Summary and General Discussion
Future Perspectives
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Hyperparathyroidism (HPT) is a common complication secondary to end-stage renal disease (ESRD). Over the last decades, the landscape of ESRD-related HPT has changed significantly. However, up to 2020, the only international guideline for the treatment of ESRD-related HPT is the monodisciplinary chronic kidney disease (CKD) – mineral bone disease (MBD) guideline of the KDIGO Working Group. With a variety of treatment options available, it remains a challenge to reach consensus on the optimal treatment of HPT during the advancing stages of ESRD.

Chapter 1 provides a general introduction and outline of the thesis. In this thesis, the complexity of HPT in relation to ESRD is illustrated by the analogy of an underground railway system of a large city. The ESRD patient travels from one stage to another and transfers between different courses of treatment. A universal treatment algorithm for every ESRD patient with HPT does not exist as every patient has a unique journey. The question remains unsolved how to determine the optimal therapy for the individual patient during each stage of the disease. This thesis aims to provide recommendations for the treatment of patients with ESRD-related HPT by generating evidence on the outcomes of parathyroidectomy (PTx) and the role of PTx and calcimimetics in the ESRD-related HPT treatment algorithm.

Part I: ESRD-related HPT

Chapter 2 summarizes the pathogenesis of ESRD-related HPT, clinical presentation and diagnostic work-up, and discusses indications for the available treatment options for patients with ESRD-related HPT. Increase of the circulating hormone FGF-23, possibly due to loss of renal alpha-klotho secretion, is one of the first manifestations of kidney failure. Elevated FGF-23 levels suppress synthesis of 1,25 dihydroxyvitamin D (1,25(OH)\textsubscript{2}D), which is essential for the absorption of calcium by the intestinal tract. Next, high concentrations of phosphate and low levels of calcium stimulate the parathyroid glands to produce and excrete parathyroid hormone (PTH), in attempt to restore homeostasis. The net effect of PTH is lowering phosphate concentrations, while increasing serum calcium levels. In ESRD, due to a prolonged disturbed calcium and phosphate metabolism, patients will eventually experience high levels of PTH, calcium and phosphate, known as ESRD-related HPT. ESRD-related HPT has been associated with a variety of clinical manifestations such as pain in the bones, fatigue and forgetfulness, but also with an increased risk of cardiovascular disease and all-cause mortality. Among treatment options are (active) vitamin D repletion, phosphate binders, calcimimetics, and finally PTx. The calcimimetic
agents cinacalcet and etelcalcetide significantly lower circulating serum PTH, calcium and FGF-23 levels, but their use is accompanied by adverse effects as vomiting and diarrhoea in a significant proportion of patients. PTx is currently only recommended in patients who fail to respond to pharmacological therapy according to the KDIGO CKD-MBD guidelines. PTx is effective in lowering PTH and calcium levels, but is an invasive procedure with associated surgical risks.

In Chapter 3, we illustrate the clinical consequences of a disturbed calcium and phosphate metabolism in kidney transplantation on graft and patient outcomes. Disruptions in PTH, calcium, and phosphate homeostasis prior to kidney transplantation, often remain at least partly deregulated after transplantation. We investigated the impact of disturbed serum calcium or phosphate concentrations after kidney transplantation and graft and patient survival. We found that patients with post-transplant hyperphosphatemia have a significantly increased risk of developing death-censored graft failure (DCGF) and mortality compared to patients who are normophosphataemic. An increased risk of mortality was also observed in patients with hypercalcemia compared to levels within the normal range. These findings show the compelling impact of a disturbed calcium-phosphate homeostasis in kidney transplant recipients and support the recommendations made by the KDIGO Working Group, stating that “it is reasonable to manage abnormalities in calcium and phosphate as for patients with CKD stages 3-5”, which had up to now only limited supporting evidence.

Part II: Surgical treatment for ESRD-related HPT

In literature, PTx is sometimes portrayed as high-risk surgery associated with significant mortality and morbidity. In Chapter 4, we evaluate the safety and efficacy of PTx in 187 dialysis and kidney transplant patients in four academic medical centers in the Netherlands. We observed no mortality and very low 30-day morbidity rates; admission to the intensive care unit was required in 2.4% of the patients, and postoperative complications were rare. Next, PTx was very effective in lowering increased PTH levels, as we observed a median drop of PTH concentration of 93%. Lastly, serum adjusted calcium and phosphate levels lowered to within the reference range, which upheld during long-term follow-up of 5 years. The results of this chapter underline recommendations of both national and international surgical societies that parathyroid surgery should be performed in high-volume medical centers. PTx rates decreased rapidly after the introduction of calcimimetics in 2004, without strong evidence to support this practice. There should be no reluctance in referring these patients – despite having extensive comorbidities – for PTx in case of failure to response to medical treatment. Although an invasive procedure,
postoperative recovery is fast and without a high risk of complications.

Using data collected by the Dutch Hyperparathyroidism Study Group (DHSG), we assessed the impact of the timing of PTx, prior or after kidney transplantation (KTx), on kidney function after KTx in Chapter 5. Recovery of kidney function after successful transplantation leads to improved calcium and phosphate homeostasis. Therefore, it could be argued to await kidney transplantation in dialysis patients, potentially averting the need for PTx. On the other hand, increased PTH levels may have an adverse effect on renal graft outcomes, supporting the argument to perform PTx prior to KTx. Within the multicenter DHSG cohort study, we showed that timing of PTx, performed before or after KTx, does not independently impact the long-term course of graft function after KTx. Consequently, our findings support the approach to postpone PTx until after KTx, in case transplantation is expected within a reasonable timeframe in order to allow spontaneous HPT regression. The incidence of KTx surgeries is still increasing; in The Netherlands, especially the proportion of patients who receive a kidney graft from a living donor has increased from 1 out of 4 donors to over 50% in the last 15 years (Chapter 1, Figure 1). Therefore, patients are expected to be on the waiting list for transplantation for a shorter period of time. This might increase the probability of HPT regression, as shorter time on dialysis prior to transplantation has been identified as a significant beneficial factor for resolution of HPT after transplantation. Naturally, the need for and timing of PTx in relation to KTx should be evaluated for every patient individually taking the severity of the disease, quality of life and the patient’s preference into consideration. These findings accentuate the importance of a continuous discussion between nephrologists, endocrinologists and endocrine and transplantation surgeons on the optimal management for each individual patient, for example discussed in a multidisciplinary meeting.

The impact of potential therapeutic options on subjective patient experience is key in evaluating the treatment algorithm of ESRD-related HPT. In general, patients with ESRD and associated HPT have a decreased quality of life (QoL). The impact of several PTx strategies on QoL in ESRD has been studied poorly. In collaboration with the University of Sao Paulo, we investigated the impact of various surgical approaches on QoL of ESRD-related HPT patients (Chapter 6). Sixty-nine patients were randomized to three currently accepted PTx strategies: subtotal PTx, total PTx with autotransplantation of 45 fragments, and total PTx with autotransplantation of 90 fragments. QoL significantly improved in all patients, towards norms of the general healthy population. We found no difference in impact on QoL according to the various surgical approaches. Subtotal PTx and total PTx with autotransplantation has been shown to be equally effective in improving serum
calcium levels and recurrence and persistence rates, and these data illustrate there is also no difference in the impact on QoL between the various approaches, in a randomized setting. Especially in countries such as Brazil, where KTx is not as readily available as in the Netherlands in terms of a living donor program, PTx – regardless of the type of the operation – continues to play an important role in the treatment algorithm of ESRD-related HPT. Based on the results of chapter 6, surgeons can counsel their patients for either subtotal PTx or total PTx + AT according to their preference and preoperative characteristics.

In countries where kidney transplantations are widely available – such as the Netherlands and Australia – and the length of the waiting list is subject to change over time, the treatment algorithm of ESRD-related HPT might have to change accordingly. When ESRD patients are likely to receive a kidney transplant after a relatively short period of time on the waiting list or even pre-emptively, HPT secondary to ESRD might become a temporary issue. This might implicate that when PTx is indicated, a less aggressive approach would be feasible to avoid postoperative hypocalcemia without increasing the risk of recurrent or persistent disease. In Chapter 7, we report the surgical and biochemical outcomes of PTx for ESRD-related HPT according to three surgical approaches: limited, subtotal, and total PTx. We found that in patients who underwent limited PTx (e.g. removal of less than 3 parathyroid glands), persistent and recurrent rates were higher compared to patients who underwent subtotal or total PTx. PTH levels were also significantly higher in the limited PTx group. On the other hand, patients who underwent total PTx had postoperative PTH levels below the reference range, which is no longer desirable in an era with an increasing availability of kidney grafts, as permanent hypocalcemia is likely to occur. Together with the findings in chapter 3, it could be argued that normal to high PTH levels, leading to normocalcemia, might even be beneficial for kidney transplant recipients. The possibility of a kidney transplantation in the near future should be an important factor in weighing the various therapy approaches and the appropriate treatment should be determined for each patient individually.

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

In part III of this thesis, we evaluate the role of PTx in relation to calcimimetics in the treatment strategy of ESRD-related HPT. In 2004, the calcimimetic drug cinacalcet was introduced and immediately gained much interest. After its introduction, cinacalcet was primarily compared to placebo or conventional treatment, including phosphate binders and vitamin D analogues in patients with uncontrolled HPT. Surprisingly,
cinacalcet has never been compared to surgery, the former golden standard for patients with uncontrolled HPT, in a randomized controlled setting in dialysis patients. The use of cinacalcet is accompanied by significantly more side effects, such as vomiting and diarrhoea, compared to placebo, which leads to discontinuation of the drug in almost one out of five patients. We systematically reviewed the literature to compare the impact of PTx and cinacalcet on QoL of patients with ESRD-related HPT (Chapter 8). All studies addressing PTx demonstrated a significant improvement in QoL in comparison with pre-PTx measurements. Mean physical component summary scores (PCS) and mental component summary score (MCS) of the Short-Form 36 QoL questionnaire even improved towards levels of the healthy population. None of the included studies assessing the impact of cinacalcet on QoL demonstrated significant improvement in QoL. The lack of QoL improvement among cinacalcet users is probably attributed to the high prevalence of side effects, which may counteract potential improvements due to PTH lowering. ESRD patients deal with multiple QoL-lowering factors such as intensive dialysis regimens, the use of many drugs and ESRD-related symptoms including fatigue. Altogether, it should be considered pivotal to take the impact of potential therapies on QoL into account.

We extended our comparison between cinacalcet and PTx in Chapter 9, comparing the outcomes of both treatment options regarding graft and patient survival. In order to compare cinacalcet and PTx without a costly and timely randomized controlled trial, we performed propensity score matching using the aforementioned DHSG database, and particularly focused on patients who underwent PTx or received cinacalcet prior to their first kidney transplantation. Although PTH levels were significantly higher in the cinacalcet group during follow-up after KTx compared to the PTx group, we found no difference in the prevalence of graft failure between the two groups. Also, survival rates were not significantly different. Interestingly, severe KTx-related complications occurred more frequently in the cinacalcet group compared to the patients who underwent PTx prior to KTx. The pathophysiological mechanism contributing the to the increased risk of KTx-related complications remains unknown. As pre-KTx PTH levels were comparable between the two groups, PTH might not independently increase the risk of developing graft failure or acute rejection. Our data suggest that there is no difference in terms of graft failure and patient survival between patients who were treated with cinacalcet or underwent PTx prior to transplantation.

In Chapter 10, we investigated how the introduction of cinacalcet affected the ESRD population ultimately requiring PTx. We divided patients undergoing PTx for ESRD-related
HPT into two groups; those who underwent PTx before the era of cinacalcet (1991 – 2004) and those during the era of cinacalcet (2005 – 2015). We found a 22-month delay from diagnosis to PTx in patients with ESRD-related HPT since the introduction of cinacalcet. Although the majority of patients were treated during the cinacalcet era indeed received calcimimetics prior to surgery, preoperative PTH levels were not significantly different compared to patients who underwent PTx before the introduction of cinacalcet. In our study cohort, PTx rates remained the same over the study period. These findings suggest that since the introduction of cinacalcet, patients are exposed to persistently increased PTH levels and harmful disturbances of the calcium-phosphate homeostasis as described in chapter 3, for a considerably prolonged period of time before they undergo definite treatment for their HPT, which seems still underutilized.

Besides side effects accompanying cinacalcet use, long-term cinacalcet therapy is costly, as other studies have shown that PTx is already cost effective after 7.3 months of cinacalcet treatment. These findings, next to the results of the EVOLVE trial – concluding that cinacalcet does not significantly lower the risk of cardiovascular events and mortality compared to placebo – led to the removal of calcimimetics from the reimbursed drug list in 2015. In Chapter 11, we repeated the study presented in chapter 10 in the Royal North Shore Hospital in Sydney, Australia. We added a third comparison group: patients who underwent PTx after the cinacalcet era. We clearly found that referral behaviour altered according to the availability of cinacalcet in Australia. We observed a decline in the number of patients that were referred for PTx after cinacalcet was approved by the Therapeutic Goods Administration. PTx rates further decline after approval by the Pharmaceutical Benefits Advisory Committee in 2007, meaning that cinacalcet was reimbursed as of 2007. In contrast, PTx rates started to rise again after the publication of the EVOLVE trial in 2012, followed by the removal of cinacalcet from Pharmaceutical Benefits Scheme listing in 2015. Preoperative PTH levels were significantly increased in patients undergoing PTx during and after the cinacalcet era, compared to the group undergoing PTx before the cinacalcet era. The KDIGO CKD-MBD guidelines suggest maintaining PTH levels within 2 – 9 times the upper limit of normal, yet we observed preoperative PTH levels of 19 to more than 25 times the upper limit of normal, implicating a more advanced stage of disease. Clinical implications of high PTH levels in this fragile patient population remain controversial.

In Chapter 12, we addressed our concerns regarding the changing treatment algorithm of ESRD-related HPT without strong evidence. In recent years, many studies have investigated the outcomes of cinacalcet treatment and reported a decrease of PTx rate
as a beneficial outcome, implying that refraining from PTx as long as possible should be the preferred strategy. It can hardly be used as an objective outcome measure as surgical referral is highly physician-dependent. Moreover, as shown in this thesis, PTx is a highly effective and safe treatment option, despite its invasive nature. After initial studies reporting positive outcomes of cinacalcet treatment, more and more studies question whether cinacalcet is truly effective in lowering PTH levels and improving quality of life in a real-world setting. Nevertheless, despite all favourable evidence of the efficacy of PTx, it has almost disappeared from the treatment algorithm, potentially driven by the pharmaceutical industry. We advocate a patient-tailored advice for each individual patient taking patient-specific factors such as comorbidity, potential prompt kidney transplantation, patient preference, QoL, and the severity of the disease into account. This will lead to the optimal choice of treatment, decided on by physician and patient together, which needs to be re-evaluated when one of these factors changes.
Future Perspectives

With the persistently increasing number of patients suffering from end-stage renal disease (ESRD), it will remain a challenge to treat hyperparathyroidism (HPT). As the ESRD patient moves through advancing stages of kidney disease, including the possibility of undergoing kidney transplantation (KTx), different HPT treatment modalities may be appropriate. Studies described in this thesis aimed to improve patient-specific decision making in the search for the optimal patient-tailored treatment of ESRD-related HPT. Despite the growing number of scientific articles published regarding this topic, many challenges are still ahead finding the optimal treatment for each individual patient with ESRD-related HPT. As the landscape of the treatment of ESRD is constantly changing – e.g. increasing numbers of kidney transplantations are performed each year – the treatment of ESRD-related HPT must be carefully reconsidered accordingly. Based on the results of this thesis, we propose a treatment algorithm for HPT according to each stage of the ESRD patient. As presented in Figure 1, again the analogy with the subway map is made.

In future literature, a clear distinction needs to be made between dialysis patients with ESRD-related HPT without a kidney transplantation and kidney transplant recipients with persistent HPT. Likely, the optimal treatment for patients with a functioning kidney graft and persistent HPT is utterly different compared to the preferred therapy for dialysis patients. Up to now, these patients are often addressed as one patient population. Below, treatment recommendations derived from this thesis are made for dialysis patients and kidney transplant recipients separately.

Dialysis patients with ESRD-related HPT

In the last decade, the mean time frame for waiting for a kidney transplant decreased substantially in the Netherlands (average 4.2 years in 2006 to 2.6 years 2016), and the proportion of pre-emptive transplantations has doubled in 10 years’ time. As dialysis vintage is a key determinant of the severity of HPT, ESRD-related HPT will likely become a more temporary problem in the future, at least in patients eligible for transplantation. Moreover, dialysis vintage is identified as a predictive factor for persistent HPT two years after kidney transplantation. Therefore, the aim of HPT treatment in dialysis patients is changing to a bridging strategy towards transplantation (Figure 1, green line). Along this track, calcimimetics are expected to play a crucial role. PTx will be reserved for patients who still insufficiently respond to calcimimetic therapy (grey dashed line) and to patients with persistent HPT post-transplantation (green dashed line). Cost-effectiveness needs
to be reassessed in this scenario, but cinacalcet may be cost-effective compared to PTx in dialysis patients who would expect to receive a kidney transplant rather quickly.\textsuperscript{9}

Novel calcimimetics may further improve bridging strategies. Etelcalcetide was introduced in 2017 as an intravenous calcimimetic. Due to its longer half-life, sufficient results are achieved when administering etelcalcetide during trice weekly dialysis sessions only. Biochemically, etelcalcetide acts similar to cinacalcet, achieving a comparable decrease in serum calcium levels.
in PTH levels. Gastrointestinal side effects are, despite intravenous administration, the same as cinacalcet. Improved patient adherence of etelcalcetide might lead to improved biochemical response compared to cinacalcet, although its incremental cost-effectiveness ratio is estimated between $28,000 to $56,000 per quality adjusted life years.\textsuperscript{10,11} Therefore, in the near-future etelcalcetide may only serve as a second-line treatment option, in patients incompliant to cinacalcet and when PTx is undesirable.

Recently, a another calcimimetic agent has been introduced in Japan: evocalcet (trade name Orkedia).\textsuperscript{12} Evocalcet is claimed to have less gastrointestinal side effects due to its high specificity to the parathyroid glands, offering an interesting scope for further research and future clinical use.\textsuperscript{14} An initial non-inferiority trial comparing evocalcet with cinacalcet revealed that evocalcet is as effective in suppressing PTH concentrations compared to cinacalcet, but is associated with significantly less gastrointestinal adverse events. Currently, a multicenter phase III trial evaluating the long-term safety and efficacy of evocalcet is currently being conducted (NCT03822507).\textsuperscript{14} Evocalcet may play an important role in the future treatment algorithm of dialysis patients with ESRD-related HPT, as a bridging approach to kidney transplantation with, possibly, ameliorated QoL.

In case of severe ESRD-related HPT, with no prospect of prompt kidney transplantation, PTx will remain a safe and efficient treatment option (blue line). Several PTx techniques have been studied intensively, but again, with the change in the landscape of ESRD-related HPT, PTx strategies might change conjointly. A less aggressive approach compared to conventional strategies – e.g. resecting 2 to 3 parathyroid glands – might become a novel standard PTx approach in (future) kidney transplant patients, potentially decreasing the risk of developing postoperative hypoparathyroidism, as described in chapter 7. Especially if the patient eventually will receive a kidney transplant (yellow dashed line), the risk of recurrent disease might be low. Moreover, by averting the need for a four-gland exploration, the risk of recurrent laryngeal nerve damage and vocal cord palsy will decrease substantially as do the postoperative risks during reoperation for persistent or recurrent disease. Naturally, after consideration of factors including severity of disease, operability, dialysis, and biochemical values, conventional treatment still has an important role in the treatment algorithm of non-KTx patients with HPT (red line).

**Kidney transplant recipients with ESRD-related HPT**

Calcimimetics have only been extensively investigated in dialysis patients and are in fact, only approved by the Food and Drug Administration, the European Medicines Agency, and
the Dutch National Health Care Institute to be prescribed to dialysis patients. Interestingly, cinacalcet is frequently prescribed off-label to kidney transplant recipients. In the current thesis we show the strong relationships between post-transplant calcium and phosphate concentrations and graft failure and mortality (Chapter 3). Normalization of calcium-phosphate homeostasis by means of calcimimetics or PTx may improve clinical outcomes including graft and patient survival. Future research is required to investigate the role of vitamin D analogues, calcitriol, phosphate binders, bisphosphonates, calcimimetics, but also parathyroid surgery in finetuning calcium-phosphate homeostasis and improving mineral bone disease, and graft and patient survival of kidney transplant recipients. To date, PTx is the treatment of choice in persistent HPT after KTx (green dashed and pink dashed lines).

When ESRD-related HPT still persists two years post-transplantation, it seems unlikely that the HPT will resolve spontaneously. This implies that, when treated pharmacologically, kidney transplant recipients with persistent HPT require life-long cinacalcet therapy. So far, one small randomized controlled trial comparing cinacalcet with PTx has been performed, concluding that PTx is superior to cinacalcet in controlling hypercalcemia in patients with persistent ESRD-related HPT after transplantation after a follow-up of 12 months.15 In this subset of patients, further research should aim to compare calcimimetic treatment with PTx in kidney recipients with persistent HPT. Outcome measures for such trial may include patient reported outcome measures such as QoL and pill burden, as well as mineral bone markers, fracture rate, graft and (cardiovascular) survival and pharmaco-economics with a long-term follow-up.

Until any of the calcimimetic agents are proven to have long-term benefit in the management of ESRD-related HPT in the kidney transplant recipient population, it is best reserved for kidney transplant recipients who are not surgical candidates. As in dialysis patients, PTx may transform to a less aggressive approach in kidney transplant recipients, in case more subtle corrections in the calcium-phosphate homeostasis are needed and strict normalization of calcium and phosphate levels are warranted.

**Overall conclusion**
This thesis describes the role and outcomes of calcimimetics and parathyroidectomy as part of the treatment of HPT related to ESRD. The complexity of ESRD-related HPT requires a patient-specific and multidisciplinary approach taking all relevant influencing factors into account. Continuous collaboration between nephrologists, endocrine surgeons, and transplant surgeons will lead to an improved, patient-tailored treatment
algorithm of patients with ESRD-related HPT. As the kidney transplant population will further increase, multidisciplinary guidelines will cover evidence-based and objective recommendations on the treatment of ESRD-related HPT in kidney transplant recipients. Quality of life, patient’s preference, graft function, risk of cardiovascular events, and mortality should fuel the debate on the optimal treatment for each individual patient rather than biochemical values with unknown clinical relevance.
References


