REVIEW

The treatment of renal hyperparathyroidism

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Abstract

Renal hyperparathyroidism (rHPT) is a complex and challenging disorder. It develops early in the course of renal failure and is associated with increased risks of fractures, cardiovascular disease and death. It is treated medically, but when medical therapy cannot control the hyperparathyroidism, surgical parathyroidectomy is an option. In this review, we summarize the pathophysiology, diagnosis, and medical treatment; we describe the effects of renal transplantation; and discuss the indications and strategies in parathyroidectomy for rHPT. Renal hyperparathyroidism develops early in renal failure, mainly as a consequence of lower levels of vitamin D, hypocalcemia, diminished excretion of phosphate and inability to activate vitamin D. Treatment consists of supplying vitamin D and reducing phosphate intake. In later stages calcimimetics might be added. RHPT refractory to medical treatment can be managed surgically with parathyroidectomy. Risks of surgery are small but not negligible. Parathyroidectomy should likely not be too radical, especially if the patient is a candidate for future renal transplantation. Subtotal or total parathyroidectomy with autotransplantation are recognized surgical options. Renal transplantation improves rHPT but does not cure it.

Introduction

Hyperparathyroidism is relatively common. Primary hyperparathyroidism is the third most common endocrine disorder with a lifetime risk of 1% (Shindo et al. 2016). Secondary hyperparathyroidism has an external etiology and can be caused by vitamin D deficiency, liver disease, lithium therapy or, most commonly, chronic kidney disease (CKD). Typical of secondary hyperparathyroidism in CKD is that it is driven by hypocalcemia and hyperphosphatemia. Eventually the parathyroid glands become unresponsive to plasma calcium levels and autonomously produce high levels of parathyroid hormone in the presence of hypercalcemia; this condition is defined as tertiary hyperparathyroidism. The hyperparathyroidism of CKD is the focus of this review and we will refer to it as renal hyperparathyroidism (rHPT).

Key Words
- chronic kidney disease
- hyperparathyroidism
- parathyroid hormone
- vitamin D
- parathyroidectomy

Pathophysiology

Chronic kidney disease

Chronic kidney disease, CKD, is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health (KDIGO 2013). It is a general term that includes many heterogenous disorders that all affect kidney structure and function (KDIGO 2013). Due to the heterogenous origin of renal disease, CKD can range from a mild asymptomatic decrease in renal function that remains stable for decades to a rapidly decreasing renal function with multiple complications and finally end-stage renal disease (ESRD). A failing kidney has a widespread impact on the organism and affects almost all organs in the human body. Patients with ESRD have 10–20 times higher...
mortality rates compared to the general population and the major cause of mortality is cardiovascular (Foley et al. 1998). Patients with ESRD also develop bone disease. The complex relation between vascular calcifications, bone and kidney has led Kidney Disease Improving Global Outcomes (KDIGO) to produce clinical guidelines for the management of chronic kidney disease – mineral and bone disorder (CKD-MBD) (KDIGO 2009). An outline of these relations is presented in Fig. 1.

Renal hyperparathyroidism, rHPT, with increasing levels of parathyroid hormone (PTH) and parathyroid gland hyperplasia, is a major part of CKD-MBD and develops in all patients with CKD as renal function deteriorates. CKD is divided into five stages based on glomerular filtration rate (GFR), ranging from stage 1 where the GFR is >90 mL/min/1.73 m², to stage 5 where GFR is <15 mL/min/1.73 m² (Table 1) (KDIGO 2013). In a recent review the global prevalence of CKD stages 3–5 was found to be about 10% (Hill et al. 2016). Thus, CKD is common and with an aging population with increasing prevalence of hypertension and diabetes it is a growing global problem (Coresh et al. 2007). Both death and disability-adjusted life years lost due to CKD are increasing (Jager & Fraser 2017). The medical costs attributable to CKD are substantial and increase as disease severity worsens, particularly if renal replacement therapy (RRT) has to be initiated (Honeycutt et al. 2013). Renal hyperparathyroidism is a direct cause of vascular and bone-related outcomes as well as mortality in CKD (Young et al. 2004).

FGF23 and klotho

A central hormone in the rHPT process is fibroblast growth factor 23 (FGF23), produced by osteoblasts and osteocytes. It is the major phosphate regulatory hormone (Isakova et al. 2011). FGF23 is induced by high levels of phosphate, active vitamin D and PTH (Meir et al. 2014, Bon et al. 2018) and increases early in CKD (Isakova et al. 2011). FGF23 binds to its receptor FGF receptor 1 (FGFR1) which requires a co-receptor, α-klotho, to function (Kurosu & Kuro 2009). α-Klotho is expressed in the kidney and in parathyroid tissue (Lim et al. 2015). FGF23 decreases the phosphate reuptake in the distal tubuli and thus lowers blood levels of phosphate (Sneddon et al. 2016). FGF23 also downregulates 1-α-hydroxylase and upregulates D-24-hydroxylase in the kidney with a net effect of lower levels of active vitamin D and lower uptake of phosphate in the intestines (Shimada et al. 2004). With declining renal function, the level of soluble α-klotho is reduced, which contributes to FGF23 resistance (Drew et al. 2017). Due to the FGF23 resistance, levels of FGF23 rise to compensate (Sakan et al. 2014). Resistance to FGF23 leads to enhanced secretion of PTH from the parathyroid gland since PTH acts in a phosphaturic manner, in the same way as FGF23. In early CKD and early stages of rHPT, high FGF23, low soluble klotho, normo- or hyperphosphatemia and a slight increase in PTH are the usual findings (Drueke 2000).

Thus, early in the course of declining renal function there is a cascade of physiological changes due to the renal tubules’ failing ability to maintain homeostasis in the
Table 1  Chronic kidney disease, CKD, is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.

<table>
<thead>
<tr>
<th>GFR stages in CKD</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 1a</td>
<td>≥90</td>
<td>Normal</td>
</tr>
<tr>
<td>2a</td>
<td>60–89</td>
<td>Normal to mildly decreased</td>
</tr>
<tr>
<td>3a</td>
<td>45–59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>3b</td>
<td>30–44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

*In the absence of kidney damage neither of the categories qualifies as CKD.
CKD, chronic kidney disease; GFR, glomerular filtration rate.

Calcium–phosphate–vitamin D axis, see also Fig. 1. This is long before secondary hyperparathyroidism becomes manifest. In fact, the first sign that something is wrong is a rise in FGF23. FGF23 exerts endocrine effects on the proximal tubules. However, due to the lack of heparin-binding sites on FGF23, it is dependent on both α and β klotho as well as specific FGF receptors to exercise its effects.

FGF23 has two key effects on calcium-phosphate-vitamin D homeostasis: it suppresses the activation of vitamin D in the proximal tubules, functioning as a counter-regulatory hormone for 1,25 dihydroxyvitamin D₃ (calcitriol) and it suppresses the reabsorption of phosphate, thus inducing phosphaturia. In the course of progressive renal failure FGF23 increases first, followed by a decrease in 1,25 dihydroxyvitamin D₃ after which levels of parathyroid hormone increase. Usually phosphate levels are affected last and start to rise in CKD stage 5. Thus, FGF23 probably has primary responsibility for maintaining phosphaturia, while the rise in PTH is most likely a direct response to the decrease in 1,25 dihydroxyvitamin D₃ and a decrease in plasma calcium concentration. Finally, plasma phosphate further stimulates hyperparathyroidism (Isakova et al. 2011, Kuro 2019).

Vitamin D comprises a group of lipid-soluble molecules. 25-Hydroxyvitamin D (25(OH)D) is the major form in circulation and is activated to 1,25-dihydroxyvitamin D by 1α-hydroxylase, which is expressed in the proximal tubule. 25(OH)D has a half-life of 3 weeks, which is the longest in the group. FGF23 limits the production of 1,25-dihydroxyvitamin D by suppressing 1α-hydroxylase, while 1,25-dihydroxyvitamin D stimulates FGF23, creating a feedback loop (Goldsmith 2016).

Laboratory analyses

At present, FGF23 is not routinely analyzed in clinical practice. The latest KDIGO update on management of CKD-MBD suggests that 25(OH)D might be analyzed starting during CKD stage 3 (KDIGO 2009). In consequence a cascade of pathophysiological events go under the clinician’s radar. These changes become apparent when plasma calcium levels decrease, PTH rises and plasma phosphate increases. It is important to note that there are diurnal variations and fluctuations in these concentrations. Therefore, physicians are recommended not to act on a single value, but rather to analyze the trend in a series of laboratory results before starting or adjusting treatment (KDIGO 2009).

Phosphate retention

A positive phosphate balance is another central factor in the development of rHPT. With declining renal function the ability to maintain mineral homeostasis is impaired, both by reduced capacity to filter phosphate due to loss of renal function but also by disturbed function of the bone. In CKD various types of bone disease occur, all characterized by excessive bone resorption compared to formation (Drueke & Massy 2016). This occurs early in CKD and reduces the capacity for the skeleton to buffer phosphate load. Instead, the skeleton contributes to hyperphosphatemia (Hruska et al. 2008). The positive phosphate balance leads to elevated levels of FGF23. Phosphate also stimulates the release of PTH. The phosphaturic actions of PTH together with FGF23 keep phosphate levels regulated in early CKD (Sneddon et al. 2016). Phosphate levels in the blood remain normal until CKD stages 4–5, when hyperphosphatemia is common (Levin et al. 2007). This is due to the loss of functioning nephrons and because tubular reabsorption is already maximally inhibited by FGF23 and PTH. In almost all other situations involving phosphate retention, the skeleton pools excessive phosphate to keep blood levels unchanged. In CKD, due to bone disease, the phosphate reservoir is shifted to soft tissue (e.g. vasculature), a process driven by multiple bone-specific signaling pathways, many of them directly activated by phosphate itself (Hruska et al. 2008). Long-lasting hyperphosphatemia thus leads to vascular calcifications (Mathew et al. 2008) and is a central element of the development of CKD-MBD and rHPT, see also Fig. 1.
Vitamin D and calcium

Vitamin D plays an important role in mineral homeostasis. Native vitamin D (25-hydroxyvitamin D) is activated in the kidney via 1-α-hydroxylase (Brunette et al. 1978) to the active form 1,25-dihydroxyvitamin D. Activated vitamin D acts via the vitamin D receptor (VDR) in the intestines to stimulate calcium and phosphate uptake (Xue & Fleet 2009). Vitamin D receptors are also present in the parathyroid gland where, if activated, they lead to reduced production and release of PTH and a suppression of parathyroid gland proliferation (Silver et al. 1986). The elevated levels of FGF23 in early CKD contribute to low levels of activated vitamin D, and later on, loss of nephrons also contribute to a deficiency of active vitamin D (Levin et al. 2007). Patients with CKD also have low levels of native vitamin D due to albuminuria, low exposure to sunlight, and poor dietary intake (Obi et al. 2015). The result of vitamin D deficiency is hypocalcemia. In late CKD both high phosphate and vitamin D deficiency leads to hypocalcemia which is the most potent stimulator of PTH release via the calcium-sensing receptor in the parathyroid gland (CaSR) (Brown et al. 1993). Apart from other effects of PTH described earlier, the most potent effect is to increase serum calcium levels by enhancing renal tubular calcium reabsorption, stimulating net bone resorption and increasing the production of activated vitamin D (1,25(OH)2D3) (Pocotte et al. 1991). Low levels of active vitamin D also directly result in PTH release and parathyroid cell proliferation.

Parathyroid gland hyperplasia

The leading factors for parathyroid gland hyperplasia are active vitamin D, calcium and phosphate. Transforming growth factor-alpha (TGF-α) has been shown to be a potent proliferative agent for parathyroid cells via the activation of EGF receptor (EGFR). Activation of EGFR both leads to proliferation of parathyroid cells and to lesser expression of VDR (Arcidiacono et al. 2008). The anti-proliferation pathway is mediated via cyclin-dependent kinase inhibitor p21 and also reduced expression of TGF-α. Both active vitamin D and high levels of calcium inhibit parathyroid cell proliferation through this pathway (Cozzolino et al. 2001, Cordero et al. 2002). Thus, low levels of active vitamin D in CKD contribute to parathyroid cell proliferation (Tokumoto et al. 2002). In uremic rats, high dietary intake of phosphate increases TGF-α and low dietary intake of phosphate enhances the expression of p21 independent of vitamin D, which is why phosphate also contributes to parathyroid cell proliferation (Dusso et al. 2001). In early CKD the parathyroid gland often shows polyclonal proliferation, and in late CKD monoclonal/nodular proliferation is more common. However, different pathological changes often coexist in the same parathyroid gland (Basile et al. 2006). With more severe rHPT the expression of VDR CaSR and α-klotho is reduced (Fukuda et al. 1993, Komaba et al. 2010, Lee et al. 2013).

Tertiary hyperparathyroidism

Long-standing CKD with rHPT leads to polyclonal and eventually monoclonal proliferation of parathyroid tissue with a loss of regulatory receptors (van der Plas et al. 2019). This condition is generally defined as tertiary hyperparathyroidism due to general hyperplasia of the parathyroid gland or autonomous adenoma. Both conditions are characterized by high levels of PTH in the presence of persistent hypercalcemia (Pitt et al. 2009). A histological finding of severe hyperplasia or parathyroid adenomas with high levels of parathyroid hormone and persistent hypercalcemia and often also hyperphosphatemia in patients with rHPT is associated with failure to respond to medical treatment (Tominaga et al. 2007). Tertiary HPT is a complication of long-term CKD most often after many years of dialysis treatment and can persist after successful renal transplantation. Two years after renal transplantation an incidence of about 30% has been reported (Shindo et al. 2016). It is noteworthy, however, that some authors define tertiary hyperparathyroidism as a persistent HPT after renal transplantation (Dulfer et al. 2017). In this review we have chosen to define tertiary hyperparathyroidism as refractory rHPT.

Symptoms and signs

rHPT is not only manifested by deranged laboratory analyses. It also affects patient well-being, see Table 2 for some common signs and symptoms. Initial symptoms are pruritus and thirst. As rHPT becomes more pronounced, muscle weakness and tiring easily become prominent. Albeit, that all these symptoms are also typical during the later stages of CKD. Findings such as vascular calcification and osteodystrophy can occur already during CKD stage 3 and evolve as GFR declines, due to an increased imbalance in the FGF23-calcium-phosphate-vitamin D-PTH axis. Once rHPT advances to tertiary hyperparathyroidism patients can experience mood swings, conjunctivitis...
**Table 2** Some signs and symptoms in rHPT.

<table>
<thead>
<tr>
<th>Sign / Symptom</th>
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<tbody>
<tr>
<td>Pruritus</td>
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<tr>
<td>Thirst</td>
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<tr>
<td>Headaches</td>
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<tr>
<td>Muscle weakness</td>
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<tr>
<td>Bone pain</td>
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<tr>
<td>Joint pain</td>
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<tr>
<td>Tiring easily</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Mood swings and/or depression</td>
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<tr>
<td>Conjunctivitis – red eye syndrome</td>
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<tr>
<td>Vascular calcification</td>
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<tr>
<td>Osteodystrophy</td>
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<tr>
<td>Brown tumors in the mandible</td>
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<tr>
<td>Brown tumors in the bones of the extremities</td>
</tr>
<tr>
<td>Low bone mineral density</td>
</tr>
<tr>
<td>Fragility fractures</td>
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</tbody>
</table>

Data from Pasieka & Parsons (2000).

as well as bone and joint pain. Eventually they develop brown tumors in their bones.

**Diagnosis**

Diagnosis of rHPT is a process. Initially plasma calcium (low to normal), phosphate (elevated), PTH (elevated) and vitamin D (low) are sufficient for the diagnosis of rHPT. Moreover, in patients with evidence of CKD-MBD or osteoporosis monitoring of bone mineral density with dual-energy X-ray absorptiometry (DEXA) is recommended (KDIGO). As long as rHPT can be controlled with the therapy options described in sections ‘Vitamin D: ergocalciferol or cholecalciferol’ to ‘Active vitamin D analogs’ further investigations are generally not required. However, when PTH, plasma calcium and phosphate no longer can be controlled and the question of tertiary hyperparathyroidism arises, further investigation is necessary. Firstly, patient symptoms should be explored in order to guide the extent of the investigation. Once, the nephrologist is convinced that the patient has tertiary rHPT, that is, renal HPT resistant to medical treatment, contact with an endocrine surgeon is established. Secondly, if the patient has bone and/or joint pain an X-ray, scintigraphy or CT of the mandible, hands, legs and arms are recommended. The degree of vascular calcification can be investigated by a lumbar X-ray to determine the abdominal aortic calcification score.

**Treatment**

**Medical**

Treatment options are summarized in **Table 3**.

**Vitamin D: ergocalciferol or cholecalciferol**

In accordance with the described sequence of pathophysiological events, the first line of treatment should be medical, aiming to compensate for the dwindling number of nephrons. Thus, supplementation with calciferol is recommended as the first line of treatment in non-dialysis patients with CKD stages 3a to 5 (KDIGO 2009, Goldsmith 2016). 25(OH) insufficiency or deficiency in patients with CKD stages 3 to 5 should be treated according to the recommendations for the general population (KDIGO 2009). The same treatment strategy should be employed in patients with CKD stage 5D (KDIGO 2009, Goldsmith 2016). There is still controversy regarding the long-term effects of this treatment, mainly due to the fact that there is insufficient evidence from solid, long-term randomized controlled trials comparing vitamin D with other treatment modalities. However, in a recent randomized controlled trial in patients with CKD stages 3 and 4, 12 weeks of supplementation with cholecalciferol resulted in a decrease in PTH with stable levels of plasma calcium (Westerberg et al. 2018).

**Control of calcium and phosphate**

**Restriction of dietary intake** As plasma phosphate starts to rise, a restriction of dietary phosphate intake is recommended. This is not always easy for the patient to adhere to. There are usually high levels of phosphate in processed foods, which can add an extra burden for the patient if they are unaccustomed to preparing their meals using fresh and whole ingredients. In patients with CKD stages 4 and 5, protein restriction per se will provide a certain phosphate restriction, but in patients on dialysis the increased protein requirements can make phosphate restriction more complicated. Thus, most patients will to some degree require treatment with phosphate binders.

**Treatment with phosphate binders** Phosphate binders are central to the treatment of hyperphosphatemia, usually starting during CKD stages 4 and 5 and continuing through stage 5D. Numerous studies have shown that increased levels of phosphate are associated with increased mortality (Tentori et al. 2008, 2015). Hypercalcemia is associated with increased morbidity and mortality mainly due to valvular, coronary artery, and aortic calcification (Floge & Ketteler 2004, Ogawa & Nitta 2018). The oldest phosphate binder is aluminum hydroxide and should not be used due to the deleterious effects of aluminum overload. Calcium-based phosphate binders, usually calcium carbonate, can be used, but it is essential to
**Table 3** An overview of medical treatment options for renal HPT.

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>Restriction of phosphate intake</th>
<th>Phosphate binders</th>
<th>Non-selective vitamin D receptor activators</th>
<th>Selective vitamin D receptor activators</th>
<th>Calcimimetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergocalciferol</td>
<td>Avoid processed foods</td>
<td>Sevelamer hydrochloride</td>
<td>Calcitriol</td>
<td>Paricalcitol</td>
<td>Cinacalcet</td>
</tr>
<tr>
<td>Cholecalciferol</td>
<td>Avoid drinks with high phosphate</td>
<td>Lanthanum carbonate</td>
<td>Alfacalcidol</td>
<td>Maxacalcitol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avoid certain foods with high phosphate</td>
<td>Ferric citrate</td>
<td>Doxercalciferol</td>
<td></td>
<td>Etelcalcide (only i.v. administration)</td>
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</table>

Start treatment options by using medication in the left column and proceed toward the right as the severity of the condition progresses.

Avoid hypercalcemia. Modern phosphate binders, such as sevelamer hydrochloride and lanthanum carbonate have been shown to be effective and safe (Patel et al. 2016). The most recent additions are based on iron, such as ferric citrate and sucroferric oxyhydroxide (Habbous et al. 2017). Moreover, sevelamer also seems to have positive effects on arteriosclerosis which are not directly related to its phosphate-binding capacity (Patel et al. 2016). Phosphate control is an important priority and levels should be maintained within the normal range (KDIGO 2009). This is easier said than done. The burden of pills necessary to control phosphate is usually high and can amount to around 15–20 extra tablets a day, which should be taken with a meal. Moreover, many patients can experience mild gastrointestinal disturbances due to the phosphate binders. The multi-professional nephrology team needs to be involved to help motivate the patient and explain the long-term advantages.

**Active vitamin D analogs** The active vitamin D analogs actively bind to the vitamin D receptors in many tissues such as the parathyroid gland and the intestine. There are a number of non-selective vitamin D receptor activators: the first generation comprises calcitriol (1α25-dihydroxyvitamin D$_3$), and the second generation alfacalcidol (1α-hydroxyvitamin D$_3$) and doxercalciferol (1α-hydroxyvitamin D$_2$). They are effective in controlling PTH but can cause hypercalcemia (Zand & Kumar 2017). The third generation of vitamin D receptor activators are selective and comprise paricalcitol (1,9-nor-1α25-dihydroxyvitamin D$_3$) and maxacalcitol (22-oxa-1,25-dihydroxyvitamin D$_3$) (Darabian et al. 2012). In a meta-analysis calcitriol and alfacalcidol had similar efficacy in suppressing PTH compared with paricalcitol and maxacalcitol (Xie et al. 2017). The risks of hypercalcemia and hyperphosphatemia were similar for the non-selective VDRAs compared with the selective VDRAs (Xie et al. 2017). Another meta-analysis in non-dialysis-dependent patients with CKD compared paricalcitol with placebo and found that paricalcitol effectively decreased PTH levels (Han et al. 2013). They also found a statistically nonsignificant trend toward hypercalcemia in the paricalcitol-treated patients compared to those on placebo (Han et al. 2013).

**Calcimimetics** In some patients, hyperparathyroidism is uncontrollable with the therapy options described earlier. Before the advent of cinacalcet they would need surgical treatment to control their PTH and calcium levels. In 2002 cinacalcet was shown to successfully lower PTH in patients on hemodialysis (Goodman et al. 2002). A randomized controlled trial in 2004 showed that cinacalcet could decrease PTH and induce lower plasma calcium and phosphate levels in patients on hemodialysis (Block et al. 2004). Similar positive results were also reported in patients with CKD stages 3–4 (Charytan et al. 2005). Disappointingly, cinacalcet has not been as effective as initially expected for long-term treatment of hyperparathyroidism in patients with CKD. In an observational study using French registry data the authors found that the use of cinacalcet did not significantly impact PTH values compared with patients without the treatment (Brunaud et al. 2016). The expectations that cinacalcet treatment would reduce the risk of death or major cardiovascular end points were not corroborated in the EVOLVE trial (EVOLVE Trial Investigators 2012). However, in a trial focusing on renal osteodystrophy, cinacalcet significantly decreased high rates of bone formation and some biochemical markers of high-turnover bone disease as PTH was reduced, with 26% of the patients...
achieving normal bone histology after 12 months of treatment (Behets et al. 2015). There are some unwanted side effects of treatment with cinacalcet. All studies report that hypocalcemia, nausea and vomiting were frequent and difficult side effects in patients treated with cinacalcet (Block et al. 2004, EVOLVE Trial Investigators 2012, Brunaud et al. 2016). The gastrointestinal symptoms were often a reason that patients discontinued treatment.

The latest calcimimetic, etelcalcide, is administered intravenously. In a randomized controlled trial in hemodialysis patients the effects of etelcalcide on PTH were found to be non-inferior to cinacalcet (Block et al. 2017). The frequency of nausea and vomiting was similar in both treatment groups, but the etelcalcide group was more likely to experience hypocalcemia compared with the cinacalcet group (Block et al. 2017).

In summary, medical treatment is not the sine qua non for treatment of hyperparathyroidism in patients with CKD. A problem that has not been adequately addressed when evaluating the efficacy of different treatment modalities is whether a patient only suffers from an increased production of PTH or whether there is hyperplasia of or adenoma in the parathyroid glands. It is likely that the boundary for success of medical treatment runs here, and when there are manifest anatomical changes in the PTH glands, surgical treatment becomes necessary.

Renal transplantation

After successful renal transplantation the mineral homeostasis is completely changed. The remaining high FGF23 and PTH now exert actions on a functioning kidney that will increase the secretion of phosphate in the urine, resulting in hypophosphatemia (Bhan et al. 2006). Levels of FGF23 decrease and the expression of α-klotho increases after transplantation (Kimura et al. 2015). Levels of vitamin D and calcium increase (Reinhardt et al. 1998). Hypercalcemia in the first 1–6 months is common and is associated with high levels of PTH (Amin et al. 2016). Levels of PTH accumulate during ESRD thus a rapid decrease in PTH is seen immediately after transplantation. Thereafter, levels of PTH keep decreasing slowly and stabilize after the first 6 months (Isaksson & Sterner 2012). The majority of patients have PTH levels above the reference range 1 year after transplantation (Sprague et al. 2008). Risk factors for post-transplant rHPT are pre-transplant levels of PTH and calcium, time spent on dialysis before transplantation and nodular hyperplasia of the parathyroid glands (Taweesedt & Disthabanchong 2015).

Cardiovascular disease is the leading cause of death in renal transplant recipients (Kasiske et al. 1996) and there are some data supporting an association with rHPT (Bleskestad et al. 2014, Pihlstrom et al. 2015). The fracture risk is high after renal transplantation (Naylor et al. 2013) and renal transplant patients have varying patterns of bone disease. Studies of bone biopsies in renal transplant recipients show a marked decrease in bone turnover following transplantation and low bone turnover as the predominant pattern (Evenepoel et al. 2017, Keronen et al. 2019). Bone disease after renal transplantation is both due to rHPT but also to factors specific to transplantation such as corticosteroids and immunosuppressive agents (Julian et al. 1991, Weisinger et al. 2006). The correlation between bone histology and non-invasive diagnostic tools (bone mineral density, biomarkers) is weak (Keronen et al. 2019) and bone biopsies are infrequently used in clinical practice. Additionally, most findings regarding HPT post-transplantation are based on small observational studies. Thus, recommendations of evaluation and treatment of post-transplant rHPT are not very specific.

Surgical: parathyroidectomy

Indications

As stated earlier, rHPT is initially a physiologic adaptation to the decreasing renal function. However, with time, hyperparathyroidism becomes deleterious, increasing the risk for cardiovascular and skeletal disease and can lead to shortened survival in patients with CKD. Most patients are successfully managed medically, as outlined above. However, in a small but important subset of patients, medical treatment cannot control rHPT. In these patients, surgical treatment with parathyroidectomy (PTX) is an option. KDIGO CKD-MBD guidelines state that PTX is indicated in ‘patients with ESRD and severe HPT who fail to respond to pharmacological treatment’. The European Society of Endocrine Surgeons published a consensus report in 2015 stating that PTX is an option in any patient with rHPT, but that in most patients, the condition can be managed medically. Specifically, PTX would be indicated when medical treatment fails to correct metabolic parameters: PTH >85 pmol/L, hypercalcemia and hyperphosphatemia.

There are no randomized trials comparing PTX to medical treatment. Hence, guideline recommendations rely on data from observational studies. Given the heterogeneity of patients with rHPT, the differences in types of dialysis, whether patients had or had not previously received a renal transplant, differences in
medication, and so forth, it is hard to define specific indications for surgery in a given patient. It is likely that indications differ according to sex, age, type of underlying renal disease, whether the patient has a functioning transplant and/or the chance of receiving a transplant.

Epidemiologic studies indicate that parathyroidectomy rates decreased in the first years after the introduction of calcimimetics, but have since risen again (Akaberí et al. 2014). They also point to regional differences within and between countries, probably due to different access to nephrologists and/or endocrine surgeons, and to different therapy strategies between institutions. Multiple regression models suggest that women, younger patients and non-diabetic patients have a greater probability of undergoing PTX (Akaberí et al. 2014).

Evidence indicates that PTX is associated with reduced risk of fractures (Isaksson et al. 2017), cardiovascular disease (Ivarsson et al. 2019) and mortality (Ivarsson et al. 2015). Studies also show that PTX is related to improved quality of life (van der Plas et al. 2017) and that is more cost-efficient than calcimimetics in most patients with ESRD (Narayan et al. 2007). Unless the patient has a high risk of dying soon or an imminent transplantation is expected, PTX is more cost-effective, given the high costs of maintenance treatment with calcimimetics (Narayan et al. 2007). However, perioperative morbidity and even mortality is not insignificant (Kestenbaum et al. 2004, Ishani et al. 2015); hence, in all patients, surgical risk must be weighed against potential long-term improvement in outcomes.

Even if most of these studies tried to adjust for confounders, a selection bias cannot be completely ruled out. Patients that are referred for parathyroidectomy are likely healthier and with a better expected outcome than patients who do not get referred for surgery, all other things equal. Unfortunately, it is unlikely that a randomized trial comparing medical treatment to PTX will ever be performed, given the large number of centers that would be needed to perform such a study.

Whether to perform PTX or not is also influenced by potential future or previous renal transplantation. As discussed earlier, renal transplantation can be expected to ameliorate some but not all renal hyperparathyroidism.

**Surgical technique**

PTX is performed as either subtotal PTX, where the aim is to keep parathyroid tissue corresponding to one normal gland, and total parathyroidectomy, aiming at removing all parathyroid tissue. Parathyroidectomy is usually performed with open surgery through a Kocher cervical incision in general anesthesia (Lorenz et al. 2015), although there have been reports on minimally invasive PTX (Barboros et al. 2009, Sun et al. 2009, Alesina et al. 2010). Subtotal and total PTX can both be combined with transcervical thymus resection and/or parathyroid autotransplantation. The lower parathyroids are often found in or close to the thymus, and nests of parathyroid tissue are also often found in normal thymic tissue. Hence, many authors recommend performing transcervical thymectomy together with PTX (Schneider et al. 2013, Lorenz et al. 2015).

There has been a debate among endocrine surgeons as to whether less (subtotal/focused) or more (total) radical surgery is optimal in rHPT. Large population-based studies (Isaksson et al. 2019) and meta-analysis (Chen et al. 2015) have not found any evidence of differences in long-term outcomes such as risk of fracture, cardiovascular disease and mortality between the two types of procedures. Furthermore, there has been a misunderstanding in that some authors believe that rHPT can be cured (Burgstaller et al. 2018), analogous to primary HPT (pHPT), which has very high cure rates with the resection of one or more parathyroid glands (Bergenfelz et al. 2009). However, pHPT and rHPT are different entities. It is evident from the discussion above that rHPT also persists even in mild renal dysfunction, if the patient receives a renal transplant (Lou et al. 2015). Hence, PTX can never cure rHPT. Instead, the aim of PTX is to reduce the amount of parathyroid tissue to such an extent that an optimal level of PTH post-PTX is achieved. This is similar to the situation in hereditary pHPT, for example, multiple endocrine neoplasia type 1 (MEN1), which also cannot be cured, and the goal of surgery is to give the patient as many years with normocalcemia as possible (Schreinemakers et al. 2011).

The optimal level of PTH after PTX for rHPT is unknown. Probably, profound hypoparathyroidism is just as detrimental as severe hyperparathyroidism – in patients with rHPT, as we have seen earlier, the initial adaptation of the parathyroids is physiological, helping the body get rid of excess phosphate not cleared by the kidneys. Hence, leaving too little viable parathyroid tissue is probably not optimal. On the other hand, leaving too much increases the risk of reoperation (due to persistent and/or recurrent disease). Thus, the question for the endocrine surgeon is not how much to remove, but how much to leave behind. In this regard, there have been studies examining the correlation between PTH levels and long-term outcomes in patients with ESRD. Thus, a report from the DOPPS

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study in 2008 showed that PTH levels between 100 pg/mL and 600 pg/mL were associated with the lowest risk of mortality (Tentori et al. 2008). The authors re-examined this topic and in 2015 reported similar findings. In their multivariate analysis, patients in the reference group with levels of PTH between 150 and 300 pg/mL had the lowest mortality risk (Tentori et al. 2015). Data also show that PTH levels vary significantly after both subtotal and total PTX (Burgstaller et al. 2018, Isaksson et al. 2019).

Intraoperative measurement of parathyroid hormone (ioPTH)
In primary HPT, intraoperative measurement of PTH (ioPTH) helps the surgeon to determine if there is more hyperfunctioning tissue left after resection or whether the operation can be terminated. There has been numerous studies investigating whether ioPTH also helps in PTX for rHPT (Lokey et al. 2000, Seebofer et al. 2001, Haustein et al. 2005, Weber et al. 2005, Meyer et al. 2009, Freriks et al. 2010, Sohn et al. 2015, El-Husseini et al. 2018, Marcadis et al. 2018). Most but not all of these studies indicate that there is a correlation between ioPTH and postoperative PTH and that ioPTH is helpful. Since PTH is cleared by the kidneys, the half-life of PTH, and hence, the time needed to wait for a drop in intraoperative PTH, is longer after PTX for renal HPT. Probably, PTH should be measured no earlier than 15–20 min post resection. Different criteria on the optimal level of ioPTH post resection have been proposed, but there is no consensus on what level of ioPTH yields the best outcomes.

Preoperative localization
The outcome of PTX is highly dependent on the skills and experience of the surgeon. In experienced hands, the main cause of persistent or recurrent rHPT after PTX is the inability to localize ectopic parathyroid glands (Dotzenrath et al. 2003). From a surgical point of view, a distinction exists between a minor ectopy (such as in the thyrothymic horn and upper anterior mediastinum, or beneath thyroid capsule) and a major ectopy (such as low mediastinal, retro esophageal, above the level of the hyoid, in the carotid sheath, or within the thyroid parenchyma - truly intrathyroidal) (Taieb et al. 2013). Ectopic and/or supernumerary glands are common in rHPT (Lorenz et al. 2015), and it is essential that the surgeon has identified all parathyroid glands. The experienced surgeon will usually find all non-ectopic glands; preoperative localization should therefore positively and accurately localize all ectopic parathyroid glands. Similar to primary HPT, preoperative imaging, with modalities such as ultrasonography, 99-Technetium sestamibi scintigraphy, and four-dimensional CT (4D-CT), has been evaluated but has not been shown to have greater accuracy in finding all parathyroid glands than traditional surgical exploration. A meta-analysis (Caldarella et al. 2012) reported that the sensitivity of 99mTc-sestamibi scan in secondary HPT was only 58%. They concluded that 99mTc-sestamibi is not a first-line diagnostic imaging method in this situation. Sensitivity of US for detection of enlarged parathyroid glands has been reported to be 46–81% in patients with secondary HPT (Sukan et al. 2008, Yuan et al. 2016, Li et al. 2017). The combination of US with 99mTc-sestamibi SPECT/CT had a higher sensitivity than US or 99mTc-sestamibi SPECT/CT alone (Yuan et al. 2016). Most authors thus conclude that ultrasound and sestamibi scintigraphy offer little benefit in localizing ectopic glands and rarely change the conduct of a standard four-gland exploration (Alkhalili et al. 2015, Karipineni et al. 2018, van der Plas et al. 2019). However, some authors have found that SPECT-CT offered useful information (Taieb et al. 2013). On the contrary, in the setting of re-PTX, that is, surgery for persistent or recurrent HPT after previous PTX, imaging studies are mandatory (Lorenz et al. 2015).

Intraoperative angiography
A further issue complicating PTX is that it is difficult to be certain that the parathyroid tissue left in the neck at surgery is viable: devascularization of the parathyroid glands is common. Recently, intraoperative angiography of the parathyroids using indocyanine green has shown great promise in aiding the surgeon to determine whether parathyroid glands are functioning or not (Cui et al. 2017). Combined with ioPTH and possibly with cross-sectional imaging, these tools might enable the surgeon to deliver a more precise PTX, yielding an optimal postoperative level of PTH.

Surgical complications
Risks of PTX include damage to the recurrent laryngeal nerve, bleeding and infection. These risks are small in the hands of experienced surgeons, and nationwide studies have shown these complications to be rare (van der Plas et al. 2018). However, complications related to abnormal mineral metabolism are common and expected.

Postoperative management
Patients undergoing PTX for renal hyperparathyroidism are best managed by nephrologists, with input from the...
endocrine surgeon if needed. Profound postoperative hypocalcemia is not uncommon, and perhaps ameliorated with preoperative calcitriol loading (Alsafran et al. 2019). Admissions to intensive care units for hypocalcemia, and re-admissions due to mineral metabolism imbalances are common. However, as stated earlier, data indicate that PTX is associated with a decrease in long-term risk of fractures, cardiovascular disease and mortality.

**Conclusion**

Renal hyperparathyroidism develops early in renal failure, mainly as a consequence of reduced levels of vitamin D, hypocalcemia, diminished excretion of phosphate and inability to activate vitamin D. RHPT is associated with increased morbidity and mortality. RHPT is a continuum and diagnosis depends on demonstrating elevated levels of parathyroid hormone, PTH. Treatment consists of supplying vitamin D, reducing phosphate intake and treatment with active vitamin D analogs. In later stages calcimimetics might be added. In RHPT, parathyroid glands grow and can become refractory to medical treatment. Patients with rHPT refractory to medical treatment should be considered for parathyroidectomy, PTX. A close collaboration between nephrologists and endocrine surgeons is required to achieve optimal outcomes. Risks of surgery are small but not negligible. Surgery should likely not be too radical, especially if the patient is a candidate for future renal transplantation. Subtotal or total parathyroidectomy with autotransplantation are recognized surgical options. Intraoperative measurement of PTH can be helpful; the value of preoperative imaging studies to localize parathyroid glands has not been definitely established for PTX in rHPT.

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