yes in CKD (98-100) Yes in dialysis (101-103)	Conflicting	Non-selective VDRA Requires 25-hydroxylation in the liver
Doxercalciferol (1-alpha hydroxyvitamin D2)	Yes in CKD (104) Yes in dialysis (105-107)	Conflicting	Non-selective VDRA Requires 25-hydroxylation in the liver
Paricalcitol (19-nor-1,25-dihydroxyvitamin D2)	Yes in CKD (108, 109) Yes in dialysis (110-112, 114-116)	Yes	Selective synthetic VDRA

Abbreviations: chronic kidney disease, CKD; secondary hyperparathyroidism, SHPT; parathyroid hormone, PTH; vitamin D receptor activator, VDRA.

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