General introduction and outline of the thesis

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Advances in Diagnosis and Management of Secondary Hyperparathyroidism

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General introduction

End-stage renal disease
Globally, 850 million people are affected by chronic kidney disease (CKD). CKD is characterized by progressive loss of kidney function, and may ultimately lead to end-stage renal disease (ESRD), the final stage of chronic gradual loss of kidney function requiring dialysis or kidney transplantation. In the Netherlands, the prevalence of patients requiring renal replacement therapy (RRT) has increased with 137% in the past decade (Figure 1). In 2018, the number of Dutch people receiving RRT was 17,657, and is expected to further increase. Frequent complications of ESRD include hypertension, malnutrition, anaemia, hyperkalaemia, increased infection risk and finally, hyperparathyroidism. Patients with ESRD, and particularly patients on dialysis, have a strongly increased risk of mortality, morbidity and a decreased quality of life. Cardiovascular complications, primarily due to severe vascular calcification, are the leading cause of death in CKD patients. The pathophysiological mechanism causing vascular calcification is complex, and not fully understood, yet disturbances in the calcium-phosphate metabolism and hyperparathyroidism are thought to play a prominent role.

Parathyroid glands and PTH
Parathyroid hormone (PTH) is produced by four small parathyroid glands, surrounding the thyroid gland in the neck. The parathyroid glands were first identified by Sir Richard Owen (1804 – 1892), who had been allowed to dissect and preserve all animals that died in the London Zoo. In 1849, after 15 years of life in captivity, an Indian rhinoceros named Clara died during an altercation with an elephant. Sir Richard Owen spent over 12 months dissecting the 2000 kilograms weighing animal investigating the cause of
her tragic death. Clara appeared to have broken multiple ribs causing a pneumothorax. In his extensive anatomy report, sir Richard Owen described “a small compact yellow glandular body attached to the thyroid”. Subsequently, it was the Swedish medical student Ivor Sandström (1852 – 1889) who named the glands, after identifying the glandulae parathyroideae - first in a canine specimen, and later in numerous other animal species, including 50 human bodies.

Production and excretion of PTH by the parathyroid glands is influenced by extracellular concentration of electrolytes calcium and phosphate. The parathyroid gland is able to sense extracellular levels of calcium via the calcium-sensing receptor (CaSR) on the parathyroid cells. CaSR senses and maintains extracellular calcium concentration within a certain range by regulating parathyroid chief cell secretion of PTH. The actions of increased extracellular levels of calcium on the CaSR lead to a reduction of serum calcium levels, mainly by inhibiting the release of secretory granules with PTH by the parathyroid glands, and increasing urinary calcium excretion. Apart from the reduction of PTH secretion, CaSR stimulation reduces PTH synthesis in general, as well as parathyroid cell proliferation. Thus, there is a direct relationship between serum PTH levels and levels of calcium illustrated by the sensitivity of the control mechanism. A schematic overview of PTH physiology is depicted in Figure 2. In the bones, PTH binds to the parathyroid hormone 1 receptor (PTH1R) on osteoblasts which, via a complex ligand dependent pathway, stimulate osteoclasts. In turn, osteoclasts enhance bone resorption through which calcium is released into the bloodstream. PTH stimulates renal active reabsorption of calcium in the distal tubule, but has the opposite effect to phosphate: it inhibits the absorption of phosphate in the proximal tubule. Lastly, PTH enhances the conversion of 25-hydroxycholecalciferol to 1,25(OH)₂D, the active metabolite of vitamin D.

Calcium absorption is regulated by 1,25(OH)₂D in the intestinal tract. Thus, the net effect of PTH is lowering of serum phosphate levels, while increasing the serum calcium level. In response to increased levels of 1,25(OH)₂D, osteocytes and osteoclasts secrete the protein fibroblast growth factor (FGF)-23. FGF-23 acts on the sodium-phosphate cotransporter in the proximal tubules of the kidneys in the presence of membrane-bound protein Klotho, causing a decrease in the reabsorption and increase in excretion of phosphate. The net effect of FGF-23 is phosphaturia. Hyperparathyroidism (HPT) is characterized by an increased blood concentration of parathyroid hormone (PTH). In primary HPT, this overproduction is in most cases caused by a single hyperplastic adenoma. In contrast, secondary and tertiary HPT are defined by parathyroid hormonal disturbances caused
by an external stimulus and leads to hyperplasia of all four glands. The most common cause of secondary HPT is end-stage renal disease (ESRD). Other causes include calcium malabsorption (e.g. by vitamin D deficiency, bariatric surgery or celiac disease), the use of loop diuretics, bisphosphonates, or denosumab. This thesis focuses on ESRD-related secondary and tertiary HPT.

Hyperparathyroidism related to end-stage renal disease

HPT secondary to renal failure has been described in case reports dating from the late 1930s and 1940s. At that time however, the prognosis of ESRD was poor and patients did not live long enough to develop severe HPT. It was only after the Dutch physician Willem Johan Kolff built the first artificial dialyzer in 1943, that the life-expectancy of patients with renal failure started to increase. Long-term hemodialysis was established with the development of the arteriovenous shunt in the early 1960s by doctor Belding Scribner.

Despite adequate dialysis treatment, patients with long-term ESRD develop virtually inevitably hyperphosphatemia due to impaired renal phosphate excretion, probably in part due to decreased functional renal mass, and in part due to the loss of 1,25(OH)_{2}D. To enhance phosphate excretion, FGF-23 levels already increase in early stages of CKD. Secondary to a decreased serum concentration of calcium, and increased levels of serum phosphate and FGF-23, the parathyroid glands are stimulated to excrete PTH, in an
attempt to return to maintain balance. An increase in serum PTH levels can already be observed in pre-terminal stages of kidney failure. Eventually, over 80% of patients with an estimated glomerular filtration rate (eGFR) below 20 ml/min have PTH levels above the upper limit of normal (>65 pg/ml or 6.9 pmol/L). In ESRD, the parathyroid glands are chronically exposed to low extracellular calcium and high extracellular phosphate levels, first leading to polyclonal, followed by monoclonal hyperplastic parathyroid tissue. These morphologic changes are accompanied by a decreased expression of both the CaSR and the vitamin D receptor (VDR), although the number of secretory chief cells as well as the total number of parathyroid cells increase. Ultimately, this process leads to autonomous PTH synthesis and secretion, regardless of serum calcium concentrations. Hence, the parathyroid-bone-kidney feedback loop becomes irreversibly distorted. This phenomenon leads to severe hypercalcemia, also known as tertiary HPT.

The exact definitions of and distinction between secondary and tertiary HPT have been a matter of debate for many years. In general, secondary HPT is characterized by increased PTH levels in combination with hypocalcemia and hyperphosphatemia in the presence of ESRD. In tertiary HPT, patients have both increased PTH levels, as well as hypercalcemia and hyperphosphatemia, due to a disturbed feedback system after a prolonged period of secondary HPT. Tertiary HPT becomes most clear after successful kidney transplantation (KTx). By eliminating metabolic and biochemical disturbances with a successful KTx, the external stimulus triggering the parathyroid glands to produce and secrete PTH, is removed. However, HPT only resolves spontaneously in 6 out of 10 patients after KTx, thus 40% of patients have persistently elevated PTH, calcium and phosphate levels after KTx. The term ESRD-related HPT covers both HPT before and after KTx.

Clinical manifestations
Patients with disturbances in mineral metabolism present with various serious conditions such as: pruritus, bone pain, calciphylaxis, pathologic fractures, and muscle weakness. Many patients with increased PTH and calcium levels also present with a wide range of non-specific complaints that are less known such as concentration difficulties, feeling depressed, and forgetfulness. In the majority of patients, these symptoms in ESRD-related HPT patients result in a significant decrease in quality of life. Serious clinical manifestations related to mineral and bone disorder and HPT may vary from progressive bone loss due to increased bone turnover to an increased risk of cardiovascular disease and mortality due to accelerated cardiovascular calcification. The impact of long-term increased PTH, calcium, and phosphate levels on the kidney and especially on a future kidney transplant are a matter of debate. HPT in ESRD patients seems to be an
independent risk factor for renal graft loss and glomerular filtration rate (GFR) decline after transplantation. Lastly, ESRD-related HPT has been associated with increased all-cause mortality.

**Therapeutic options**

The Chronic Kidney Disease – Mineral Bone Disease (CKD-MBD) guideline by the Kidney Disease Improving Global Outcomes (KDIGO) Working Group are the only international, yet mono-disciplinary, guidelines on the treatment of ESRD-related HPT. Treatment options include vitamin D supplements, phosphate binders, calcimimetics, and parathyroid surgery. The management of ESRD-related HPT remains complex and correction of all mineral bone markers, including calcium, phosphate, PTH, and FGF-23 should be striven for.

Nutritional vitamin D deficiency is already seen in almost 90% of pre-dialysis patients, despite (excessive) sun exposure. The cause of the high prevalence of vitamin D deficiency in the CKD population is thought to be multifactorial, including proteinuria, nutritional factors, and hyperpigmentation. Therefore, vitamin D repletion is one of the first steps in the prevention of ESRD-related HPT. As phosphate retention is one of the earliest manifestations of renal excretion failure and ESRD-related HPT, phosphate binders can be initiated as soon as PTH and FGF-23 levels start to rise. Unfortunately, in almost all dialysis patients, vitamin D supplements and phosphate binders are insufficient in restoring calcium-phosphate homeostasis. Moreover, excessive supplementation of active vitamin D in a 1,25(OH) \_2D deficient patient may induce hypercalcemia.

Therefore, as part of PTH- and calcium-lowering therapy, calcimimetics can be added to the combination of vitamin D analogues and phosphate binders. Calcimimetics are allosteric modulators of the CaSR, not only activating the CaSR itself, but also increasing the sensitivity of the CaSR to extracellular calcium. As a result, PTH production and excretion by the parathyroid glands is inhibited. Calcimimetics are available both for oral use (cinacalcet) and since 2016, for intravenous administration (etelcalcetide). To date, the majority of secondary HPT patients is managed medically. A meta-analysis comparing 24 RCTs with over 10,000 dialysis patients concluded that cinacalcet leads to a significant reduction of PTH, calcium, and phosphate. In 2012, the EVOLVE trial was conducted to evaluate the impact of cinacalcet on the risk of death and nonfatal cardiovascular events in hemodialysis patients. In primary analyses of this large randomized controlled trial, the authors did not find a significant difference in the risk of death or cardiovascular event between patients who used cinacalcet compared to patients receiving placebo.
However, in censored analysis, adjusting for age, statistical significance was reached for the primary composite endpoint. Cinacalcet is only registered for hemodialysis patients and it is not FDA approved for kidney transplant patients with persistent HPT, although frequently off-label prescribed.

This thesis mainly focuses on a more definite treatment option for ESRD-related HPT: parathyroidectomy (PTx). The first parathyroidectomy (PTx) was performed by dr. Mandl in 1925 in Vienna, in a male tram car conductor with advanced osteitis fibrosa. surgeons started to operate on the parathyroid glands in patients with ESRD-related HPT in the early 1960s. Before the calcimimetic era, PTx was the only next step when the HPT was insufficiently controlled by vitamin D analogues and/or phosphate binders. The outcomes of the preferred surgical strategies, subtotal PTx or total PTx with autotransplantation, have similar outcomes with regard to amelioration of biochemical values and risk of persistent or recurrent disease. The risk of mortality and cardiovascular events, and fracture risk decreases significantly after PTx, although these observations come from retrospective uncontrolled studies.

As chronic kidney failure is the underlying cause of secondary and tertiary HPT, the ultimate treatment for these patients is a kidney transplantation (KTx). Indeed, a reduction of parathyroid functional mass has been seen after kidney transplantation. As stated, ESRD-related HPT resolves in 57% of cases two years after KTx.

Although the biochemical impact of the available treatment options is well investigated, most options lack evidence with regard to important patient outcomes such as quality of life, overall survival, progression of renal failure, and survival of kidney transplant. There are also only a handful of studies comparing the available treatment options, or combinations of them. Therefore, most of the recommendations made by the CKD-MBD KDIGO Working Group are based on level 2 (weak) and grade B or C (moderate of low quality) evidence.

Over time, the patient with chronic kidney disease moves through advancing stages of kidney disease, towards dialysis treatment or kidney transplantation with, in parallel, different stages of HPT. An analogy could be made with a complex underground railway system: while a patient travels from one stage of the disease to the other, it is possible to transfer to several different treatment options (Figure 3). Commonly, a patient with ESRD will receive dialysis at first, while HPT is progressing (green, blue and pink line). HPT during dialysis might be treated with calcimimetics or PTx prior before undergoing
KTx (green line). When HPT persists after kidney transplantation, a patient may receive calcimimetics (pink line). For some patients, calcimimetics will not sufficiently suppress the HPT or are not tolerated, and the patient still has to undergo PTx (blue line). In countries with a good availability of living kidney donors as the Netherlands, considerable numbers of patients receive a pre-emptive kidney transplant, averting the need for dialysis treatment (red and yellow line). Such patients have a lower risk of developing severe HPT compared to dialysis patients, but might still need either calcimimetics (yellow line) or PTx (red line). Unfortunately, sometimes a train back to a previous station needs to be taken, for example when a kidney graft fails and the patient requires dialysis treatment again (grey dashed line). Figure 3 emphasizes the complexity, variety, and versatility of patients require treatment of HPT related to ESRD. Along all these different paths a patient with ESRD travels, HPT in some degree is likely to occur and progress, which complicates finding the optimal treatment for each individual.

Figure 3 – Complex pathways of the ESRD patient with HPT
Aim and outline of the thesis

The overall aim of this thesis is to provide evidence-based recommendations for the treatment of patients with ESRD-related HPT. Our goal is to evaluate outcomes of PTx in patients with ESRD-related HPT and to address the role of PTx and calcimimetics as potential treatment modalities in ESRD-related HPT.

Part I: ESRD-related HPT

To this purpose, the first part of this thesis reviews ESRD-related HPT and its consequences. Chapter 2 presents an overview of the pathogenesis, clinical presentation and implications, required diagnostic work-up of ESRD-related HPT and discusses indications, strategies and outcomes for the available treatment options. In Chapter 3, we assessed the relationship of serum calcium and phosphate levels with kidney graft and patient outcomes in a large cohort of kidney transplant recipients. Using 138,496 time-updated serum calcium and phosphate measurements of 2,769 kidney transplant patients, we were able to investigate the impact of increased and decreased plasma calcium and phosphate levels on kidney graft failure and all-cause mortality. By studying this relationship, better insight in therapeutic target levels for serum calcium and phosphate after transplantation is gained.

Part II: Surgical treatment for ESRD-related HPT

The second part of this thesis focuses on the outcomes of PTx in terms of safety, efficacy, and quality of life in patients with ESRD-related HPT. ESRD is a severe systemic disease which puts the patient in increased risk of complications after surgery. On top of this, as the calcium-phosphate homeostasis is a highly delicate equilibrium, abrupt changes after PTx might possibly harm the patient. Therefore, in Chapter 4, we evaluated the safety of PTx in patients with ESRD-related HPT, as well as the impact of PTx on biochemical values including PTH, calcium and phosphate. The ESRD-related HPT population is a complex and mixed patient group, because some of the patients are on dialysis, and others have received a well-functioning kidney graft. A dilemma arises when a patient might undergo KTx in the future: should PTx precede KTx to potentially improve graft outcomes, or should possible spontaneous resolution of the disease after transplantation be awaited? In Chapter 5 we assessed the impact of the timing of PTx, prior or after KTx, on renal function after KTx in 185 patients with ESRD-related HPT. Both Chapter 4 and 5 were conducted using a nationwide database collected at the initiative of the Dutch Hyperparathyroidism Study Group (DHSG).

As previously mentioned, ESRD-related HPT affects the patients’ quality of life (QoL).
When treating HPT, improved laboratory measurements as serum calcium and PTH levels should be achieved, but more importantly, increase in QoL should be gained. Collaborating with the University of Sao Paulo, we analysed the impact of several PTx approaches on the QoL of 69 patients on dialysis, in a randomized controlled trial comparing subtotal PTx and total PTx with autotransplantation of two different amounts of parathyroid tissue (Chapter 6). After evaluation of the current surgical practice, we assessed PTx in an era with increasing number of available kidney transplants. In this changing treatment landscape, the surgical approach for patients with ESRD-related HPT might have to change subsequently. Thus, we investigated the outcomes of selected patients that underwent a less aggressive PTx compared to the conventional subtotal or total PTx. We investigated persistent and recurrent disease rates in a prospectively collected database of 195 patients undergoing PTx for ESRD-related HPT (Chapter 7).

**Part III: Evaluation of the role of parathyroidectomy and calcimimetics in a changing treatment algorithm of ESRD-related HPT**

Relatively new to the treatment algorithm of secondary HPT are calcimimetic agents. When the oral calcimimetic cinacalcet was introduced in 2004, calcimimetics immediately gained an important role in the treatment algorithm of ESRD-related HPT. In part three of this thesis, we compare calcimimetics with surgical treatment and evaluate how this change influenced the position of PTx in the treatment algorithm of ESRD-related HPT. After its introduction, promising results were published showing that cinacalcet lowers PTH and serum calcium levels. However, cinacalcet use is commonly accompanied by several side effects including nausea, vomiting and diarrhea.\(^{51}\) We therefore systematically reviewed the literature to compare the impact of both cinacalcet and PTx on QoL of patients with ESRD-related HPT (Chapter 8). We also compared cinacalcet and PTx with regard to their impact on graft and overall survival using the national database set up by the DHSG (Chapter 9). Up to now, no randomized controlled trial has been conducted that directly compared the outcomes of dialysis patients with ESRD-related HPT undergoing PTx or using cinacalcet. Using propensity score matching, selection bias between the PTx and cinacalcet group could be reduced, and therefore they could be compared more reliably.

Next, we investigated the impact of the introduction of calcimimetics on the timing of PTx in patients with ESRD-related HPT (Chapter 10). We compare patient characteristics, time from diagnosis to surgery, and PTx efficacy and safety before and after the introduction of calcimimetics. Interestingly, after the publication of the EVOLVE trial, concluding that there is no clear evidence that cinacalcet reduces the risk of death or major cardiovascular events, cinacalcet ceased to be subsidized through the Australian
Pharmaceutical Benefits Scheme in 2015. We were therefore able to perform parallel analyses in a Australian ESRD-related HPT population adding a third comparison group: patients who were treated after the removal of cinacalcet from the reimbursed drug list (Chapter 11). We addressed our findings and concerns, and make our recommendations on the treatment of ESRD-related HPT in Chapter 12 from a Dutch surgical perspective endorsed by both the International as the American Association of Endocrine Surgeons. Finally, Chapter 13 summarizes the findings of this thesis, discusses its implications, and provides an overview of the future perspectives and directions for future studies on the search for the optimal patient-tailored treatment for patients with ESRD-related HPT.
References


Part I

End-stage renal disease related hyperparathyroidism