Clinical Studies In (Para)Thyroid Surgery

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COLOFON

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Contents

Chapter 1 General Introduction

CALCIUM-PHOSPHATE HOMEOSTASIS

The parathyroid glands play an important role in calcium and phosphate homeostasis. The glands secrete parathyroid hormone (PTH) in response to a decrease in serum calcium concentration. This response is mediated by the calcium-sensing receptor (CaSR)[1] on the parathyroid glands. PTH has important skeletal and renal effects. Next to PTH there are two other important hormones in calcium and phosphate homeostasis. This are 1,25$(OH)_2$-vitamin D (calcitriol) and fibroblast growth factor 23 (FGF-23).

The action of PTH on bone results in an increase of calcium release by 2 pathways[2]. It mobilizes calcium from skeletal stores that are readily available and PTH stimulates bone resorption and subsequent calcium release. PTH also stimulates the production of FGF-23 by bone osteocytes and osteoblasts[3].

PTH has three renal actions. It stimulates the reabsorption of calcium in the distal nephron by increasing the expression of several calcium transport proteins[4]. PTH also inhibits the renal reabsorption of phosphate in both the proximal and distal tubule. Third, PTH stimulates the renal production of calcitriol by stimulating renal 1-alpha-hydroxylase[5].

Calcitriol has skeletal, renal and intestinal effects. The skeletal effects of calcitriol consist of an increase in bone resorption and of stimulation of the production of FGF-23[6]. The renal effects of calcitriol on calcium are in the distal and collecting tubule, where it increases the reabsorption of calcium by increasing the expression of calcium transport proteins[7]. In the proximal tubule, calcitriol increases phosphate reabsorption.[8] Calcitriol stimulates the intestinal uptake of phosphate and also increases the expression of the transient receptor potential channel 6 receptor on the apical membrane of the duodenum and proximal jejunum thereby increasing the intestinal uptake of calcium[8,9]. The resulting rise in serum calcium concentration results in a decreased secretion of PTH by the parathyroid glands.

FGF-23 inhibits renal phosphate reabsorption and renal calcitriol production. It inhibits intestinal phosphate uptake and inhibits PTH production[10,11].

To summarize, PTH causes a rise in serum calcium and a fall of serum phosphate concentrations; calcitriol causes serum calcium and phosphate concentration to increase. FGF-23 causes serum phosphate concentrations to decrease.

DISORDERS OF THE PARATHYROID

Primary hyperparathyroidism

In primary hyperparathyroidism (HPT) there is an overproduction of PTH. The subsequent increase in bone resorption, intestinal calcium absorption and renal calcium absorption result in hypercalcaemia. In 80-85% of patients the PTH overproduction is the result of a single parathyroid adenoma whereas double adenomas occur in approximately 5% of patients[12]. Other causes of primary HPT can be glandular hyperplasia (about 6%) or parathyroid carcinoma (<1%). Conditions associated with primary HPT are MEN syndrome, familial hypocalciuric hypercalcaemia, thiazide therapy and lithium therapy[13-16].

The incidence of primary HPT has increased in the last decades. However, the introduction of routine measurement of serum calcium in biochemical screening has led to an immediate increase in the incidence of primary HPT[17]. After this introduction the incidence of primary HPT has continued to rise and primary HPT is often found by chance[18,19].

The classical symptoms of primary HPT are also known as "bones, stones, abdominal moans and psychic groans". The most common classical symptoms are renal stones and osteoporosis[20]. Other common symptoms are constipation, anorexia, nausea and fatigue. However, the introduction of routine measurement of serum calcium has identified a group of patients with biochemical hyperparathyroidism without classical symptoms, referred to as asymptomatic primary hyperparathyroidism[21]. These "asymptomatic" patients represent the majority of patients diagnosed with primary hyperparathyroidism. The indications for treatment of these patients are summarized in a consensus statement of the fourth international workshop[22].

Patients with primary HPT are known to also have neuropsychiatric symptoms which can include impaired mental functioning, lethargy and depressive symptoms[23]. Primary HPT can also influence the Quality of Life (QoL) of patients[24]. Although this is known, these symptoms are not part of the criteria for treatment of primary HPT. However, during the international workshops of 2008 and 2014 these symptoms were identified as a recommended area for further studies[22,25].

Treatment of primary HPT consists of surgical excision of the pathologic parathyroid gland(s). Historically this was by means of a bilateral neck exploration where all parathyroid glands are identified and pathological glands are removed[26]. However, in a majority of patients the cause of primary HPT is a single parathyroid adenoma[12]. The combination of this fact and the availability of ultrasound and sestamibi scanning has led to the introduction of the minimal invasive parathyroidectomy (MIP). After successful identification

by both ultrasound and sestamibi scan the MIP has a success rate of 95%[27,28]. Besides being very effective the MIP is also a safe and cost-effective procedure, with some centers also performing the MIP as a day-care procedure[29,30].

Secondary hyperparathyroidism

The PTH overproduction in secondary HPT occurs as a response to metabolic abnormalities, and is very common among patients with chronic kidney disease (CKD)[31]. Important consequences of CKD that contribute to the development of secondary HPT are decreased phosphate excretion resulting in hyperphosphatemia, decrease in serum calcium concentration, decreased calcitriol concentration, an increase in FGF-23 concentration and also in reduced expression of the calcium-sensing receptor (CaSR) and vitamin D receptor (VDR) on the parathyroid[32]. Continuous stimulation of the parathyroid glands due to this abnormalities leads to diffuse hyperplasia followed by nodular hyperplasia and results in autonomous production of PTH[33].

A variety of symptoms is associated with secondary HPT and can include fatigue, abdominal pain, pruritus, forgetfulness and concentration difficulties[34]. A rare complication of long standing secondary HPT is calcific uremic arteriolopathy, or calciphylaxis, which has a poor survival rate of only 45% after 1 year[35]. Secondary HPT also has various negative effects on health status. There is an increased risk of fractures, cardiovascular disease and overall mortality and a reduced quality of life[36-40].

First line treatment of secondary HPT used to consist of correction of metabolic abnormalities by means of phosphate binders and vitamin D analogs, and if unsuccessful followed by treatment with calcimimetics or parathyroidectomy[41]. The recommendation from the updated KDIGO guideline is to treat with cinacalcet, calcitriol or vitamin D analogs, or a combination of these therapies[36].

Until 2004 a parathyroidectomy (PTx) was the only treatment option for patients with insufficient response to phosphate binders and vitamin D analogs. A PTx in hyperparathyroidism due to renal failure encompasses two procedures. In a subtotal parathyroidectomy a 4-gland exploration is performed, with excision of 3,5 glands. A total parathyroidectomy consists of a 4-gland exploration, excision of all 4 glands and a auto-transplantation of 0.5 of the parathyroid glands. The results of these procedures are comparable, and the term total-PTx can refer to both procedures[42-44]. Even though patients on dialysis represent a fragile population, complication rates are low[45]. A large advantage of PTx in treatment of secondary HPT is that it lowers the risk of major cardiovascular events and death as well as lower the risk of fractures[46-48].

In 2004 the calcimimetic drug cinacalcet was introduced (Mimpara®; Amgen, Thousand Oaks, California, USA) and registered for use in patients with secondary HPT. This drug acts on the calcium-sensing receptor on the parathyroid glands, and increases the sensitivity to extracellular calcium and reduces PTH secretion[49]. This drug successfully lowers serum PTH, calcium and phosphate[50,51]. These promising results caused in a shift in treatment of secondary HPT, and in the 2009 KDIGO guidelines it was recommended to treat with cinacalcet before considering PTx[41]. However, in 2012 the results from the EVOLVE trial were published[52]. This large multinational randomized controlled trial did not demonstrate a significant effect of cinacalcet on cardiovascular events of death in 3883 hemodialysis patients, compared with placebo, but did report a 45,9% rate of adverse effects such as vomiting and nausea. This was supported by a meta-analysis of randomized trials[53]. It has been calculated that treatment of 1000 patients for 1 year "has no effect on mortality, prevents 3 patients from experiencing parathyroidectomy and leads to 60 individuals experiencing hypocalcemia and 150 individuals experiencing nausea". These findings resulted in the removal of cinacalcet from the national pharmaceuticals benefits scheme in Australia[54].

In the 2017 KDIGO guideline update cinacalcet remains the treatment of choice for secondary HPT, and parathyroidectomy is the option only if other PTH-lowering therapies fail[36]. Prospective randomized trials comparing these treatment modalities have not yet been performed, and the optimal treatment of secondary HPT remains unclear.

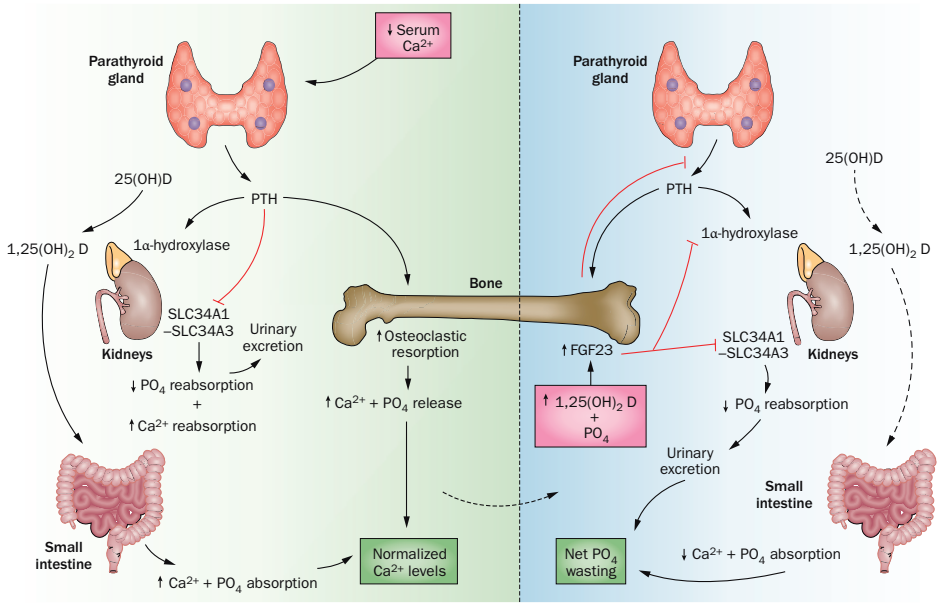

Figure 1. The regulation of calcium and phosphate homeostasis by PTH, vitamin D and FGF23.

Tertiary hyperparathyroidism

The metabolic abnormalities leading to secondary HPT can be corrected by a successful kidney transplantation[55]. The decline of PTH after transplantation is the greatest in the 3 months after transplantation, but PTH continues to decline during the first post-transplant year. Further decline after this period is unlikely[42]. After a successful transplantation 17-50% of patients remain hyperparathyroid[42,56,57]. This condition is called tertiary or post-transplant HPT[58].

Tertiary HPT has several effects. It increases the risk of both renal allograft dysfunction as well as renal allograft loss[59,60]. It is also a major risk factor for bone fractures and osteoporosis[61,62].

The only registered treatment for tertiary HPT is PTx. The procedure in patients with tertiary HPT is the same procedure as in patients with secondary HPT. In recent years the off-label use of cinacalcet in patients with tertiary HPT has gained popularity. The use of cinacalcet in patients after kidney transplantation appears to be safe, although has been studied mainly in small non-randomized studies[63]. The two treatment modalities (PTx and cinacalcet) have only been compared directly in one randomized controlled trial. In this study with 30 patients, PTx was superior in achieving normocalcemia than cinacalcet.

Hypoparathyroidism

A majority of the parathyroid disorders exist of the different forms of hyperparathyroidism. Another parathyroid disease is hypoparathyroidism, which is very uncommon and results in hypocalcaemia. The deficit in PTH results in less calcium mobilization from bone, less reabsorbing of calcium in the distal nephron and it stimulates renal 1α-hydroxylase activity insufficiently. As a result 1,25-dihydroxyvitamin D is insufficiently generated and therefore intestinal calcium absorption is inadequate[64].

The most common cause of hypoparathyroidism is anterior neck surgery[65], and constitutes about 75% of all cases. Other diseases causing hypoparathyroidism are rare but include autoimmune hypoparathyroidism, radiation-induced destruction of parathyroid tissue, deposition of heavy metals in parathyroid tissue, severe magnesium depletion or hypermagnesemia and mutations in the PTH gene or mutations in transcription factors and mitochondrial DNA[64].

Hypoparathyroidism after thyroid surgery is a common complication. Hypocalcaemia resulting from hypoparathyroidism occurs in up to 60% of patients undergoing a total or completion thyroidectomy[66-68]. In a minority of patients parathyroid function

does not recover, and if patients still require calcium supplementation one year after thyroidectomy the hypoparathyroidism is very unlikely to improve, and this is called persistent hypoparathyroidism. Rates of persistent hypoparathyroidism are reported up to 14% after thyroid surgery[69-72]. Treatment consists of symptom control by means of supplementation of both calcium and active vitamin D[73].

At this moment it's not possible to reliably predict which patients will develop persistent hypoparathyroidism and in which patients parathyroid function will recover. Being able to predict persistent hypoparathyroidism will help clinicians counsel their patients and will help tailor individual treatments. Recent studies have described various risk factors for persistent hypoparathyroidism which cannot be influenced, but have also described the value of postoperative PTH levels to determine the chance of direct postoperative hypocalcemia[74]. One study has evaluated the value of PTH levels one month after surgery for predicting persistent hypoparathyroidism[75]. It has not yet been evaluated whether direct postoperative PTH levels can predict which patients will develop persistent hypoparathyroidism.

Outline of thesis

Chapter 2 presents the results of a prospective study on surgical treatment of primary hyperparathyroidism. In this study it is investigated if parathyroidectomy in a daycare setting is safe and feasible.

Chapter 3 describes the results of a retrospective analysis and prospective study on patients undergoing hemithyroidectomy. It is investigated whether it is safe to perform a hemithyroidectomy in a daycare setting.

Chapter 4 presents the results of a case-control study on quality of life of patients with primary hyperparathyroidism. In this study it is investigated whether surgical treatment of primary hyperparathyroidism improves quality of life.

Chapter 5 presents a systematic review of studies describing quality of life in dialysis patients treated for secondary hyperparathyroidism. It is investigated whether surgical or medical treatment by means of cinacalcet has the most beneficial effect on quality of line.

Chapter 6 presents a systematic review of studies describing treatment for tertiary hyperparathyroidism. In this study the results of surgical treatment and medical treatment with cinacalcet are compared.

Chapter 7 presents the results of a retrospective study on tertiary hyperparathyroidism. The outcomes of surgical treatment and medical treatment by means of cinacalcet are described in this study.

Chapter 8 presents the results of a prospective study of patients undergoing total or completion thyroidectomy. In this study it is investigated whether postoperative PTH values can predict which patients develop persistent hypoparathyroidism.

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Chapter 2

Operative treatment of primary hyperparathyroidism in daycare surgery

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ABSTRACT

Objective

The standard of care for primary hyperparathyroidism is surgical removal of hyperfunctional parathyroid tissue. Here we describe twenty patients with PHPT who were treated surgically in the setting of daycare surgery.

Design

Prospective observational study

Methods

Twenty patients with primary hyperparathyroidism were operated between March 2005 and May 2010. The follow-up period had a median of 41 weeks (5-245). Results are presented as mean (± standarddeviation) or median (minimum-maximum).

Results

Twenty patients (15 women, mean age 54±14 years) were included. Nine patients were provided with postoperative calcium supplementation. One of them patient visited the emergency department (ED) the next day with paresthesias and normocalcaemia, this patient was send home. Four patients, without prophylaxis, also reported themselves to the ED. Only one had a mild hypocalcaemia (2,09 mmol/L) and was supplemented. Comparing the ED-group (n=5) with the others, we found that preoperative calcium levels were similar (p=0.40), however the ED-group had significantly lower postoperative calcium levels (2.27±0.14 vs. 2.55±0.25, p=0.008) and the decrease-percentage was significantly higher (17.5% ±5.4 vs. 10.5% ±6.4, p=0.21).

Conclusion

Parathyroidectomy in the daycare setting is feasible and safe. However many patients return to the ED. This could be related to the strict information that is provided or due to a large decrease in their calcium levels, albeit normocalcaemia. Calcium supplementation is cheap and safe, so we will provide all future patients with calcium supplementation and herewith aim to reduce the amount of emergency department visits.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is caused by one or more overactive parathyroid glands producing high levels of parathyroid hormone (PTH) which leads to hypercalcaemia. It is seen in about 20 per 100.000 people, with 2-3 times as many women affected as men[1]. PHPT is often detected by chance when elevated serum calcium levels are found[2]. Operative treatment is the treatment of choice, since it is the only curative therapy. Until the 1990s the bilateral neck exploration was the golden standard. In this procedure the surgeon tries to identify all parathyroid glands and excises only the pathologically enlarged glands. For that matter, in 90% of the cases there is only one enlarged hyperactive gland. This fact, combined with the introduction in the mid 1990s of imaging studies with high sensitivity and specificity – such as radionucleotide scans– has led to a new approach: minimally invasive parathyroidectomy. (MIP) After identification of the pathological gland by ultrasound, nuclear imaging or computed tomography, MIP has a 95% chance of success[3, 4].

Benefits of a minimal invasive procedure are, besides the better cosmetic outcome, decreased risk of post-operative hypocalcaemia and shorter operating times. The success rate and the risk of complications of a MIP are equal to those in the bilateral neck exploration[5]. Furthermore, an increasing number of patients undergoing MIP can be discharged on the day of surgery. MIP in one-day surgery is safe, also for over-70-year-olds[6], cost-effective and the patients are satisfied[7, 8]. In the Netherlands more and more non-parathyroid surgeries are being carried out as day care procedures[9]. In view of the favourable results in international literature, and the potentially higher cost-effectiveness, and patient satisfaction, we introduced day care surgery for PHPT in our centre in 2005. In this article we describe our care pathway and present the results of the first 20 patients with special attention to postoperative hypocalcaemia.

METHODS

Between March 2005 and May 2010 a total of 139 patients underwent parathyroidectomy in our centre. These patients had either primary, secondary or tertiary hyperparathyroidism or MEN syndrome. The diagnosis PHPT was based on elevated serum calcium levels in combination with high normal or elevated PTH levels. Pre-operative imaging consisted of an ultrasound of the neck and a ^{99m}Technetium-sestamibi scan, completed with a computed tomography if needed. All patients were discussed in a multi-disciplinary meeting pre-operatively and were operated by or under the supervision of the last author. The 20 patients considered fit for day surgery were included at

the joint clinic of the endocrinologist, surgeon and nurse practitioner. The inclusion and exclusion criteria are listed in table 1. They consist of both daycare specific criteria, e.g. the availability of a person who would accompany the patient after discharge and the first night, and of disease specific criteria, e.g. MEN syndrome.

Table 1. In- and exclusion criteria for parathyroidectomy in day care surgery

Inclusion criteria	ASA[1] classification 1 of 2 Concordant localizing study (Sestamibi scan and ultrasound neck) Adequate informal care Primary hyperparathyroidism
Exclusion criteria	ASA[1] classification 3 or higher Discordant localizing study (Sestamibi scan and ultrasound neck) Absent informal care Intra-operative PTH[3] measurements - Secondary or tertiary hyperparathyroidism - Genetic disorders (e.n. MEN[2]-syndrome) - Familiary primary hyperparathyroidism - Lithium use - Re-exploration for relapsing hyperparathyroidism

[1]ASA (American Society of Anesthesiologists), [2]MEN (Multiple endocrine neoplasia), [3]PTH (parathyroid hormone)

Demographic and clinical data were collected prospectively. All operations were conducted on a Friday morning under general anaesthesia with the patient in supine position and the neck in slight hyperextension. Both the anaesthesiologist and the surgeon needed to consent for discharge on the same day. On discharge, patients received information about the operation, a letter to the general practitioner and standardized discharge instructions. These instructions included information about hypocalcaemia, pain medication, outpatient wound control and monitoring. Patients were instructed to contact the general practitioner or the hospital upon signs of hypocalcaemia (e.g. paraesthesia and muscle cramps). The study protocol did not provide for prophylactic calcium supplementation; however, some patients received it at surgeon's own discretion. All patients were contacted by telephone after the operation, in accordance with the Erasmus MC daycare surgery standards, and were asked about pain, satisfaction and any other problems. Patients were either seen in the outpatient setting in our hospital or patients' general practitioners or referring specialists from other hospitals checked calcium levels and noted possible complications of surgery. This is according to patients preferences. All patients were monitored for wound healing and serum calcium and PTH levels. We aimed to check all patients at one, six and 52 weeks after surgery or advise the other physicians to do so accordingly. Low or normal calcium levels during the first six months post-operatively are indicative of recovery; rising levels point at persisting disease. Hypercalcaemia after this six month period is considered relapse.

Results are presented as mean ± standard deviation (normal distribution) or as median (minimum – maximum, no normal distribution). The non-parametric Mann Whitney U test was used to compare groups. A p-value of less than 0.05 was considered significant. All data were analysed by SPSS statistics version 18.0 (IBM)

RESULTS

Twenty patients, mean age 54 ± 14 years, underwent a day care procedure between March 2005 and May 2010. Fourteen had been referred by external specialists. On presentation at the outpatient clinic patients complained about fatigue (n=6), depression (n=2), gastro-intestinal symptoms (n=7) and myogenic complaints (n=2). Six patients had no complaints.

The medical histories entailed kidney stones (n=7), chronic obstructive pulmonary disease (n=2), hypertension (n=1), peripheral vascular disease (n=1) and coronary artery bypass grafts (n=1).

Pre-operative serum calcium and PTH levels were mean 2.84±0.20 mmol/L and 19.9±11 pg/ml respectively. All patients received a pre-operative sestamibiscan and an ultrasound of the neck, which led to the removal of one enlarged parathyroid gland in 18 patients. In the remaining two cases, one gland was removed, however a re-operation was needed due to persistent disease. These cases are described below. The mean operating time was 56±19 minutes. Kocher's incision was used in six patients, MIP in the other 14. There were no perioperative complications, and all patients were discharged the same day.

Nine patients received post-operative calcium supplementation based on high pre-operative serum calcium levels or at the surgeon's discretion. One of these reported at the emergency department with paraesthesia and normocalcaemia the day after discharge, but was sent home after reassurance. Four patients without supplementation also reported at the emergency department with paraesthesia the day after discharge. One of them received calcium supplementation as mild hypocalcaemia (2,09mmol/L) was noted. Pre-operative (p=0.40) and post-operative (p=0.38) serum calcium levels did not significantly differ between patients who received calcium supplementation and those who did not. Also, the decrease in serum calcium levels (pre vs. post) did not significantly differ between these groups (p=0.85). Pre-operative serum calcium levels did not significantly differ between the five patients who reported at the emergency department and the others (p=0.40). However, those five had significantly lower post-

operative calcium levels (2.27±0.14 vs 2.55±0.25, p=0.008) and showed a significantly greater drop in serum calcium levels (17.5%±5.4 vs. 10.5%±6.4, p=0.021).

The median follow-up was 41 (5-245) weeks. Two patients showed persisting hyperparathyroidism (PTH>40 pg/ml) at follow-up. One had a parathyroid adenoma in the aortopulmonary window, which was not shown on the sestamibi scan. The other had hyperplasia of all four parathyroid glands, not shown on pre-operative imaging studies. Both patients were cured, one after thoracotomy and one after conventional neck exploration. All other 18 patients had serum calcium and PTH levels within the normal range during follow-up (Fig 1). There were no wound infections, wound hematoma's or laryngeal nerve problems.

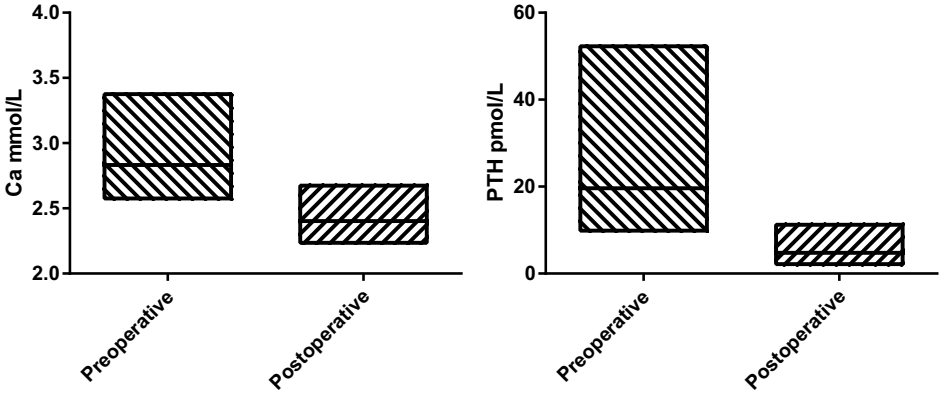

Figure 1. Pre- and post-operative serum levels of calcium and PTH. [1] PTH = parathyroid hormone [*] Post-operative follow-up = longest follow-up possible. Median follow-up is 41 weeks (range 5-245 weeks). Data represent median values and full range.

CONCLUSION

In this article we describe our experience with parathyroid surgery in a day care setting. Despite the relative small sample size we may draw some important conclusions. Patient satisfaction, as measured by the telephone interviews postoperatively, is high due to intensive cooperation between the endocrinologist, surgeon, nurse practitioner and anaesthesiologist, so that patients can be placed on the waiting list after only one hospital visit. By selecting relatively healthy patients we can safely perform parathyroid surgery in the day care setting, with similar outcomes like reported internationally[10]. Calcium levels are not checked before discharge but we inform patients clearly about the signs of hypocalcaemia and urge them to contact the hospital when these signs occur. There were no patients who failed to report to the emergency department. Four persons without calcium supplementation reported to the emergency department

the day after surgery with symptoms, but had no hypocalcaemia. Perhaps they were sensitive to symptoms because of the extensive instructions they had received and therefore more likely to visit the emergency department. Perhaps we need to tone down the post-operative information to prevent these unnecessary visits. On the other hand, the decline in serum calcium levels was significantly greater in these patients. Therefore we assume that not absolute levels, but rather relative declines in serum calcium levels lead to calcium deficits. This means that these patients validly visited the emergency department and should have been supplemented with calcium. These visits could perhaps have been prevented by prophylactic calcium supplementation, which was shown successful in large series in international literature[11]. It is also known that the absolute perioperative serum calcium levels are less predictive[12].

Based on our experience and the findings from the present study we can recommend parathyroid surgery in day care. We would like to propose prophylactic calcium supplementation for a few weeks as needed. The costs are low, and it can be given safely[11]. This is now standard care after parathyroid surgery in the day care setting in our hospital.

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Chapter 3

Introduction of daycare thyroid surgery in a Dutch non-academic hospital

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ABSTRACT

Objective

The hemithyroidectomy is the most common endocrine surgical procedure performed with low complication rates. Multiple international reports indicate that thyroid surgery in day care setting is feasible and safe. Despite these results, thyroid surgery in daycare setting is not yet implemented in the Netherlands. The objective of this study is to assess the safety of thyroid surgery in our institution and, when deemed safe, implement daycare thyroid surgery.

Methods

All patients who underwent a hemithyreoidectomy in our institution between January 2010 and December 2014 were included in the retrospective analysis. Hypothetical candidates for daycare surgery were identified. All patients undergoing thyroid surgery in 2015 were included in a prospective cohort. Data regarding baseline characteristics, surgical procedures, complications and adherence to the daycare schedule are presented.

Results

210 patients were included in the retrospective cohort. 149 patients complied with the daycare criteria. No complications occurred that would prevent daycare surgery, or make it unsafe. Daycare thyroid surgery was implemented from January 2015. In one year 43 patients underwent a hemithyroidectomy. 31 patients were eligible for daycare surgery of which 18 patients were treated in daycare. Failure of the daycare regimen was due to the patients' own choice (n=5), large retrosternal goiter (n=2) or failure of logistics (n=6). Besides transient hoarseness, no complications occurred in this group.

Conclusion

Based on a retrospective safety analysis we successfully introduced daycare thyroid surgery in our clinic. Hemithyroidectomy can safely be conducted in day care setting. However, patient selection is of vital importance to minimize the risk of complications.

INTRODUCTION

A hemithyroidectomy is the most common endocrine surgical procedure performed in daily practice and indicated mainly due to mechanical and/or cosmetic complaints of a multinodular goitre or a solitary thyroid nodule. Furthermore it is performed for diagnostic purposes in case of indeterminate cytology. Despite the increased rate of daycare surgical procedures, thyroid surgery in the Netherlands is currently solely performed with overnight stays. It is assumed that the potential risk of life threatening respiratory problems caused by postoperative bleeding, laryngeal nerve injuries or hypocalcaemia warranting (intravenous) supplementation are reasons for which thyroid surgery is not performed in the daycare setting. Recently, Segel et al[1]. published their results regarding over 1000 thyroidectomies in outpatient setting. The most feared complication, acute postoperative haemorrhage is and potentially life-threatening airway obstruction did not occur. In general, the incidence of postoperative bleeding varies between 0.1 – 1.1%, and seldom cause acute airway problems or need for reinterventions[2]. In addition, laryngeal nerve injury after a hemithyroidectomy is uncommon and the literature reports incidence rates of up to 3,7% of patients, with 0,4% permanent injuries to the laryngeal nerve[3-7]. Temporary hypocalcaemia occurred in about 3% of the outpatient patients treated in the study of Segel[1]. Wound infections occur in less than 1% of the patients, but is a late complication and poses no threat in the daycare setting[4,6].

Worldwide, the number of outpatient thyroidectomies has increased by 39% over the last 10 years[8]. Technological advancements in anesthesiological care and the widespread introduction of minimally invasive surgical techniques have fuelled this trend. The first report regarding thyroid surgery in daycare setting dates back to 1986 by Steckler[9]. Since then, multiple studies have shown that day care thyroid surgery is safe and feasible with regard to the hemithyreoidectomy and even the total or completion thyroidectomy[1,2,4-7,10-13]. The American Thyroid Association published a statement regarding outpatient thyroid surgery describing important safety criteria for selecting eligible patients[14].

Given all the encouraging reports it is peculiar why daycare thyroid surgery is not yet implemented in the Netherlands. One can only assume that the risk, albeit utterly small, of losing a patient due to respiratory distress caused by massive bleeding after discharge is the main reason. Therefore our first aim was to assess the safety of thyroid surgery in our institution by means of a retrospective risk analysis of all patients who underwent a hemithyroidectomy in a five year period from 2010 to 2014. Hereafter we present the initial results of implementing daycare thyroid surgery in our daily practice, strictly adhering to the international guidelines[14].

METHODS

All patients are operated in the 'Reinier de Graaf Gasthuis' in Delft, a non-academic teaching hospital in the Netherlands, by one of two dedicated endocrine surgeons (P.C.S and F.M.G.). The retrospective cohort (part A) consists of all consecutive patients who underwent a primary hemithyroidectomy between January 2010 and December 2014. These patients were identified by means of surgical codes from the hospital software system. All electronic patient charts were reviewed and baseline characteristics, medical history, indication for surgery, postoperative complications and hypothetical eligibility for daycare surgery were noted. Complications were retrieved by manually checking the charts in conjunction to checking our prospective database where all operations and complications are prospectively recorded. The data was analysed and an overall judgement was made regarding the safety of daycare thyroid surgery in our hospital. All patients in the retrospective cohort who were eligible for daycare surgery[14] but received necessary in hospital interventions from six hours to 24 hours postoperatively are considered "daycare safety failures". As no "daycare safety failures" occurred, we proceeded to part B of the study: implementation of daycare surgery.

All patients scheduled for their first hemithyroidectomy in 2015 were included in the prospective cohort (part B). Baseline characteristics, medical history, indication for surgery and postoperative complications were prospectively collected. All patients were assessed for eligibility for daycare surgery according to the criteria published by the American Thyroid Association[14], as listed in table 1. Patients eligible for daycare surgery and willing to participate were discharged the same day at least six hours after skin closure with permission of the surgeon and consent from the patient. All patients received information about the surgical procedure, a letter addressed to the general practitioner and standardized discharge instructions when discharged. These instructions provided information regarding pain and pain medication, wound dressings and signs of infection. Patients were instructed to contact the hospital in case of, but not limited to, voice changes, stridor, swelling of the wound and/or problems swallowing. All patients were contacted by telephone one day after discharge. Two weeks after surgery all patients were seen at the outpatient clinic for their first post-operative check-up. Hereafter, patients were referred back to their treating endocrinologist.

Statistical analysis was done using IBM SPSS software (version 21). Descriptive analysis is performed, where categorical data are expressed as frequency with percentage and nominal data are expressed as mean with standard deviation. Group differences were analysed with the Chi-square test for categorical data, and the unpaired t-test for nominal data. Significant differences are defined as $p < 0.05$.

Table 1a. Eligibility criteria for outpatient thyroidectomy[14]

No major comorbidities or ASA 4
Provision and understanding of preoperative education
Team approach to education and clinical care
Primary care giver willing and available
Social setting conductive to safe postoperative management
Proximity to skilled facility

Table 1b. Relative contra-indications to outpatient thyroidectomy[14]

Clinical	Social	Procedure
Uncompensated cardiac or respiratory disease	Excessive distance from skilled facility	Massive goiter
Dialysis for renal failure	Living alone with no person to accompany	Extensive substernal goiter
Anticoagulant or antiplatelet therapy	Lack of transportation	Locally advanced cancer
Seizure disorder	Patient preference	Challenging hemostasis
Anxiety disorder	Communication barriers	Difficult thyroidectomy with Hashimoto's thyroiditis or Graves disease
Obstructive sleep apnea		
Hearing loss		
Visual impairment		
Mental impairment		
Pregnancy		

RESULTS

Retrospective analysis

A total of 210 patients were included in our retrospective risk analysis cohort, of which 149 patients (71.0%) were eligible for daycare surgery. Baseline characteristics and complication rates are summarized in table 2. Patients eligible for day care surgery were significantly younger (48 vs 55 years, p=0.001) and had lower ASA-classifications. The overall complication rate is 4.4% and in the hypothetical daycare group this was 2,0%.

Five patients experienced transient hoarseness or vocal changes, one developed an anaphylactic reaction of unknown aetiology, and one patient experienced recurrence of a spontaneous tachycardia for which she required medical treatment. In the group not eligible for daycare surgery, one patient required a re-operation due to a wound infection (0.5%) and one postoperative hematoma occurred (0.5%), which was managed conservatively. There were no complications in the "eligible daycare group" comprising patients safety in the hypothetical outpatient setting.

Table 2. baseline characteristics retrospective cohort

	Total	Meet day care criteria	Do not meet criteria	P
N	210	149 (71,0%)	61 (29,0%)	
Age in years (mean + SD)	51 (13,77)	49 (12,72)	55 (15,06)	0,001
Female sex (percentage)	179 (85%)	128 (86%)	51 (84%)	0,335
ASA score	ASA 1 - 89 (42%) ASA 2 - 107 (51%) ASA 3 - 12 (6%) Unavailable – 2 (1%)	ASA 1 - 73 (49%) ASA 2 - 74 (50%) ASA 3 - 1 (1%) Unavailable – 1 (1%)	ASA 1 - 16 (26%) ASA 2 - 33 (54%) ASA 3 - 11 (18%) Unavailable – 1 (2%)	0,000
Indication for surgery	Mechanical complaints - 151 (71,9%) Suspected malignancy - 36 (17,1%) Other reasons – 23 (11,0%)	Mechanical complaints - 104 (70%) Suspected malignancy - 28 (19%) Other reasons - 17 (11%)	Mechanical complaints - 47 (77%) Suspected malignancy - 8 (13%) Other reasons – 6 (10%)	0,186
Type of operation	LHT - 105 (50%) RHT - 105 (50%)	LHT - 70 (47%) RHT - 79 (53%)	LHT - 35 (57%) RHT - 26 (43%)	0,086
Total complication	9 (4,4%)	3 (2.0%)	6 (9,8%)	0,008
Transient hoarseness or vocal changes	5	1 (0,7%)	4 (6,6%)	
Anaphylaxis	1 (0,5%)	1 (0,7%)	0 (0%)	
Spontaneous tachycardia	1 (0,5%)	1 (0,7%)	0 (0%)	
Rebleed	1 (0,5%)	0 (0%)	1 (1,6%)	
Wound infection	1 (0,5%)	0 (0%)	1 (1,6%)	

Values displayed as N + percentage unless stated otherwise
LHT = left hemithyroidectomy
RHT = right hemithyroidectomy

Since this retrospective analysis showed low complication rates, we concluded that a hemithyroidectomy can be performed safely in a day care setting in our institution, and proceeded to implement this new strategy (part B).

In 2015 a total of 43 patients underwent a primary hemithyroidectomy and were included in the prospective cohort. A total of 31 (72%) patients met the international guidelines for daycare thyroid surgery published by The American Thyroid Association, of which 58% (n=18) was eventually treated by means of daycare surgery. Twenty-five (58%) patients stayed overnight after surgery. A flowchart of patients undergoing hemithyroidectomy is illustrated in figure 1. Baseline characteristics and complication rates for the prospective cohort are summarised in table 3. The daycare group was younger than the clinical group (median 50 resp. 61 years). Indication for surgery in the daycare group was mechanical complaints in 89% and suspected malignancy in 11%, in the clinical group the indication was mechanical complaints in 56% and suspected malignancy in 32%.

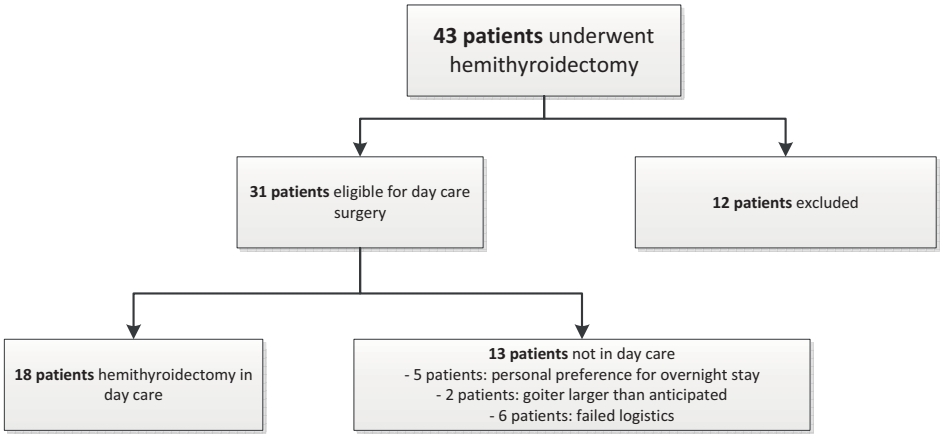

Figure 1. Flowchart

There were two minor complications (transient vocal changes, n=2) in the clinical group and there was 1 minor complication (transient vocal change) in the daycare group. There were no emergency department visits or readmissions following surgery. There were no wound infections, hematoma's or laryngeal nerve damage.

Thirteen patients (30%) were eligible for daycare surgery, but were not treated as such. Five patients (12%) chose to stay overnight, two patients had a retrosternal goiter which was larger than anticipated, and in the remaining six (14%) patients our logistics failed for example as these patients were scheduled for surgery late in the afternoon.

Table 3. baseline characteristics day care cohort

	Daycare setting	Clinical setting	P
N	18	25	
Age in years (median + range)	50 (14,86)	61 (16,37)	0,036
Female sex (percentage)	14 (78%)	21 (84%)	0,303
ASA score	ASA 1 – 6 (33%) ASA 2 – 10 (56%) ASA 3 – 2 (11%)	ASA 1 – 10 (40%) ASA 2 – 13 (52%) ASA 3 – 2 (18%)	0,440
Indication for surgery	Mechanical complaints – 16 (89%) Suspected malignancy – 2 (11%) Other reasons - 0	Mechanical complaints - 14 (56%) Suspected malignancy – 8 (32%) Other reasons – 3 (12%)	0,029
Type of operation	LHT – 7 (38%) RHT – 11 (61%)	LHT – 10 (40) RHT – 15 (60%)	0,471
Total complication	1 (5,6%)	2 (8,0%)	0,378
Transient hoarseness or vocal changes	1 (5,6%)	2 (8,0%)	
Rebleed	0 (0,0%)	0 (0,0%)	
Wound infection	0 (0,0%)	0 (0,0%)	
Meet daycare criteria	n.a.	13 (52%)	

Values displayed as N + percentage unless stated otherwise
LHT = left hemithyroidectomy
RHT = right hemithyroidectomy

DISCUSSION

The retrospective analysis shows that daycare surgery could be safely implemented in our institution. Thereafter, daycare thyroid surgery was implemented and 58% of the eligible patients were treated as such. This is the first cohort in the Netherlands where thyroid surgery is performed in the daycare setting. Patient safety is of paramount importance when installing a new regimen. Only one patient in the daycare group experienced a complication, namely temporary hoarseness. No postoperative hematomas necessitating urgent interventions occurred. However, even though daycare thyroid surgery was already reported in 1986[9], it remains an delicate topic as airway compromise due to hematoma formation is a feared complication. This complication did not occur in both our retrospective and prospective cohort. We do have to acknowledge the fact that our low number of patients if prone to be biased with respect to complication rates. In the literature, Snyder et al[7] has published the largest series of outpatient thyroidectomies, with over 1000 procedures in their cohort. Postoperative hematoma requiring re-operation was present in only one patient undergoing hemithyroidectomy.

31 patients met the international guidelines for daycare thyroid surgery, however only 18 were treated in daycare surgery. In 6 patients our own logistics failed, so this is a major item to improve with this new strategy. Furthermore, it is important to interview patients to determine factors for which they chose to stay overnight, after which preoperative information can be adapted to address this factors.

Patients expressed their satisfaction when contacted by telephone on the next day, however no objective measurement of patient satisfaction was performed. Measurement and documentation of patient satisfaction is important to improve patient selection and improve pre-operative information.

Despite the logistical hurdles and the low number of patients in this study, we advocate the introduction of daycare thyroid surgery in the Netherlands.

However, although complications rates are supposedly very low, it is important to stay vigilant and carefully select patients suitable for day care surgery adhering to international guidelines.

CONCLUSION

Hemithyroidectomy performed in day care is feasible and safe with low complication rates provided that adequate patient selection is performed.

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Chapter 4

Impact of parathyroidectomy for primary hyperparathyroidism on quality of life; a case-control study using SF-36

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ABSTRACT

Background

Physical and mental complaints are common in patients with primary hyperparathyroidism (PHPT) and negatively impact quality of life. Subjective symptoms in current guidelines are not considered an indication for surgery. The aim of this study was to assess the effect of parathyroidectomy on quality of life (QoL) in patients with PHPT.

Methods

This multicentre case-control study investigated preoperative and postoperative QoL scores in patients operated for PHPT, measured with the SF-36 questionnaire. Results were compared with patients undergoing an hemithyroidectomy, the control group.

Results

Fifty-two patients and 49 controls were included. PHPT patients had significantly lower QoL scores preoperatively and improved significantly after successful surgical treatment. Postoperatively, no differences were observed between the two groups.

Conclusion

QoL was significantly lower in patients with untreated PHPT. Surgical treatment was associated with a significant increase in QOL. Decreased QoL should also be considered as an indicator for surgical treatment in patients with PHPT.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is caused by overproduction of parathyroid hormone (PTH) leading to hypercalcaemia. In 85-95%[1] of the cases PHPT is caused by a single parathyroid adenoma. Serum calcium levels are increased through enhanced bone resorption, increased intestinal calcium absorption and decreased urinary excretion[2]. Classical symptoms are often referred to as "bones, stones, abdominal moans and psychic groans". Osteopenia/osteoporosis, nephrolithiasis, constipation, anorexia, nausea and fatigue are among the most common symptoms. However, mental symptoms can also be present, including disorientation, confusion, mood swings, inability to concentrate and memory problems.

Surgical removal of hyper functioning gland(s) is the only curative option for patients with PHPT. Current indications for treatment are documented in a consensus statement of the National Institutes of Health (2009) and include different parameters e.g. osteoporosis, serum calcium levels, high calcium excretion in urine and kidney stones[3]. Impaired mental functioning is not considered to be an indication for surgery in these treatment guidelines.

Several recent nonrandomized, longitudinal studies have focussed on the effect of treatment of PHPT on QoL. These studies suggested that hyperparathyroidism is associated with impaired QoL, which is indeed restored after surgery, both short-[4] and long term[5-8] after the parathyroidectomy. One small study did not show a positive effect of surgery on quality of life, however an unvalidated measure of QoL was used[9]. Two randomized trials[10,11] comparing surgery with observation in PHPT patients showed improved quality of life scores after surgery. The workshop on the Management of "Asymptomatic Primary Hyperparathyroidism" in 2009 also addressed neurocognitive domains in patients with PHPT. It identified a number of categories for further investigation, i.e. prospective cohort studies with emphasis on neurocognitive functioning and impact of parathyroidectomy on quality of life[3].

The aforementioned studies[10-13] compared patients who were surgically treated for PHPT with patients who were only observed. Although these studies are important indicators of the presumed beneficial effects of parathyroidectomy on QoL in PHPT patients, a control group that is subject to a neck operation is mandatory. We therefore included a control group undergoing an almost similar surgical procedure to minimize the possible placebo effect induced by surgery. Euthyroid patients scheduled for diagnostic hemithyroidectomy were included as control group. The aim of this study was to investigate

whether surgery for primary hyperparathyroidism improves QoL as measured by means of the SF-36[14] and a symptom questionnaire.

METHODS

This is a prospective multicentre case-controlled trial. Cases were defined as patients with biochemically proven primary hyperparathyroidism scheduled for surgery, according to the criteria of the 2002 NIH meeting[15]. Patients underwent either a targeted approach by means of one small incision (including unilateral explorations) or a conventional four gland exploration on both sides. Controls were euthyroid patients scheduled for open hemithyroidectomy because of benign disease. Exclusion criteria were: pre- or postoperative diagnosis of malignant disease, secondary or tertiary hyperparathyroidism, primary hyperparathyroidism in multiple endocrine neoplasia (MEN-syndrome) patients, hyper- or hypothyroidism, lithium therapy, inability to give informed consent and age < 18 years. Patients were recruited from April 2007 until December 2010. All patients were followed for one year. Patients were recruited from two academic hospitals and two peripheral hospitals. However, the majority was recruited from one academic center and one peripheral center. Logistical difficulties led to early cessation of inclusions in the second academic hospital. The second peripheral hospital joined the study later and included 7 consecutive patients after which the study was completed. Figure 1 outlines the study flow chart. The Medical Ethical committee approved this study protocol.

General data such as gender, age, blood values, preoperative diagnosis, postoperative pathology results and follow-up laboratory results were obtained from medical records. Quality of Life was measured using the validated SF-36 questionnaire[16]. The Short-Form 36 (SF-36) questionnaire is a validated instrument for the measurement of QoL. It measures both physical and mental functioning[16], and it's widespread use renders it useful to compare different studies. [5-7,10,11,17-22] It is composed of 36 questions and standardized response choices, organized in eight dimensions of health related quality of life. It generates scores for physical functioning, bodily pain, role limitations due to physical problems (role physical), general health, vitality, social functioning, role limitations due to emotional problems (role emotional) and mental health. From these scales, 2 summary measures can be obtained, physical health and mental health.

In addition patients were asked about physical complaints possibly related to primary hyperparathyroidism (table 2). We designed a custom-made "symptom questionnaire" including 17 symptoms related to primary hyperparathyroidism. These are all symptoms that are associated with primary hyperparathyroidism. Patients could indicate if they did

not experience that symptom (1), experienced this sometimes (2) or experienced this often (3). This is not summarized in a separate score. All questionnaires were completed pre-operatively and 3 and 12 months post-operatively.

Statistical analysis was performed using IBM SPSS statistics 21 software. The SF-36 data was normalized for the Dutch population. With this transformation, the Dutch population has a mean of 50 and a standard deviation of 10, and higher scores represent more favourable quality of life. The Mann-Whitney U test was used for analysing differences between the two groups. A general linear model was used in order to compare means of the SF36 (sub)scores, adjusted for age. The Wilcoxon signed ranks test was used for the differences between time points. The symptom questionnaire was analysed using respectively the chi-squared and McNemar test for the group and time point differences.

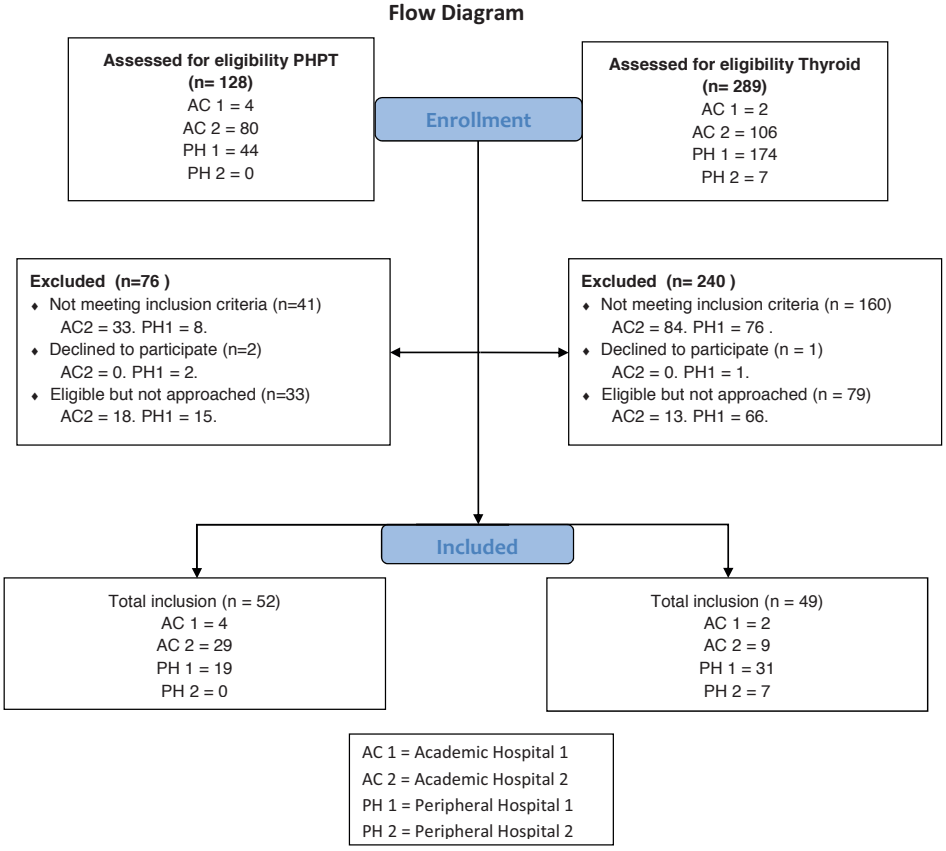

Figure 1. Flow diagram

RESULTS

We included 101 patients according to the inclusion and exclusion criteria, fifty two cases ("PHPT") and 49 controls ("thyroid") (figure 1). PHPT patients were significantly older, with a mean difference of 6 years (58 vs 52, p=0.026). Gender distribution was equal between both groups.

The response rates for the SF-36 questionnaire were 96.2% and 88.5% at 3 and 12 month assessments respectively for the PHPT group. The thyroid group had response rates 89.8% and 89.8% at 3 and 12 months respectively. The rates for the symptom questionnaire were 88,5% and 82,7% for the PHPT group, and 87.7% and 87.5% for the thyroid group at 3 and 12 months respectively.

Overall complication rate was low. In the PHPT group one patient had persisting disease and 4 patients experienced transient vocal change. In the thyroid group one patient had a haemorrhage requiring reoperation, and one patient had a transient neurological event.

All PHPT patients had elevated preoperative serum calcium levels (2.75 (2.68-2.87) mmol/L), which normalized after surgery (Table 1). Control thyroid patients underwent surgery for benign disease, either goitre or nodular disease. All patients had normal levels of serum thyroid stimulating hormone, free thyroxin and calcium.

Quality of life was measured with the SF-36 questionnaire. Preoperatively, PHPT patients had significantly lower results in the role physical and general health domain(Table 3). The median physical component score was significantly lower preoperatively in the PHPT group compared to the thyroid group (42.24 vs. 46.65, $p < 0.05$). Three and twelve months after surgery these differences had disappeared (Table 3). Significant improvements on all domains were observed in the pHPT group within three months after surgery (Table 4a). Thereafter quality of life remained unchanged. For thyroid patients, almost no changes in quality of life occur after the surgical procedure. Only the mental health domain improved significantly within the first three months postoperatively (Table 4b).

Prior to surgery the PHPT group revealed significantly more complaints about dyspepsia, polydipsia and polyuria in the symptom questionnaire compared to the thyroid group (Table 2). Three months after surgery these differences disappeared, however PHPT patients complained significantly more often about nycturia. One year after surgery no significant differences in complaints between the groups were present.

Table 1. baseline characteristics

	PHPT	Thyroid	P value °
Patients	52	49	
Age (years)	58 (50-68)	52 (43-63)	0.03*
Male frequency (percent)	17 (32%)	13 (27%)	NS†
Marital status (percentage married)	32 (61.5%)	30 (61.2%)	NS†
Education level[1] (percentage lower education)	19 (36.5%)	18 (36.7%)	NS†
Pre-operative			
Calcium (mmol/L)	2.75 (2.68-2.87)	2.38 (2.36-2.43)	0.00*
Phosphate (mmol/L)	0.87 (0.70-0.97)	-	
PTH (pmol/L)	13.90 (8.6-27.1)	-	
Albumin (g/L)	44.50 (40.25-47.75)	-	
3 months postoperative			
Calcium (mmol/L)	2.36 (2.30-2.48)	2.35 (2.31-2.43)	NS
Phosphate (mmol/L)	0.96 (0.89-1.07)	-	
PTH (pmol/L)	7.80 (4.14-11.1)	-	
Albumin (g/L)	44.00 (40.00-46.00)	-	
12 months postoperative			
Calcium (mmol/L)	2.38 (2.29-2.47)	2.31 (2.22-2.39)	NS
Phosphate (mmol/L)	0.97 (0.86-1.09)	-	
PTH (pmol/L)	7.10 (4.30-9.40)	-	
Albumin (g/L)	43.00 (40.00-45.75)	-	

PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.
Values displayed as median (p25-p75), unless stated otherwise.
°The Mann-Whitney U test † Chi-squared test
* $p < 0.05$
NS: not significant
Reference values: Calcium: 2.20-2.65 mmol/L, Phosphate: 0.8-1.4 mmol/L, PTH: 1.4-7.3 pmol/L, Albumin: 35-50 g/L.
[1]Basic education: primary school or basis levels of high school

Focussing on the within-group changes of the PHPT group the symptom questionnaire shows that three and twelve months after surgery patients in the PHPT group had significantly fewer complaints of fatigue, muscle aches and nycturia (figure 2). At three months there were fewer complaints about dyspepsia, polyuria and nausea, however this difference does not last at 12 months.

In total, 87% of PHPT patients underwent a targeted surgical procedure (35% minimally invasive parathyroidectomy (MIP), 52% unilateral exploration). Bilateral four gland exploration was performed in 11% of the cases and a hemithyroidectomy in 2%. Both the median domain scores and the median physical component, mental component and overall SF-36 score did not differ between the 2 groups (MIP vs other procedures).

Table 2. Symptom Questionnaire, PHPT compared with controls preoperatively and 3 and 12 months post-operatively.

		Pre-operative			3 months postoperative			12 months postoperative		
	Category^	PHPT	Thyroid	p†	PHPT	Thyroid	p†	PHPT	Thyroid	p†
Fatigue	1	8 (15,4)	13 (26.5)		17 (37.0)	12 (27.9)		21 (50.0)	12 (27.9)	
	2	15 (28.8)	15 (30.6)	NS	23 (50.0)	17 (39.5)	NS	15 (35.7)	17 (39.5)	NS
	3	29 (55.8)	21 (42.9)		6 (13.0)	14 (32.6)		6 (14.3)	14 (32.6)	
Muscle ache	1	20 (38.5)	24 (49.0)		27 (57.4)	22 (51.2)		23 (52.3)	20 (46.5)	
	2	20 (38.5)	19 (38.8)	NS	16 (34.0)	12 (27.9)	NS	16 (36.4)	14 (32.6)	NS
	3	12 (23.1)	6 (12.2)		4 (8.5)	9 (20.9)		5 (11.4)	9 (20.9)	
Back pain	1	26 (50.0)	22 (44.9)		26 (53.1)	24 (55.8)		26 (60.5)	24 (55.8)	
	2	17 (32.7)	13 (26.5)	NS	16 (32.7)	10 (23.3)	NS	12 (27.9)	8 (18.6)	NS
	3	9 (17.3)	14 (28.6)		7 (14.3)	9 (20.9)		5 (11.6)	11 (25.6)	
Weakness	1	23 (45.1)	23 (46.9)		26 (56.5)	22 (51.2)		25 (61.0)	23 (53.5)	
	2	19 (37.3)	18 (36.7)	NS	17 (37.0)	15 (34.9)	NS	14 (34.1)	15 (34.9)	NS
	3	9 (17.6)	8 (16.3)		3 (6.5)	6 (14.0)		2 (4.9)	5 (11.6)	
Dyspepsia	1	32 (61.5)	41 (83.7)		41 (83.7)	34 (81.0)		29 (65.9)	32 (74.4)	
	2	15 (28.8)	7 (14.3)	0.04*	7 (14.3)	6 (14.3)	NS	14 (31.8)	7 (16.3)	NS
	3	5 (9.6)	1 (2.0)		1 (2.0)	2 (4.8)		1 (2.3)	4 (9.3)	
Polydipsia	1	26 (51.0)	36 (75.0)		33 (68.8)	34 (79.1)		29 (65.9)	35 (81.4)	
	2	18 (35.3)	9 (18.8)	0.05*	12 (25.0)	5 (11.6)	NS	12 (27.3)	6 (14.0)	NS
	3	7 (13.7)	3 (6.3)		3 (6.3)	4 (9.3)		3 (6.8)	2 (4.7)	
Constipation	1	32 (65.3)	36 (75.0)		41 (85.4)	29 (72.5)		34 (79.1)	30 (69.8)	
	2	10 (20.4)	8 (16.7)	NS	5 (10.4)	7 (17.5)	NS	8 (18.6)	9 (20.9)	NS
	3	7 (14.3)	4 (8.3)		2 (4.2)	4 (10)		1 (2.3)	4 (9.3)	
Polyuria	1	23 (45.1)	36 (73.5)		33 (67.3)	34 (79.1)		30 (68.2)	33 (76.7)	
	2	20 (39.2)	7 (14.3)	0.01*	12 (24.5)	5 (11.6)	NS	12 (27.3)	7 (16.3)	NS
	3	8 (15.7)	6 (12.2)		4 (8.2)	4 (9.3)		2 (4.5)	3 (7.0)	
Nycturia	1	23 (44.2)	32 (65.3)		31 (63.3)	35 (81.4)		29 (65.9)	28 (65.1)	
	2	23 (44.2)	12 (24.5)	NS	15 (30.6)	3 (7.0)	0.02*	14 (31.8)	12 (27.9)	NS
	3	6 (11.5)	5 (10.2)		3 (6.1)	5 (11.6)		1 (2.3)	3 (7.0)	
Anorexia	1	40 (76.9)	35 (71.4)		46 (93.9)	35 (81.4)		41 (93.2)	35 (81.4)	
	2	10 (19.2)	14 (28.6)	NS	2 (4.1)	7 (16.3)	NS	2 (4.6)	7 (16.3)	NS
	3	2 (3.8)	0 (0.0)		1 (2.0)	1 (2.3)		1 (2.3)	1 (2.3)	
Itch	1	42 (80.8)	39 (79.6)		39 (81.3)	33 (76.7)		33 (76.7)	31 (72.1)	
	2	7 (13.5)	7 (14.3)	NS	7 (14.6)	7 (16.3)	NS	8 (18.6)	9 (20.9)	NS
	3	3 (5.8)	3 (6.1)		2 (4.2)	3 (7.0)		2 (4.7)	3 (7.0)	
Nausea	1	37 (71.2)	40 (81.6)		41 (83.7)	33 (76.7)		38 (86.4)	36 (83.7)	
	2	10 (19.2)	7 (14.3)	NS	7 (14.3)	7 (16.3)	NS	6 (13.6)	6 (14.0)	NS
	3	5 (9.6)	2 (4.1)		1 (2.0)	3 (7.0)		0 (0.0)	1 (2.3)	

Table 2. Symptom Questionnaire, PHPT compared with controls preoperatively and 3 and 12 months post-operatively. (continued)

		Pre-operative			3 months postoperative			12 months postoperative		
	Category^	PHPT	Thyroid	p†	PHPT	Thyroid	p†	PHPT	Thyroid	p†
Depression	1	26 (51.0)	30 (61.3)		34 (69.4)	26 (60.5)		24 (55.8)	27 (62.8)	
	2	19 (37.3)	14 (28.6)	NS	12 (24.5)	11 (25.6)	NS	15 (34.9)	13 (30.2)	NS
	3	6 (11.8)	5 (10.2)		3 (6.1)	6 (14.0)		4 (9.3)	3 (7.0)	
Amnesia	1	23 (44.2)	28 (57.1)		28 (58.3)	25 (58.1)		27 (61.4)	26 (61.9)	
	2	21 (40.4)	16 (32.7)	NS	16 (33.3)	16 (37.2)	NS	13 (29.5)	12 (28.6)	NS
	3	8 (15.4)	5 (10.2)		4 (8.3)	2 (4.7)		4 (9.1(	4 (9.5)	
Weight loss	1	38 (73.1)	42 (87.5)		43 (87.8)	38 (88.4)		37 (84.1)	39 (90.7)	
	2	11 (21.2)	5 (10.4)	NS	4 (8.2)	4 (9.3)	NS	6 (13.6)	4 (9.3)	NS
	3	3 (5.8)	1 (2.1)		2 (4.1)	1 (2.3)		1 (2.3)	0 (0.0)	
Bruises	1	44 (86.3)	43 (87.8)		43 (87.8)	39 (90.7)		38 (90.5)	37 (86.0)	
	2	6 (11.8)	4 (8.2)	NS	4 (8.2)	3 (7.0)	NS	4 (9.5)	4 (9.3)	NS
	3	1 (2.0)	2 (4.1)		2 (4.1)	1 (2.3)		0 (0.0)	2 (4.7)	
Hematuria	1	47 (92.2)	48 (98.0)		47 (97.9)	42 (97.7)		42 (97.7)	43 (100.0)	
	2	4 (7.8)	1 (2.0)	NS	1 (2.1)	1 (2.3)	NS	1 (2.3)	0 (0.0)	NS
	3	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

PHPT, primary hyperparathyroidism; † chi-squared test;* $p < 0.05$

^ 1= no complaints, 2= sometimes, 3= often Data presented as frequency (percentage)

Table 3. Mean SF-36 outcomes, comparing PHPT and Thyroid patients, both before and after surgery and adjusted for age

	Pre-operative			3 months			12 months		
	PHPT	Thyroid	p†	PHPT	Thyroid	p†	PHPT	Thyroid	p†
PF	43.12 (1.54)	46.05 (1.58)	0.19	46.71 (1.45)	48.24 (1.56)	0.48	46.92 (1.63)	46.69 (1.67)	0.92
RP	38.93 (1.80)	44.26 (1.85)	0.04*	45.80 (1.83)	45.14 (1.93)	0.81	46.24 (1.83)	45.67 (1.87)	0.83
BP	46.28 (1.61)	49.12 (1.66)	0.23	48.54 (1.64)	48.98 (1.75)	0.86	48.83 (1.79)	47.33 (1.83)	0.56
GH	41.86 (1.37)	46.51 (1.42)	0.02*	44.61 (1.53)	46.83 (1.61)	0.32	45.77 (1.74)	46.39 (1.82)	0.81
VIT	45.38 (1.60)	48.13 (1.63)	0.24	50.46 (1.53)	48.93 (1.63)	0.50	50.27 (1.63)	49.28 (1.65)	0.68
SF	42.79 (1.58)	45.74 (1.62)	0.20	47.09 (1.61)	46.24 (1.71)	0.72	47.47 (1.57)	47.23 (1.63)	0.92
RE	44.05 (1.80)	46.39 (1.88)	0.38	48.93 (1.60)	47.73 (1.70)	0.61	47.57 (1.68)	48.70 (1.70)	0.64
MH	46.51 (1.64)	46.03 (1.68)	0.84	49.97 (1.61)	49.00 (1.72)	0.68	49.10 (1.71)	49.86 (1.73)	0.76
PSC	42.24 (1.56)	46.65 (1.59)	0.05*	45.58 (1.46)	47.47 (1.56)	0.39	46.23 (1.72)	45.75 (1.74)	0.85
MCS	47.31 (1.50)	47.21 (1.53)	0.96	51.34 (1.43)	49.39 (1.53)	0.36	50.59 (1.34)	50.09 (1.36)	0.80

Data are presented as marginal mean (SD).

PHPT = Primary Hyperparathyroidism

PF = Physical functioning; RP = Role-Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role-Emotional; MH = Mental Health; PCS = Physical Component Score; MCS = Mental Component Score

† F-test for comparing marginal means using a General linear model

* $p < 0.05$

Table 4a. Median SF-36 outcomes in PHPT patients preoperatively, 3 months and 12 months postoperatively

	Pre-operative	3 months	12 months	p† 0-3	p† 0-12	p† 3-12
PF	45.84 (34.92 - 51.85)	49.80 (41.47 - 54.58)	49.12 (41.47-56.76)	0.001*	0.01*	0.893
RP	33.37 (25.97 -55.56)	55.56 (33.37-55.56)	48.17 (33.37-55.56)	0.000*	0.002*	0.967
BP	44.27 (35.57-60.40)	49.38 (40.03-60.40)	49.37 (39.61-60.40)	0.02*	0.02*	0.707
GH	39.98 (35.27-49.89)	44.94 (34.77-52.37)	44.94 (35.02-54.85)	0.04*	0.04*	0.245
VT	44.71 (39.91 - 54.29)	51.89 (42.31-59.08)	51.89 (41.11-56.68)	0.001*	0.000*	0.650
SF	40.57 (34.99 - 51.74)	51.74 (40.57-57.33)	51.74 (40.57-57.33)	0.01*	0.01*	0.772
RE	45.57 (30.44 - 55.66)	55.66 (45.57-55.66)	55.66 (35.48-55.66)	0.01*	0.08	0.383
MH	50.64 (37.32 -55.09)	52.87 (41.76-59.53)	50.64 (41.76-57.31)	0.01*	0.03*	0.553
PCS	42.29 (33.91 - 50.91)	47.20 (38.21-53.51)	45.31 (38.96-55.74)	0.01*	0.002*	0.476
MCS	49.15 (38.35 - 55.33)	54.59 (44.04-58.40)	52.22 (41.30-57.68)	0.002*	0.01*	0.064

Data are presented as median (p25-75).
PHPT = Primary Hyperparathyroidism
PF = Physical functioning; RP = Role-Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role-Emotional; MH = Mental Health; PCS = Physical Component Score; MCS = Mental Component Score
* $p < 0.05$
† Wilcoxon Signed ranks test
SF-36 scores on the different time points were compared. Pre-operative vs. 3 months, pre-operative vs. 12 months and 3 months vs. 12 months.

Table 4b. Median SF-36 outcomes in thyroid patients preoperatively, 3 months and 12 months postoperatively

	Pre-operative	3 months	12 months	p† 0-3	p† 0-12	p† 3-12
PF	50.21 (37.10 - 56.76)	51.03 (47.75 - 56.76)	52.39 (41.47-56.76)	0.09	0.16	0.262
RP	48.17 (25.97-55.56)	55.56 (25.97-55.56)	55.56 (33.37-55.56)	0.78	0.58	0.703
BP	53.61 (35.57-60.40)	51.91 (41.09-60.40)	49.37 (35.36-60.40)	0.82	0.19	0.056
GH	47.41 (39.98-52.37)	47.42 (39.98-54.23)	47.42 (41.59-55.47)	0.52	0.97	0.400
VT	51.89 (37.51-55.49)	49.50 (42.31-54.29)	51.89 (39.91-59.08)	0.33	0.64	0.578
SF	46.16 (37.78 - 57.33)	51.74 (34.99-57.33)	51.74 (40.57-57.33)	0.42	0.72	0.864
RE	55.66 (35.48 - 55.66)	55.66 (35.48-55.66)	55.66 (45.57-55.66)	0.32	0.34	0.904
MH	48.42 (35.10 - 55.09)	52.87 (39.54-57.31)	50.64 (39.54-59.53)	0.002*	0.03*	0.756
PCS	50.62 (39.54 - 55.10)	49.31 (41.78-55.83)	49.45 (34.72-56.39)	0.63	0.62	0.334
MCS	49.51 (37.24 - 56.28)	53.33 (41.95-60.48)	53.65 (40.72-57.16)	0.05*	0.06	0.883

Data are presented as median (p25-75).
PF = Physical functioning; RP = Role-Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role-Emotional; MH = Mental Health; PCS = Physical Component Score; MCS = Mental Component Score
* $p < 0.05$
† Wilcoxon signed ranks test
SF-36 scores on the different time points were compared. Pre-operative vs. 3 months, pre-operative vs. 12 months and 3 months vs. 12 months.

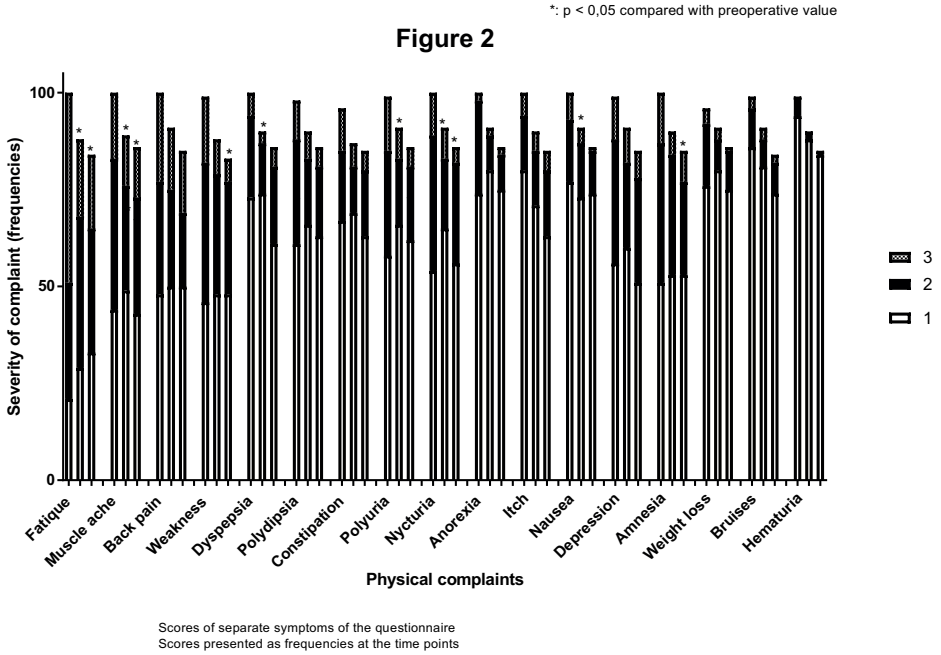

Figure 2. Changes in reported symptoms regarding PHPT. The first bar per symptom represents the preoperative score, the second the three month score and the third the one year score.

DISCUSSION

This study investigated quality of life in patients undergoing parathyroidectomy for primary hyperparathyroidism compared to patients undergoing thyroid surgery. These results demonstrated a low preoperative QoL compared to the control group and a significant increase in QoL after parathyroidectomy to comparable levels as the control patients.-

PHPT patients complained significantly more often about nycturia 3 months after surgery. This is probably a coincidental finding, as no medical explanation exists.

Four studies included PHPT patients and a control group consisting of patients with thyroid disease. First, in the study of Eigelberger et al.[23] 202 cases and 63 controls were included. They found that patients in both parathyroid groups (those who met or did not meet the NIH criteria for parathyroidectomy) benefited from successful parathyroidectomy. Unfortunately, no quality of life analysis was performed.

Recently Weber et al.[22] described a large multicentre case-control study with 194 PHPT patients and 186 controls. Quality of life was evaluated using the SF-36 questionnaire and reported as physical and mental component scores. The authors reported significantly lower pre-operative SF-36 scores, on both components, in PHPT patients compared to the thyroid controls, in line with the results of the present study. In addition, they described a similar increase in quality of life after parathyroidectomy, which seemed to be sustained over a period of one year. However, 57% of the control patients underwent a total thyroidectomy leading to life-long thyroid hormone supplementation and a risk for alterations in neuropsychological symptoms. This is not addressed in the study results.

Kahal et al.[24] described a smaller series of 24 PHPT patients and 23 controls undergoing diagnostic hemithyroidectomy for benign thyroid nodules. They used the Hospital Anxiety and Depression scale (HAD) and the Mood Rating Scale (MRS)measuring symptoms pre-operatively and 3 months after surgery. They reported that parathyroidectomy was associated with improved symptoms, as measured by the HAD and the MRS. Follow-up in this study was only three months and therefore no conclusions on long-term effect could be drawn. Furthermore, all patients were subjected to a four gland exploration, which could be associated with less improvement in quality of life[19]. Nowadays, the targeted approach by means of small incisions is used more frequently. In our study only 11% of the cases were operated by means of a bilateral neck exploration. Although this group is too small for further subgroup analysis, we assume that the influence on the overall results is limited. However, the impact of type of surgery remains an interesting point for future studies.

In addition, Roman et al.[4] described a series of 27 PHPT patients and 28 controls. They used the Beck Depression Inventory and Spielberger State-Trait Anxiety Inventory assessing depression and anxiety, and the Rey Auditory Verbal Learning Test and Groton Maze Learning Test evaluating cognitive function. They found that PHPT was associated with higher depression scores and greater problems in spatial learning, relative to the control group, and that these outcomes improved after parathyroidectomy. No data regarding QoL were reported.

This study provides additional information regarding the effect of parathyroidectomy on quality of life in PHPT patients. We were able to achieve high response rates (almost 90%) during follow-up of one year after surgery. Furthermore we included only euthyroid patients undergoing hemithyroidectomy for benign disorders as controls.

There are some limitations that need to be mentioned as well. The median age of the cases was higher than the median age of the controls. We have adjusted the analysis for

this difference. Marital status and educational level was comparable between the two groups. Information about other possible covariates is not available.

Our study is a non-randomized study. We used a non-validated symptom questionnaire to assess the complaints related to hyperparathyroid disease. A validated thyroid-specific questionnaire is not available. The SF-36 gives us information about QoL, but does not give us information on cognitive functioning or other sequelae. In addition, we acknowledge the fact that no correction for multiple comparisons was made, increasing the risk for type 1 errors. Due to our difficulties with the accrual of patients, we missed a large group of potential subjects, with a risk of selection bias. We evaluated the baseline characteristics of the missed subjects and compared them with the included group. They were comparable by means of age and gender. Furthermore it would have been interesting to address other factors such as long term risk of fractures, nephrolithiasis and recurrence. Our study size was too small to analyse these outcomes and larger trials are needed to assess these long term effects of parathyroidectomy in pHPT patients.

CONCLUSION

This study evaluates quality of life in patients with primary hyperparathyroidism using the SF-36 questionnaire before and after surgery. Regarding role physical domain, general health domain and the physical component score, quality of life in patients with PHPT was significantly lower preoperatively compared with patients undergoing thyroid surgery. After surgery for PHPT, quality of life increased on all domains, and was comparable to that of control patients. Our findings suggest that patients with PHPT, if fit for surgery, might benefit from surgical treatment and might be considered candidate for surgical treatment, even if they do not meet the current NIH criteria. Quality of life should be considered in adjunct to the NIH criteria.

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Chapter 5

Effect of Parathyroidectomy and Cinacalcet on Quality of Life in Patients with End-Stage Renal Disease Related Hyperparathyroidism: a Systematic Review

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ABSTRACT

Background

Patients with end-stage renal disease (ESRD) have a decreased quality of life (QoL), which is in part attributable to ESRD-related hyperparathyroidism (HPT). Both cinacalcet and parathyroidectomy (PTx) are treatments for advanced HPT, but their effects on QoL are unclear. We performed a systematic review to evaluate the impact of cinacalcet and PTx on QoL.

Methods

A systematic literature search was performed using PubMed and Embase databases to identify relevant articles. The search was based on the following keywords: "parathyroidectomy" or "cinacalcet", "secondary hyperparathyroidism" or "renal hyperparathyroidism" combined with "quality of life" or SF-36" or "symptomatology". Only studies reporting on QoL at baseline and during follow-up were included. QoL scores were extracted from the selected manuscripts and weighted means were calculated. Due to lack of available data on QoL improvement in patients using cinacalcet, a meta-analysis could not be performed.

Results

Eight articles reached our inclusion criteria. Five articles reported on the effect of PTx on QoL. All PTx studies were observational and non-controlled. The physical component scores (PCS) of SF-36 increased significantly with a weighted mean of 35.5% ($p<0.05$). Mental component scores (MCS) increased with 13.7% ($p<0.05$). Parathyroidectomy Assessment of Symptoms (PAS) scores improved from 561 preoperatively to 302 postoperatively (-259 points; -46.2%). Visual Analogue Scale (VAS) scores reduced significantly for skin itching (46.6%), joint pain (30.4%) and muscle weakness (28.7%) ($p<0.05$). Three studies on the effect of cinacalcet on QoL were included, including one RCT. None of these studies showed significant improvement of PCS and MCS scores.

Conclusions

PTx improves QoL in patients treated for ESRD-related HPT, whereas cinacalcet did not. The difference of impact between PTx and cinacalcet on QoL has not been compared directly.

INTRODUCTION

Deregulated mineral metabolism is a hallmark of end-stage renal disease (ESRD).(1) Specifically, hyperparathyroidism (HPT) with hyperplastic or hypertrophic parathyroid glands occurs commonly in patients with ESRD (30-50%).(2, 3) Eventually HPT contributes to progressively disturbed calcium-phosphate homeostasis and eventually to autonomous PTH overproduction and hypercalcaemia remaining irrespective of renal function: tertiary HPT. Clinical HPT-related manifestations vary from somatic symptoms such as fatigue and abdominal pain, to psychological symptoms such as forgetfulness, mood swings and concentration difficulties.(4) Furthermore, HPT has been associated with versatile detrimental effects on health status, especially with respect to bone disorders, cardiovascular disease, increased risk of mortality and even reduced quality of life (QoL).(5-8) QoL of ESRD patients is often already decreased both due the symptoms of ESRD itself and the burden of dialysis treatment.(9)

In the management of HPT, different treatment modalities are available. According to the Kidney Disease Improving Global Outcome (KDIGO) guidelines patients with ESRD related HPT should initially receive medical therapy, with vitamin D analogs and phosphate binders. Upon failure of initial therapy, prescription of the calcimimetic agent cinacalcet is recommended.(10) Cinacalcet increases the sensitivity of the calcium-sensing receptor (CaSR) located within the parathyroid glands, aiming to reduce excretion of PTH and balance calcium-phosphate homeostasis.(11) KDIGO guidelines recommend parathyroidectomy (PTx) only in patients with severe HPT (>800 pg/mL) who are refractory to medical therapy. Since its introduction in 2004, cinacalcet has gained a dominant role in the treatment algorithm of ESRD related HPT and PTx is less often performed.(12) However, emerging data suggest that the reticent position of surgery in the treatment algorithm of HPT might be questionable. In a previous study, we showed that PTx is a very safe and effective treatment.(13) Furthermore, Narayan and co-authors showed that PTx is more cost-effective than cinacalcet after 7.25 months of treatment.(14) Since no randomized controlled trial (RCT) comparing PTx with cinacalcet has been performed so far, the optimal treatment of ESRD related HPT remains unclear.

In order to provide a patient-tailored approach to HPT it is of paramount importance to also assess the effect of these interventions QoL, in line with the increasing interest in patient reported outcome measures (PROMs).(15) It is known that PTx improves QoL in patients with primary HPT, however whether there is an additional positive effect of PTx or cinacalcet in patients with concurrent ESRD remains uncertain.(16) Therefore, we performed a systematic review of studies measuring QoL in patients with HPT who received cinacalcet or underwent (sub)total PTx.

METHODS

Search strategy

To identify relevant articles a systematic literature search was conducted using PubMed and EMBASE. The following search terms were used to identify articles on the effect of PTx on QoL: *parathyroidectomy, secondary hyperparathyroidism, tertiary hyperparathyroidism, quality of life, SF-36, symptomatology*. Next, we used the following search terms to identify articles describing the effect of cinacalcet on QoL: *secondary hyperparathyroidism, tertiary hyperparathyroidism, cinacalcet hydrochloride, quality of life, SF-36, symptomatology.* Additionally, we searched for abstracts and unpublished studies on the websites of the FDA, EMA, ASN and EDTA. The search protocol has not been published or submitted to an ethical committee.

Article selection and data extraction

Only original research papers written in English and published between 1980 and 2015 were included for further analysis. These abstracts were screened by two independent reviewers (RD, WYvdP) and all articles complying with the following criteria were selected: (1) studies assessing QoL using any kind of health questionnaire. Both general and disease-specific questionnaires were included. (2) QoL was assessed both at baseline and during follow-up after PTx or initiation of cinacalcet in HPT patients. In case of disagreement a third reviewer was consulted (TMvG or SK). After this selection process all full text articles were studied and cross reference check was performed. Our online search yielded 277 articles, to which two articles were additionally found by cross-referencing. Eventually, five publications on PTx met the inclusion criteria and were included in this review. Three relevant manuscripts on the effect of cinacalcet on QoL were selected (Figure 1). Corresponding authors were asked to provide additional data if the articles did not contain the required information. Secondary endpoints of our analyses were biochemical measurements including parathyroid hormone (PTH), calcium and phosphate levels before and after intervention. No additional studies or abstracts where found on the websites of the FDA, EMA, ASN or EDTA.

Quality assessment

All eligible articles were independently scored regarding their quality by three reviewers blinded to each other's results (WYvdP, RD and SK). In case of disagreement the article was discussed and a definitive score was calculated based on consensus. Case series were assessed by means of the 18-criteria checklist by the Delphi panel.(17) This validated checklist includes the quality of the study objective, population, intervention and co-intervention, outcome measures, and statistical analysis. A maximum of 18 points could be awarded. A score of 14-18 points was considered high-quality, a score of 9-13 fair

quality. For case-control and cohort studies, the Newcastle-Ottawa scale was appraised. (18) The scale consists of three domains addressing the aspects of methodology including selection, comparability and outcome (cohort studies) or exposure (case-control studies) for which stars could be allotted. A total of 9 stars could be awarded. A score of 7-9 was considered high quality, 4-6 was considered fair quality. Articles reporting a randomized controlled trial (RCT) were assessed using the CONSORT 2010 statement. (19) Also, the risk of publication bias will be assessed using a funnel plot.

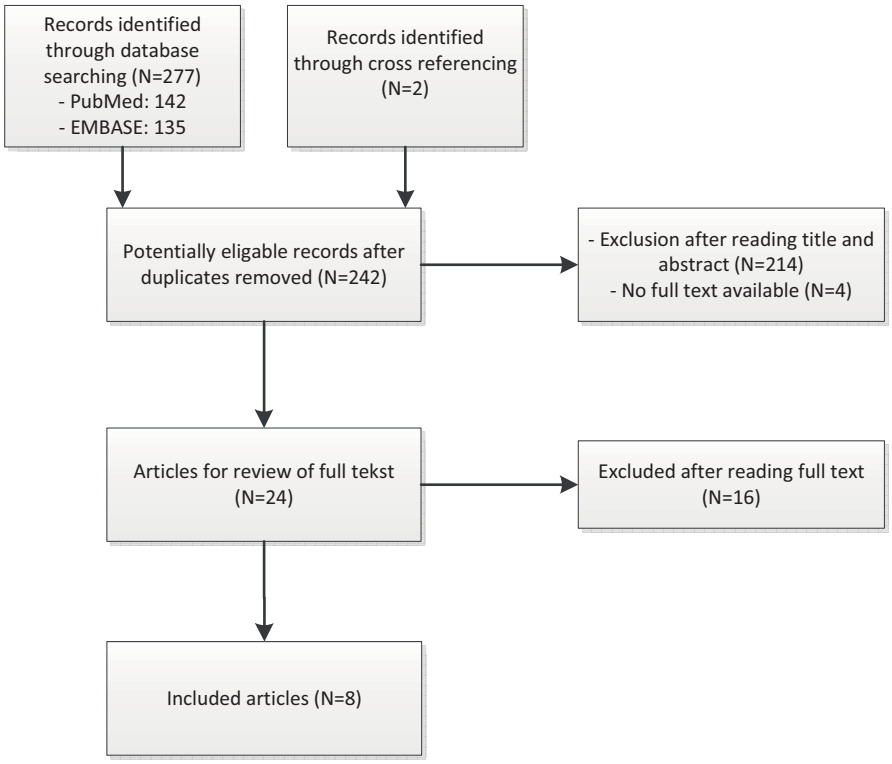

Figure 1. Flowchart of study selection

Quality of life and symptoms measurement tools

The Medical Outcomes Study Short-Form Health Survey® (SF-36®) is a commonly applied questionnaire of 36 simple questions on eight health domains. Each dimension can be transformed into a 0-100 scale, where a higher score represents better self-perceived well-being and QoL. These eight domains can be distinguished into two summery scores: the physical component summary score (PCS) and the mental component summary score (MCS). For both the PCS as the MCS a score of 50 represents the mean of the United States population with a standard deviation (SD) of 10. In hemodialysis patients,

reported mean PCS ranges from 31.6-49.8 and MCS varies from 46.0-50.2.(20-22) A change in PCS or MCS scores of minimally 2 points is thought to be clinically meaningful. (23)

The European Quality of Life 5 Dimensions (EQ-5D) assessment is another classification instrument. It encompasses 5 domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression each with three response levels.(24)

Pasieka et al. developed a disease-specific outcome tool for hyperparathyroidism. The Parathyroidectomy Assessment of Symptoms (PAS) is a questionnaire which contains all HPT-related symptoms initially designed for primary HPT.(4) This 13-item questionnaire has been validated for secondary and tertiary HPT and is correlated to the SF-36 questionnaire.(25) The visual analogue scale (VAS) ranging from 1-100 was used to assess the degree of severity per symptom. The 13 included symptoms are bone pain, fatigue, mood swings, feeling "blue" or depressed, abdominal pain, feeling weak, feeling irritable, joint pain, forgetfulness, difficulty getting out of a chair or car, headaches, itchy skin, and being thirsty. Subsequently, a maximum PAS score of 1,300 can be reached.

Statistics

Mean QoL scores were extracted from the selected manuscripts. Weighted means were calculated as follows: (amount of patients * the mean score difference) / total amount of patients.

RESULTS

Description and quality of the included studies

A description of the included studies is shown in Table 1. Of the five included studies on PTx, four articles provided SF-36 scores, three of which reported the summary scores. Two papers also assessed quality of life by means of the PAS score and one article used a general VAS system. There were no multicenter studies and follow-up ranged from 3-12 months. All studies stated a complete objective and/or hypothesis and outcome measures were clearly described in all studies. In 80% of the studies patients had been recruited consecutively. All studies reported length of follow-up, but only one of the five studies mentioned the number of participants lost to follow-up. All authors drew conclusions fully supported by their results. We considered 3 articles to be of high quality and 2 of fair quality.

Tabel 1. Characteristics of the included studies

Reference	Year	Patient population	No. of patients	Study design	Follow-up	Age	Gender (M/F)	Baseline PTH (pg/mL)*	Quality appraisal
PTX									
Bratucu (39)	2015	ESRD patients who would undergo PTx for HPT	85	Case series	6 months	51 ± 12	39/46	1379 (414-3345)	High (15/18)†
Cheng (8)	2013	ESRD patients with HPT scheduled for PTx	49	Case series	12 months	52 ± 11	18/31	1416 ± 449	Fair (13/18)†
Yang (40)	2011	ESRD patients who would undergo PTx for advanced HPT	37	Case series	3 months	55 ± 12	18/31	2086 ± 1452	Fair (11/18)†
Chow (41)	2003	ESRD patients who would undergo PTx for HPT	12	Case series	6 months	50 ± 11	5/7	2320 ± 215	High (14/18)†
Pasieka (4)	2000	ESRD patients with HPT scheduled for PTx	32	Case control	12 months	45 (23-66)	14/18	909 (131-1514)	High (8/9)‡
Cinacalcet									
Chertow (31)	2012	ESRD patients with HPT	567	Clinical trial	12 months	55 ± 14	324/245	294 (172-655)	High (14/18)†
Briggs (30)	2016	ESRD patients with HPT	1780	Double-blind RCT	64 months	55 ± 15	1041/739	N.A.	Fair (14/25)∫
Filipozzi (32)	2014	ESRD patients with HPT	124	Cohort study	12 months	67 ± 15	72/52	622 ± 161	High (8/9)‡

† 18-criteria checklist by the Delphi panel

‡ Newcastle-Ottawa scale

∫ CONSORT 2010 statement

* Data is shown as mean ± standard deviation or median (interquartile range)

RCT, randomized controlled trial; N.A., not available.

Three studies reporting the effect of cinacalcet on QoL were included. One was based on the EVOLVE trial, a multicenter RCT comparing cinacalcet with placebo.(26) All manuscripts stated clear hypotheses and endpoints were fully described.

The risk of publication bias could not be tested since <10 studies were included in this analysis.

Effect of parathyroidectomy on quality of life

All studies reported significant improvement in QoL after PTx (Table 2). These positive effects were reported both after short-term (3 months) and longer-term follow-up (12 months). The weighted mean physical component scores were 33.2 preoperatively and increased significantly to 45.3 postoperatively (weighted mean increase of 35.5%). The mental component scores increased from 44.6 preoperatively to 50.9 postoperatively (+13.7%). PAS scores improved from 561.5 preoperatively to 302.3 postoperatively (-259 points, -46.2%). Yang et al. reported VAS scores on three domains: skin itching, joint pain and muscle weakness. Pain scores of these items reduced significantly by 46.6%, 30.4% and 28.7%, respectively.

In the study by Yang et al, the MCS slightly decreased 1 month postoperatively compared with the preoperative situation.

Effect of cinacalcet on quality of life

Filipozzi et al. (N=124) reported absolute values. At baseline, PCS and MCS scores were 38.6 ± 5.3 and 45.5 ± 7.4 respectively. At the end of follow-up, PCS score was 38.7 ± 5.3 and MCS score 44.6 ± 7.7. No p-value was provided. Briggs et al. (N=1780) reported QoL data expressed as EQ-5D scores. The estimated treatment effect of cinacalcet at the end of follow-up did not reach statistical significance compared to placebo. Chertow and co-authors analyzed 567 patients who participated in an open-label clinical trial that showed that cinacalcet had a significant positive effect on 4 of 14 related symptoms at the end of study (dry skin, ache in bones, joint pain, and trouble with memory). However, no significant changes were seen in PCS and MCS scores both at the end of the efficacy assessment (16-22 weeks) and at end of follow-up (12 months).

DISCUSSION

This is the first systematic review to examine the impact of PTx and cinacalcet for the treatment of HPT on QoL. Eight peer-reviewed studies published between 2000-2015 were analyzed. Patients with secondary and tertiary hyperparathyroidism who under-

Tabel 2. Quality of Life measurements in patients who underwent PTx

Reference	Year	No. of patients	Follow-up	Main objective	Pre PTx	Post PTx	P-value
SF-36							
Bratucu (39)	2015	85	6 months	SF-36			
				Physical component summary (PCS)	29.96 ± 8.11	38.50 ± 5.36	<0.0001
				Mental component summary (MCS)	45.06 ± 11.37	47.28 ± 9.30	0.01
Cheng (8)	2013	49	12 months	SF-36			
				Physical component summary (PCS)	40.3 ± 17.1	59.0 ± 14.9	<0.0001
				Mental component summary (MCS)	47.6 ± 17.1	63.7 ± 13.0	<0.0001
Yang (40)	2011	37	3 months	SF-36			
				Physical component summary (PCS)	31.3 (20 – 45.1)	42.9 (27.7 – 48.7)	<0.001
				Mental component summary (MCS)	39.5 (25 – 48.6)	42.4 (29.8 – 49.2)	<0.05
Chow (41)	2003	12	6 months	SF-36			
				Physical functioning	59.2 ± 26.8	68.0 ± 28.6	0.01
				Role limitations – physical	27.1 ±31.0	50.0 ± 46.5	0.04
				Pain	57.9 ± 27.8	83.1 ± 16.3	0.004
PAS							
Bratucu (39)	2015	85	6 months	PAS	567 ± 136	293 ± 85	<0.0001
Cheng (8)	2013	49	12 months	PAS	545 ± 263	284 ± 201	<0.0001
Pasieka (4)	2000	32	12 months	Median symptom index score (MSIS)	572	355	<0.01
VAS							
Yang (40)	2011	37	3 months	VAS			
				Skin itching	4.31 ± 3.33	3.0 ± 2.19	<0.001
				Joint pain	4.98 ± 3.37	2.61 ± 2.19	<0.05
				Muscle weakness	4.63 ± 2.90	3.30 ± 2.19	<0.001

Results are reported as mean ± SD or median (25^{th} – 75^{th} percentile)

went PTx experienced a significant improvement of QoL. Cinacalcet on the other hand, did not convincingly have a positive effect on QoL.

HPT develops in 30-50% of all patients with ESRD.(2) It is well recognized that ESRD and accompanying complications are associated with polypharmacy, a decreased life expectancy, and a reduced QoL.(27) Strikingly, only few studies assessed the effect of PTx and cinacalcet on QoL as an endpoint in the fragile ESRD population. In this review we summarized available data related to the impact of PTx and cinacalcet on QoL in ESRD patients with HPT. Our data suggest that PTx might improve QoL in these patients, whereas cinacalcet does not seem to influence QoL.

The improvement of QoL after PTx is probably caused by the resection of almost all parathyroid tissue, resulting in a strong correction of PTH overproduction. Due to the extremely short half-life of PTH (<2 min.) serum PTH drops immediately, leading to low serum PTH levels.(28) In line, HPT related symptoms as described by Pasieka et al., such as bone pain, fatigue and depression diminish almost directly after PTx. It should be noted that none of the included articles on the effect of PTx were sham-controlled. It is likely that bias introduced by the lack of sham-controlled surgery plays a substantial role in the improvement patients experienced after PTx. Thus, although the individual studies in our meta-analysis were considered to be of reasonable to good quality, the level of evidence to support the effect of PTx on QoL remains low. On the other hand, patients require less medications after surgery, which also benefits QoL.

Several studies have investigated the influence of cinacalcet on QoL of the ESRD patient population.(29-32) These studies showed less promising results when compared to the QoL improvement after PTx. Our findings are in line with data by Cunningham et al, who undertook a compared analysis of four unpublished RCTs that QoL in patients with HPT treated with either cinacalcet (N=665) or placebo (N=471). The main outcome was that only two (bodily pain and general health) of the eight domains of SF-36 improved significantly in the cinacalcet group compared to the control group with a difference of less than two points, while only a difference of 3 to 5 points is considered clinically meaningful.(23, 29) The fact that cinacalcet does not seem effective in improving QoL may at least partly be explained by the occurrence of side effects such as nausea, vomiting, and diarrhea that may counteract potential QoL improvements due to PTH lowering.(26) We found no study comparing the effects on QoL of cinacalcet with PTx directly.

The strength of this systematic review is our methodological approach. After establishing a well-designed reproducible search string in collaboration with an experienced medical librarian, the selection and analysis were conducted by three individual reviewers.

Afterwards, selected manuscripts were assessed on their quality using validated quality assessment tools also independently by three authors. This assessment indicates that all studies were of enough quality to address our question. Limitations of this review are inherent to the study population. QoL is influenced by many factors and it remains difficult to assess the true benefit of surgery alone in the absence of sham-controls. In addition, data is limited and unfortunately, no meta-analysis was possible. Due to lack of data, we could not test the risk for publication bias. However, we do acknowledge the potential risk for publication bias, which should be taken into account when interpreting the results. Lastly, a search protocol has not been published or presented to an ethical committee.

Since the availability of calcimimetics, in daily practice PTx is now only indicated in patients with uncontrollable HPT.(10) Meanwhile, in the last decade the quality of parathyroid surgery has improved with the use of less invasive operations, heat sealing devices and improved imaging for preoperative localization.(33, 34) Notwithstanding, PTx remains a surgical procedure executed in a fragile population with cause-specific morbidity, including hypocalcaemia, emergency admissions (myocardial dysrhythmias, cerebrovascular events) as described in a large nationwide US study.(35) These data might explain the hesitance of nephrologists to refer their patients for surgery and their increased motivation for treatment with cinacalcet.(36) The intravenous calcimimetic etelcalcetide was recently approved by the European Medicines Agency and will become available on the European market in 2017, which may provide a further impulse for upfront medical management of HPT.(37) On the other hand, we demonstrated that PTx is a safe procedure with low complication rates when performed in a tertiary referral center. Postoperative complications, including surgical site problems (3.5%), temporary recurrent laryngeal nerve damage (1.8%) and intensive care admissions (0.8%) were rare. Postoperative hypocalcaemia was seen 39.8% of the patients.(13) This difference might indicate the necessity of referring these fragile patients to high-volume centers. Despite data indicating that surgical intervention is highly effective, has a positive effect on QoL, and is safe when performed in an experienced center, pharmacological treatment has so far remained the first-line treatment for advanced HPT.(13, 14, 38) In order to ultimately compare the short-term and long-term effects of cinacalcet and PTx on QoL in HPT patients both short-term as well as long-term, a randomized controlled trial (RCT) soon will be conducted (EudraCT no. 2016-002174-12). Along with results of comparing biochemical effects and cost-effectiveness, recommendations for renewed guidelines should be established.

Conclusions

Parathyroidectomy improves quality of life in patients treated for ESRD-related HPT, whereas cinacalcet did not. In order to provide a patient tailored-approach for the treatment of HPT biochemical, clinical and quality of life changes must be taken into account.

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Chapter 6

Surgical or medical treatment for tertiary hyperparathyroidism; a systematic review

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ABSTRACT

Introduction

A significant portion of patients with chronic kidney disease and secondary hyperparathyroidism (HPT) remain hyperparathyroid after kidney transplantation, a state known as tertiary hyperparathyroidism (HPT). Without treatment, tertiariy HPT can lead to diminished kidney allograft and patient survival. Parathyroidectomy was commonly performed to treat tertiary HPT until the introduction of the calcimimetic drug, cinacalcet. It is not known whether surgery or medical treatment is superior for tertiary HPT.

Methods

A systematic review was performed and medical literature databases were searched for studies on the treatment of tertiary HPT that were published after the approval of cinacalcet.

Results

A total of 1669 articles were identified, of which 47 were included in the review. Following subtotal and total parathyroidectomy, initial cure rates were 98.7% and 100% respectively, but in 7.6% and 4% of patients tertiary HPT recurred. After treatment with cinacalcet, 80.8% of the patients achieved normocalcaemia. Owing to side effects, 6.4% of patients discontinued cinacalcet treatment. The literature regarding graft function and survival is limited; however, renal graft survival after surgical treatment seems comparable to therapy with cinacalcet.

Conclusion

Side-effects and complications of both treatment modalities were mild and occurred in a minority of patients. Surgical treatment for tertiary HPT has higher cure rates than medical therapy.

INTRODUCTION

Hyperparathyroidism (HPT) is a disease caused by excessive secretion of parathyroid hormone (PTH) due to either parathyroid hyperplasia or adenomas. In primary hyperparathyroidism (HPT), an enlargement of one or more of the parathyroid glands causes overproduction of PTH, resulting in hypercalcaemia, which can cause a variety of clinical symptoms. Surgery is currently the treatment of choice for patients fulfilling the criteria as defined by the guidelines of the fourth international workshop on asymptomatic primary HPT[1]. A targeted surgical approach, with a mini-incision, is considered the standard treatment[2-4].

In secondary HPT, hypocalcaemia and phosphate retention stimulate the parathyroid glands, and this results in parathyroid hyperplasia and increased PTH concentrations. Secondary HPT is one of the first metabolic complications of chronic kidney disease (CKD) and has been associated with untoward effects such as renal bone disease, increased cardiovascular morbidity and death from (cardio)vascular calcifications[5,6]. Successful kidney transplantation can reverse secondary HPT[7]. The greatest decline in serum PTH concentrations is observed during the first 3 months after kidney transplantation, with a more gradual decline during the rest of the first post-transplant year[8,9]. Unfortunately, one year after an otherwise successful transplant, 17-50% of transplanted patients still have HPT, which is unlikely to improve spontaneously[8,10]. This condition is referred to as tertiary or post-transplant HPT[7,11]. Treatment of tertiary HPT is important as raised serum calcium concentrations and hypercalciuria increase the risk of renal allograft dysfunction[12] and graft loss[13]. In addition, tertiary HPT is a major risk factor for bone fractures during the first 5 years after transplantation[14].

Historically, secondary and tertiary HPT were treated surgically. However, since 2004 medical treatment with the calcimimetic agent cinacalcet (Mimpara®, Amgen, Thousand Oaks, CA, USA) has gained popularity[15]. Cinacalcet increases the sensitivity of the calcium-sensing receptor of the parathyroid gland, thereby suppressing the production of PTH[16]. Cinacalcet was approved for the treatment of secondary HPT by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2004. However, it has not been approved to treat tertiary HPT. Nonetheless, off-label use of cinacalcet for tertiary HPT has increased, and in small non-randomized studies with short follow-up the drug appears to be safe, with gastrointestinal intolerance being the most common side effect[17]. At present, there is only limited literature to guide clinicians when faced with making treatment decisions regarding tertiary HPT. Therefore, the aim of this systematic review was to compare the outcomes of surgical and medical treatment of tertiary HPT.

METHODS

Search strategy

A systematic search for articles on the treatment of tertiary HPT was conducted. The definition of tertiary HPT varies in international literature, and includes serum PTH levels more than twice the upper limit of normal" and persistent hypercalcaemia with increased PTH concentration after successful kidney transplantation[14,18]. In the present study, all definitions used were included.

The aim was to compare the outcomes of surgical and medical treatment of tertiary HPT. Primary endpoints were cure rate (defined as normalization of hypercalcemia), recurrent tertiary HPT (definition of recurrence dependent on the definition of tertiary HPT used), and the complications and sid- effects of each treatment modality. Second, the impact of surgical and medical therapy on renal allograft function and survival was assessed. Publications were selected using MEDLINE, Embase, Web-of-science, the Cochrane Library, Pubmed Publisher and Google Scholar. Articles had to be original full-text articles written in English, published after 2004 (when cinacalcet received FDA/EMA regulatory approval) and describing an adult human population. To ascertain that no surgical trials were missed, the search strategy was extended to include articles published before 2004. No additional studies comparing surgical treatments for tertiary HPT were identified.

Articles describing treatment of tertiary HPT, both surgical and medical, were included, as well as articles describing renal function after initiation of these therapies. The following search terms were used: Hyperparathyroidism, Parathyroid hormone, Kidney/renal transplantation, Calcimimetic/Cinacalcet/Mimpara, Parathyroidectomy/Endocrine surgery.

Two authors were involved in selecting articles. Any disagreement was discussed until consensus was reached.

Methodological quality of included case-control and cohort studies was assessed by means of the Newcastle-Ottawa scale (NOS)[19]. A score of 7-9 was considered high quality, and 4-6 as fair quality. An 18-criteria checklist developed by Moga and colleagues[20] served to assess the quality of included case series. Here, a maximum of 18 points could be rewarded to each study. A score of 14-18 was considered high quality, and a score of 9-13 as fair quality. RCTs were assessed by means of the 25-item checklist of the Consort Statement[21].

Statistical analysis

No meta-analysis could be performed owing to the lack of sufficient RCTs. When similar studies reported individual data regarding similar endpoints, data were pooled and percentages for the outcome of interest were calculated. Descriptive statistics reported in the tables consists of absolute numbers of patients and follow-up. No other statistical analysis was applied.

RESULTS

The primary search identified 2963 records, with 16 records identified through reference search. After exclusion of duplicates, publication dates and case reports, reviews, letters to the editor and conference abstracts, all titles and abstracts were screened. Eventually 232 full-text articles were assessed for eligibility. Following exclusions at this stage, a total of 47 articles were finally included in the review (Fig. 1).

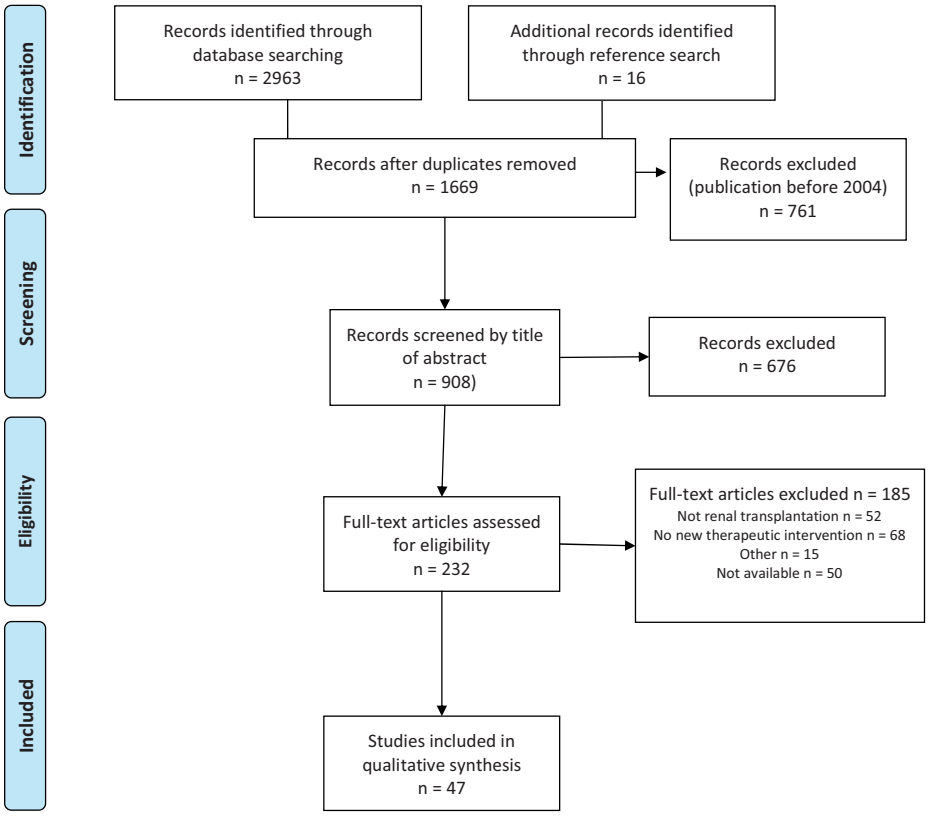

Figure 1. Flow diagram of articles included in the systematic review

Surgical management of tertiary hyperparathyroidism

Fourteen studies described the outcome of parathyroidectomy for tertiary HPT. These included one RCT[22], three prospective cohort studies[23-25], nine retrospective cohort studies[26-34] and one case series[35] (Table 1). Of the 13 observational studies, seven were considered of high quality and six fair quality. Group sizes differed between 15 and 136 patients, and follow-up ranged from a minimum of 9 months to as long as 116 months after transplantation. Data regarding persistent or recurrent tertiary HPT after parathyroidectomy was available for 240 patients[25-28,30]. Seventy-one (29.6%) of these patients had undergone a total parathyroidectomy either with (28 patients) or without (43) autotransplantation. No patient had persistent disease, although three (4%) developed recurrent disease after a mean follow-up of 31-79 months. These three patients all had a total parathyroidectomy without autotransplantation. A subtotal parathyroidectomy was performed in 158 of the 240 patients (65.8%) of whom two (1.3%) had persisting tertiary HPT and 12 (7.6%) were found to have recurrent disease after a mean follow-up of 41-79 months. The remaining 11 patients (4.6%) had undergone a limited parathyroidectomy, of whom ten (91%) had persistent or recurrent disease (not specified). A surgical procedure was defined as limited parathyroidectomy when fewer than four glands were identified or when only one or two glands were removed deliberately.

Persisting disease was defined as persistent hypercalcaemia in two studies[28,30], with no definition in the other studies. Recurrent disease was defined as recurrent hypercalcaemia 6 months after surgery in two studies[28,30], with no definition in the other studies.

There were two patients (0.7% of 274) who developed chronic hypocalcaemia. Transient hypocalcaemia[24,28,30-32,34] was observed in 15% to 23% of the patients. One study[24], however, reported a rate of 67% (8 of 12 patients) after total parathyroidectomy.

Complications after surgery, besides hypocalcaemia or persistent disease[28,30,32,33], were rare. Vocal cord paralysis, probably due to damage of the recurrent nerve, was seen in six of 280 patients (2.1%). Other rare complications were pneumonia (3 of280) and postoperative hematoma (2 of 280). No studies directly compared the different surgical strategies (subtotal parathyroidectomy, total parathyroidectomy with or without autotransplantation).

Medical management of tertiary hyperparathyroidism with cinacalcet

The experience with cinacalcet after kidney transplantation was reported in 24 articles: two RCT's[22,36] and 22 smaller observational studies [37-58] (Table 2). Of the 22 observational studies, nine were considered of high quality, and 13 were considered fair quality. The indication to prescribe cinacalcet was hypercalcaemic tertiary HPT in 22 studies, nor-

Table 1. Summary of included studies reporting of treatment of tHPT with parathyroidectomy

Study, year	Study design	Procedure	Study patients (n)	FU (months)	Persisting disease	Recurrent disease	Persistent hypocalciemia	Study quality
Kebebew[34], 2004	Retrospective cohort	SPTx	27	57.6	N/A	N/A	0	6/9~
		Unilateral	7				0	
Triponez[30], 2005	Retrospective cohort	SPTx	70	67.2	0	1	1	6/9~
Gilat[32], 2006	Retrospective cohort	SPTx	13	24	N/A	N/A	N/A	7/9~
		LTPx	5					
		SR	2					
Triponez[28], 2006	Retrospective cohort	SPTx	72	64.8	N/A	8*	0	9/9~
		LTPTx	11			10*	0	
Evenepoel[29], 2007	Retrospective cohort	SPTx	74	N/A	N/A	N/A	N/A	9/9~
		TPTx+AT	6					
		Unknown	10					
Rayes[26], 2008	Retrospective cohort	TPTx	17	31	0	0	0	9/9~
		SPTx	16	41	2	3	0	
Schlosser[35], 2008	Case serie	Primary	46	9-116	N/A	N/A	N/A	13/18^
		Redo	23					
Drakopoulos[24], 2009	Prospective cohort	TPTx	12	N/A	N/A	N/A	N/A	7/9~
Pitt[33], 2009	Retrospective cohort	SPTx/TPTx	107	79	N/A	N/A	7%	9/9~
		Limited	29				0	
Coulston[31], 2010	Retrospective cohort	TPTx	20	31	N/A	N/A	N/A	6/9~
Santos[25], 2011	Prospective cohort	TPTx+AT	28	42.9	0	0	1	6/9~
Sadideen[27], 2012	Retrospective cohort	TPTx	26	60	0	3	0	6/9~
Jager[23], 2014	Prospective cohort	TPTx+AT	15	24	N/A	N/A	N/A	7/9~
		LTPTx	8	24	N/A	N/A	N/A	
Cruzado[22] 2015	RCT	SPTx	15	12	N/A	N/A	N/A	20/25†

* indicates both persisting as recurrent disease, ~ NOS quality assessment, ^ Moga quality Assessment, † Consort checklist, SR: Selective resection, LTPTx: Less-than-total parathyroidectomy, TPTx: Total parathyroidectomy, AT: Autotransplantation, SPTX: Subtotal parathyroidectomy

mocalcaemic tertiary HPT in one study and both hypercalcaemic and normocalcaemic tertiary HPT in one study. A total of 713 patients were treated during a wide range of periods (from 2 weeks up to 53 months) after renal transplantation. All studies showed a decline in mean serum calcium and PTH concentrations. Eleven studies, including 297 patients, describe the outcome "achieving normocalcaemia". Of these patients, 240 (80.8%) achieved normocalcaemia, with individual studies reporting rates ranging from 28% (10 of 36) to 100%[22,36,38,42,45,48,50,51,54,55,57]. Overall, of 578 patients treated with cinacalcet, 37 (6.4%) discontinued treatment due to persisting hypercalcaemia or side effects such as hypocalcaemia, gastrointestinal complaints, or paraesthesia. Dose of cinacalcet ranged between 30 mg and 180 mg daily. No subgroups according to dosage were described.

Table 2. Summary of included studies reporting of treatment of tHPT with Cinacalcet

Study, year	Study design	Study patients (N)	FU (months)	Normocal-caemia	Discontinued treatment	Study quality
Kruse[38] 2005	Case serie	14	3	12/14	1/14	15/18^
Serra[42] 2005	Case serie	11	2.5	11/11	1/11	14/18^
Apostolou[37] 2006	Case serie	7	3-18	N/A	0/7	13/18^
Leca[39] 2006	Cohort, retrospective	10	12	N/A	0/10	6/9~
Srinivas[57] 2006	Case serie	11	3-18	8/11	2/11	13/18^
Szwarc[46] 2006	Case serie	9	6	N/A	3/9	13/18^
Bergua[47] 2007	Case serie	13	6	N/A	N/A	12/18^
El-Amm[43] 2007	Case serie	18	6	N/A	1/18	14/18^
Bergua[56] 2008	Case serie	9	12	N/A	1/9	15/18^
Serra[44] 2008	Case serie	10	0.5	N/A	N/A	12/18^
Carrasco[40] 2009	Case serie	14	6	N/A	2/14	13/18^
Gomez Margues[45] 2009	Cohort, retrospective	48	12	13/15	4/48	7/9~
Lopez[48] 2009	Case serie	29	3-29	27/29	1/29	14/18^
Toro Prieto[49] 2009	Case serie	27	6	N/A	N/A	14/18^
Borchhardt[55] 2010	Case serie	10	18-34	10/10	N/A	13/18^
Borstnar[41] 2010	Case serie	11	12	N/A	1/11	12/18^
Copley[50] 2010	Case serie	41	3-6	10/36	N/A	12/18^
Schwarz[54] 2011	Case serie	58	12	53/58	4/58	15/18^
Courbebaisse[52] 2012	Cohort, retrospective	34	12	N/A	N/A	9/9~
Paschoalin[58] 2012	Case serie	23	53	N/A	0/23	12/18^
Paschoalin[51] 2012	Case serie	41	31	41/41	0/41	11/18^
Evenepoel, 2014[36]	RCT	57	12	45/57	5/57	19/25†
Torregrosa[53] 2014	Cohort, retrospective	193	22	N/A	10/193	6/9~
Cruzado[22], 2015	RCT	15	12	10/15	1/15	20/25†

~ NOS quality assessment

^ Moga quality Assessment

† Consort checklist

Effect of surgery for tertiary hyperparathyroidism on renal graft function

Twelve studies[9,18,26,29,59-66] described the effect of parathyroidectomy for tertiary HPT on renal function after kidney transplantation (Table 3). Eleven of the 12 articles were considered of high quality, one article[66] was considered fair quality. In these studies, group sizes varied between 18 and 90 patients. Follow-up ranged from 6 to 62 months, with one exception[64] describing 10 year follow-up. One study reported stable renal function after parathyroidectomy; in five studies a transient decline in renal function was observed: and in six studies a permanent decline in renal function was reported. Interpretation of these studies is hampered by the lack of control groups. The two retrospective studies that compared patients undergoing parathyroidectomy with a matched cohort showed either a permanent decline at 6 months follow up[62] or a transient decline in renal function with 24 months follow-up[60].

Two studies[18,64] addressed the effect of parathyroidectomy on graft survival. Although a permanent decline in renal function was observed in many patients having parathyroidectomy, this did not reduce graft survival when compared to that following parathyroidectomy in patients with no decline in renal function, with a follow-up of 3 and 10 years respectively[18,64]. Furthermore 3- and 10-year graft survival rates were similar to those in patients undergoing renal transplantation without parathyroidectomy.

Effect of cinacalcet for tertiary hyperparathyroidism on renal graft function

Five articles[40,52-54,65] described the effect of cinacalcet on graft function after renal transplantation. Three of these were considered of high quality, two of fair quality. Three small studies[40,52,65] with a total of 61 patients, described stable graft function during treatment. This was confirmed by a large observational study of Torregrosa and co-workers[53] who found stable graft functions during treatment with cinacalcet in a group of 193 patients with tertiary HPT.

In contrast, Schwarz *et al*[54] described a cohort of 58 patients and observed a significant decline in estimated glomerular filtration rate of 9% during treatment with cinacalcet. These studies did not report data on the effect of cinacalcet on graft survival or overall survival. No studies are available that directly compared medical therapy with surgical therapy.

DISCUSSION

From this systematic review of studies reporting surgical and medical therapy with cinacalcet for tertiary HPT it can be concluded that surgical treatment has higher cure rates

Table 3. Summary of included studies reporting of renal graft function after parathyroidectomy

Study, year	Study design	Procedure	FU (months)	Study patients (n)	Effect of PTx on renal function	Study quality
Evenepoel[62], 2005	Retrospective, case-control	N/A	6	32	Significant decline in renal function	7/9~
Garcia[66], 2005	Retrospective	TPTx + AT	24	22	Deterioration until 3 months, return to baseline at 12 months	6/9~
Evenepoel[29], 2007	Retrospective, case-control	SPTx/TPTx	62	90	Deterioration at 1 month, return to baseline at 12 months	9/9~
Schlosser[61], 2007	Retrospective	TPTx ± AT/ SPTx/ Limited	12	69	Significant decrease in renal function in TPTx group	9/9~
Schwarz[64], 2007	Cohort, retrospective	SPTx/ TPTx ± AT	N/A	76	47% had a deterioration of renal function. 10 year survival equal than patients with stable renal function	8/9~
Rayes[26], 2008	Cohort retrospective	SPTx/ TPTx	31/41	33	Creatinine rise short term, long term return to baseline values	9/9~
Kandil[18], 2010	Retrospective, case control	N/A	36	19/730	Decrease in renal function at 3 years, no effect on graft survival	7/9~
Ferreira[60], 2011	Retrospective, case control	TPTx ± AT	24	19	Short term deterioration in renal function, long term stabilization and return to baseline values	7/9~
Jager[63], 2011,	Cohort, retrospective	Limited/SPTx/ TPTx + AT	60	83	Decrease in renal function at all-time points, less severe in LTPTx group	9/9~
Jeon[9], 2012	Retrospective, case control	SPTx/TPTx	12	63	Acute deterioration of renal function, not returning to baseline at 12 months	9/9~
Yang[65], 2012	Cohort retrospective	Limited/SPTx/ TPTx + AT	N/A	18	No change in renal function	8/9~
Parikh[59], 2013	Cohort, retrospective	SPTx	12	32	Transient kidney allograft dysfunction with recovery at 12 months	8/9~

SPTx: subtotal parathyroidectomy
TPTx: total parathyroidectomy
AT: autotransplantation
~ NOS quality assessment
^ Moga quality Assessment

Table 4. Summary of included studies reporting on renal graft function after treatment with Cinacalcet

Study, year	Study design	FU (months)	Study patients (n)	Effect of Cinacalcet on renal function	Study Quality
Carrasco[40], 2009	Case serie	6	14	Stable creatinine levels	13/18^
Schwarz[54], 2011	Case serie	12	58	Rise in serum creatinine levels of 13 µmol/L	15/18^
Courbebaisse[52], 2012	Cohort, retrospective	12	34	Stable creatinine levels	9/9~v
Yang[65], 2012	Cohort, retrospective	12	13	Creatinine level increase by 0,056 mg/dl (mean) in 1 year	8/9~
Torregrosa[53], 2014	Cohort, retrospective	22	193	Stable creatinine levels	6/9~

~ NOS quality assessment
^ Moga quality Assessment

with low complication rates. The only RCT[22] comparing surgical therapy with medical therapy with cinacalcet included 2 cohorts of 15 patients, with the primary endpoint being normocalcaemia at 12 months. After parathyroidectomy 100% of patients achieved normocalcaemia, compared with 10 of the 15 patients (67%) treated with cinacalcet. This is the only RCT to date, and therefore it was not possible to perform a meta-analysis. Unfortunately, trials focussing on major clinical endpoints are lacking, and in the available literature regarding this topic there is no uniform definition regarding tertiary HPT.

With regard to surgical treatment, three procedures are commonly performed: total parathyroidectomy with or without autotransplantation, subtotal parathyroidectomy and limited parathyroidectomy. An international survey among 86 endocrine surgeons[67] reports that 85 (99%) performed a (sub)-total parathyroidectomy with or without autotransplantation for secondary or tertiary HPT. A limited approach, when only enlarged parathyroid glands are removed, was rarely used. Although there are no studies directly comparing these procedures, persisting and recurrent disease rates shown in the present review indicate that limited parathyroidectomy should be avoided: 4, 8.9 and 91% for total, subtotal and limited resection respectively.

Renal function after parathyroidectomy for tertiary HPT seems to decline transiently or permanently. In cohorts of patients undergoing renal transplant, overall allograft function will decline eventually. Whether this decline in function is due to the parathyroidectomy or to chronic rejection can be determined only from studies with a control group. At present, no such studies are available. The studies in the present review show that there is no effect of parathyroidectomy on overall graft survival[18,64]. Surgical complications are rare, and parathyroidectomy appears to be a safe and feasible treatment option

for tertiary HPT. Unfortunately, the literature regarding this topic is sparce, consisting mostly of case series or cohort studies.

Medical treatment of tertiary HPT with cinacalcet significantly decreases serum calcium concentrations, but only 80.8% of the patients achieved normocalcaemia and 6.4% discontinued treatment due to side-effects such as gastro-intestinal intolerance. Renal graft function is stable during treatment with cinacalcet or may decline minimally. A meta-analysis of observational studies by Henschkowski and colleagues[68] reported an increase in serum creatinine levels of 5 µmol/l after three months of treatment with cinacalcet: no long-term data are available from this study. Again the literature consisted mostly of observational studies, with only nine of 22 studies being considered of high quality.

The present endpoints did not focus on cardiovascular morbidity or mortality, although this is an important complication for all patients undergoing dialysis or renal transplantation. Included studies did not report data regarding the effect of parathyroidectomy or cinacalcet on cardiovascular complication rates in patients with tertiary HPT. However, there is some evidence from patients with secondary HPT. In this group, parathyroidectomy leads to a decreased risk of major cardiovascular events and death in comparison with conservative treatment[69,70]. Furthermore, in 2012 the results of the EVOLVE trial[71], which randomised patients with secondary HPT to best medical treatment or best medical treatment with cinacalcet, were published. The addition of cinacalcet did not reduce the risk of death or major cardiovascular events. In addition, a meta-analysis of RCTs[72] reported that the use of cinacalcet in patients undergoing dialysis did not improve overall survival. Cardiovascular morbidity and mortality in patients with tertiary HPT should be a focus of future trials.

Another important complication for patients with tertiary HPT patients is bone disease. The rate of osteoporosis is high patients with a renal transplant[73-79], and tertiary HPT is associated with an increased risk of osteoporosis[73], and is a major risk factor for fractures[14]. Small trials[41,49,80-83] have suggested that parathyroidectomy increases bone mineral density, in contrast to cinacalcet. The development of osteoporosis should also be a focus of future trials.

Finally, cost-effectiveness remains an important consideration in the choice of treatment. Uncontrolled HPT increases the economic burden of patients with secondary HPT undergoing dialysis owing to higher medication and hospitalization costs[84]. Compared with cinacalcet treatment, parathyroidectomy is more cost-effective in these patients[85],

mainly due to the significant additional cost and chronic use of cinacalcet. Currently, there are no data regarding cost-effectiveness in treatments for tertiary HPT.

Although high quality evidence is lacking, this systematic review shows that surgical treatment for HPT appears to be more effective than medical treatment. Furthermore, complication rates after surgery are low and graft survival is comparable to that obtained with cinacalcet. Higher-quality data on important clinical end-points such as cardiovascular morbidity and renal bone disease are lacking. Future research should include randomized trials focussing on clinical end-points such as quality of life, cardiovascular morbidity and renal bone disease so that the optimal treatment for an individual patient can be chosen.

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Chapter 7

Parathyroidectomy versus cinacalcet for tertiary hyperparathyroidism; a retrospective analysis

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Submitted

ABSTRACT

Introduction

Persistent hyperparathyroidism(HPT) after kidney transplantation, also known as tertiary HPT, occurs in 17-50% of patients. Treatment of tertiary HPT is mandatory since persistent elevated PTH levels after kidney transplantation increase the risk of renal allograft dysfunction as well as osteoporosis. The introduction of cinacalcet in 2004 offered a medical treatment alternative to parathyroidectomy(PTx). However, the optimal management of tertiary HPT remains unclear. In this study we compared the outcomes of PTx and cinacalcet for tertiary HPT.

Methods

A retrospective analysis was performed of patients that received a kidney transplant in one of 2 academic centers in the Netherlands. Patients undergoing a PTx within 3 years of transplantation and patients requiring cinacalcet 1 year after transplantation were included. Primary outcomes were serum calcium and PTH concentration one year after kidney transplantation and after PTx.

Results

Our study cohort consisted of 30 patients undergoing PTx and 64 still treated with cinacalcet after kidney transplantation. Patients in the cinacalcet group had PTH concentrations above the upper limit of normal (median 22.0 pg/ml) 1 year after KT, whereas serum calcium concentrations normalized (median 2.40 mmol/L). After PTx, both serum calcium (median 2.34 mmol/L) and PTH concentrations (median 3.7 pg/ml) returned to within the normal range.

Conclusion

In patients with tertiary HPT, cinacalcet normalizes serum calcium, but does not lead to a normalization of serum PTH concentrations. In contrast, PTx leads to a normalization of both serum calcium and PTH concentrations. These findings suggest that PTx is the treatment of choice for tertiary HPT.

INTRODUCTION

Hyperparathyroidism (HPT) is a state of overproduction of parathyroid hormone (PTH) due to over activity of one or more of the parathyroid glands[1]. Secondary hyperparathyroidism (sHPT) frequently complicates chronic kidney disease (CKD). CKD causes phosphate retention, hypovitaminosis D [1,25-$(OH)_2$-D] and hypocalcaemia, leading to stimulation of the parathyroid glands and increased PTH production. Secondary HPT occurs in 25-30% of patients with end-stage renal disease (ESRD) and is associated with severe bone mineral disease[2]. Importantly sHPT is also associated with increased cardiovascular morbidity[2] and mortality[3,4]. The first line of treatment of sHPT used to consist of calcium and vitamin D supplementation followed by either medical therapy using calcimimetics[5] or surgical treatment by parathyroidectomy (PTx)[6]. For dialysis patients requiring PTH-lowering therapy the current recommendation is to treat with calcimimetics, calcitriol or vitamin D analogs, or a combination of these therapies[7].

Secondary HPT can be corrected by a successful kidney transplantation (KT)[8]. Nevertheless, 17-50% of patients who receive a kidney transplant remain hyperparathyroid one year after transplantation[9-11]. This is referred to as tertiary or post-renal transplantation HPT (tHPT), which is a state of excessive and autonomous production and excretion of PTH[8,12]. In general, the PTH concentration rapidly declines within the first three months after KT and then continues to decline more gradually over the course of the next nine months. One year after transplantation, PTH concentrations are unlikely to decline further[9-11].

As tHPT increases the risk of renal allograft dysfunction and renal allograft loss[13,14], osteoporosis[15] and bone fractures[16], adequate management is essential. Introduced in 2004, the calcimimetic drug cinacalcet (Mimpara®, Amgen Inc. Thousand Oaks, CA, USA) is frequently used for the treatment of ESRD related HPT[17,18]. Cinacalcet suppresses the production of PTH by increasing the sensitivity of the calcium-sensing receptor of the parathyroid gland to calcium[19]. The United States Food and Drug Administration and the European Medicines Agency have approved cinacalcet for the treatment of secondary but not tertiary HPT. This is despite a number of small non-randomized studies demonstrating the safety of cinacalcet in tHPT, with gastrointestinal intolerance being the most common side effect[20].

Before the introduction of cinacalcet, the only treatment option for patients with tertiary HPT was (PTx)[21]. This surgical procedure involves either subtotal parathyroidectomy or total parathyroidectomy (with or without auto-transplantation), both which are effec-

tive and safe procedures[22,23]. In secondary HPT, PTx was even associated with a lower risk of major cardiovascular events after surgery[24].

The effect of cinacalcet on cardiovascular morbidity and mortality has recently been studied in the EVOLVE trial[25]. This study in dialysis patients demonstrated that treatment with cinacalcet does not reduce the risk of major cardiovascular events or death. In an additional meta-analysis of randomized controlled trials cinacalcet did not improve overall survival in dialysis patients[26]. Consequently, the Australian Government stopped the reimbursement of cinacalcet[27].

The only randomized controlled trial comparing the effects of PTx and cinacalcet in the treatment of tertiary HPT included 30 patients concluded that 66% of patients treated with cinacalcet achieved normocalcaemia compared to 100% after PTx[28]. As this is the only trial, albeit with a small sample size, comparing these treatment modalities, additional studies with larger cohorts are warranted. Therefore, today the optimal management of tHPT remains unclear. In this study the outcomes of treatment with PTx or cinacalcet for tertiary HPT were compared in a larger cohort of patients from two academic centers.

METHODS

Study population

All patients who underwent a first KT at one of the 2 participating university medical centers between 1994 and 2015 and had a history of PTx or calcimimetic use, both before or after KT, were included in a large cohort and their demographic and clinical data were stored in a central database. This study was approved by the institutional review boards of all participating centers

Inclusion criteria for this study were tertiary HPT, age ≥ 18 years at time of KT and the availability of calcium and serum PTH concentrations after KT. Tertiary HPT was defined as the need for PTx after KT or the (continued) need of cinacalcet treatment at month 12 after kidney transplantation. Patients with previous parathyroid surgery were excluded. From this database 2 groups were identified. Group 1 (cinacalcet group) consisted of patients who received treatment with cinacalcet at 12 months after their 1st KT without a history of PTx. Group 2 (PTx group) consisted of patients who underwent a PTx within three years of their 1st KT. Outcomes of the PTx group in the first year after KT are presented for patients who had not undergone PTx at the set time points.

Primary outcomes were serum calcium and PTH concentration one year after KT and one year after PTx. Secondary outcomes were the use of co-medication (calcium supplementation, vitamin D supplementation, cinacalcet) after KT and PTx, as well as complications after KT and PTx.

Data collection

Electronic patient files were reviewed for patient data. Baseline characteristics were gender, age, primary kidney disease, type and duration of dialysis, medication use and relevant co-morbidity (e.g. diabetes mellitus and cardiovascular disease).

KT data included donor type and age, ischemia times, complications graded by the Clavien-Dindo scale[29], delayed graft function (defined as the need for dialysis in first week after KT), primary non-function, biochemical parameters until 5 years after KT (calcium, phosphate, albumin, creatinine, alkaline phosphatase and PTH) and medication use after KT (calcium or vitamin D supplementation, phosphate binders and calcimimetics). Data on the use of diuretics were not systematically collected.

PTx data included type of the surgical procedure (total or subtotal), complication rate, imaging before PTx, laboratory data before PTx until 5 years after PTx (calcium, phosphate, albumin, creatinine, alkaline phosphatase and PTH) and medication use after PTx (calcium or vitamin D supplementation, phosphate binders and calcimimetics).

Serum calcium concentrations were adjusted for albumin according to the following formula: adjusted total calcium (mmol/L) = measured calcium (mmol/l) + (0.025 * (40 – [albumin (g/L)])). The reference value for calcium was 2.20 – 2.60 mmol/L. Reference value for PTH was 1.4 – 7.3 pmol/L. PTH values were measured with the Vitros ECi assay (Ortho diagnostics) and with the Roche Cobas assay (Roche). Reference values for creatinine were 65 – 115 umol/L for male patients and 55 – 90 umol/L for female patients. Persistent postoperative hypocalcemia was defined as the need for calcium supplementation 6 months after PTx.

Statistical Analysis

Distribution was assessed using the Shapiro-Wilk normality test. Continuous variables are presented as median with interquartile range, and categorical variables were described as count (*n*) and percentage (%). Differences between the two groups were analyzed using the Mann-Whitney U test for continuous variables and the Pearson Chi-square or Fisher's exact test for nominal variables. The Wilcoxon signed ranks test was used to compare the differences between time points. Statistical analysis was performed using IBM SPSS Statistics 21 software (IBM Corp., Chicago, IL, USA).

RESULTS

Study Population

A total of 277 patients were included in our database. A total of 94 patients were included in this study based on the before mentioned in and exclusion criteria. Thirty patients were included in the PTx group whereas 64 patients were included in the cinacalcet group. A flowchart of patient selection is listed in figure 1.

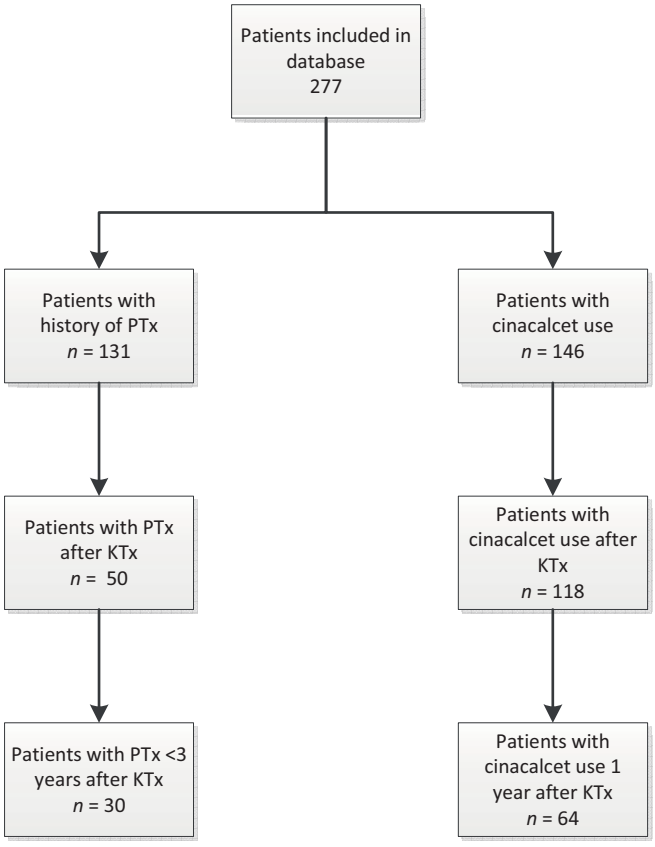

Figure 1. Flowchart of patient selection

Baseline characteristics

Patient characteristics at the time of KT are listed in Table 1. Median age of all patients at time of KT was 56.0 years (45.8 – 62.0). The median age of PTx patients at time of transplantation was lower (52.5 years (35.8 – 57.3)) compared with patients using calcimimetics (59.0 years (50.0 – 64.0)). The median duration of dialysis before KT was 42.5

months (21.0 – 63.0), 43.6% of patients were female and 25.5% of patients had a history of diabetes mellitus. At the time of KT, 81.3% of patients received phosphate binders, 66.0% received vitamin D supplements, 23.3% received calcium supplementation and 45.7% received calcimimetics. Of all KT, 55.3% was performed with a deceased donor kidney. Delayed graft function occurred in 27.7% of patients.

Table 1. Baseline characteristics

Characteristic	Cinacalcet group	PTx group	*p*-Value
No. of patients	64	30	
Age at start dialysis (years)	53.5 (45.3 – 61.8)	49.5 (32.8 – 55.8)	0.034
Sex (female)	27 (42.2)	14 (46.7)	NS
Charlson score	3 (2-5)	3 (2-4)	NS
Dialysis type			NS
- No dialysis	12 (18.8)	2 (6.7)	
- Peritoneal dialysis	19 (29.7)	11 (36.7)	
- Hemodialysis shunt	29 (45.3)	15 (50.0)	
- Hemodialysis line	4 (6.3)	2 (6.7)	
Duration of dialysis (months)	42.5 (21.3 – 67.5)	42.5 (18-54.8)	NS
History of diabetes	15 (23.4)	9 (30.0)	NS
Use of medication before KT			
- Vitamin D	47 (74.6)	15 (53.6)	NS
- Phosphate binders	52 (82.5)	22 (78.6)	NS
- Calcium suppletion	12 (19)	9 (32.1)	NS
- Cinacalcet	38 (60.3)	5 (17.2)	<0.001
Transplant characteristics			
Age at transplantation (years)	59.0 (50.0 – 64.0)	52.5 (35.8 – 57.3)	0.034
Donor type			NS
- DCD	17 (26.6)	8 (26.7)	
- DBD	18 (28.1)	9 (30.0)	
- LR	13 (20.3)	6 (20.0)	
- LUR	16 (25.0)	7 (23.3)	
Complications			NS
- Grade 2	16 (25.0)	9 (30.0)	
- Grade 3	6 (9.4)	6 (20)	
Delayed graft function	19 (29.7)	7 (23.3)	NS
Primary non function	0 (0)	2 (6.7)	NS
Cold-ischemia time (hours)	15 (12 – 19.8)	21 (16 – 24)	0.023
Warm-ischemia time (minutes)	23.5 (18 – 32)	29 (22 – 35)	0.048

Data are expressed as median (interquartile range) or *n* (%)
PTx: Parathyroidectomy

Outcomes after kidney transplantation

Pre- and post-operative laboratory values before and after KT are listed in table 2. Serum calcium concentrations were higher in the PTx group preoperatively (2.51 vs 2.42 mmol/L). There was a significant increase in serum calcium concentrations at 3 months after transplantation in both groups (cinacalcet group: p = 0.002; PTx group: p = 0.001) but this did not persist after 6 months in the cinacalcet group (p = 0.148). PTx patients not yet operated in the first post-transplant year remained hypercalcemic during the first post-transplant year. Calcium concentrations in the PTx group were higher at all time points, with a median calcium of 2.76 one year after transplantation (p < 0.001).

Table 2. KT outcomes

	Group 1 (cinacalcet)	Group 2 (PTx)	*p*-value	Number at risk PTx
N	64	30		
Corrected calcium, mmol/L				
- Pre-transplantation	2.42 (2.23 – 2.54)	2.51 (2.33 – 2.69)	0.030	30
- 3 months	2.50 (2.36 – 2.63)	2.84 (2.64 – 2.90)	<0.001	30
- 6 months	2.44 (2.34 – 2.59)	2.79 (2.65 – 2.85)	<0.001	25
- 1 year	2.40 (2.23 – 2.49)	2.76 (2.56 – 2.90)	<0.001	18
PTH, pmol/L				
- Pre-transplantation	54.4 (29.7 – 91.0)	90.0 (61.4 – 156.4)	0.013	30
- 3 months	22.7 (14.0 – 32.7)	34.3 (25.3 – 80.3)	0.007	30
- 6 months	18.2 (14.0 – 27.9)	26.3 (16.3 – 55.1)	0.056	25
- 1 year	22.0 (13.7 – 33.1)	29.8 (15.3 – 57.1)	NS	18
Creatinine, µmmol/L				
- 3 months	119 (103 – 163)	126 (112 – 179)	NS	30
- 6 months	125 (100 – 164)	118 (100 – 142)	NS	25
- 1 year	122 (101 – 161)	127 (102 – 173)	NS	18
Use of Vitamin D				
- Pre-transplantation	47 (74.6)	15 (53.6)	NS	30
- 3 months	15 (26.8)	3 (10.3)	NS	30
- 6 months	9 (15.8)	2 (8.3)	NS	25
- 1 year	9 (14.1)	2 (11.1)	NS	18
Use of Cinacalcet				
- Pre-transplantation	38 (60.3)	5 (17.2)	<0.001	30
- 3 months	38 (67.9)	2 (6.9)	<0.001	30
- 6 months	50 (87.7)	3 (12.5)	<0.001	25
- 1 year	64 (100)	3 (17.6)	<0.001	18

Data are expressed as median (interquartile range) or *n* (%)
PTx: Parathyroidectomy

Median PTH concentrations were significantly higher in the PTx group before KT (90.0 vs 54.4 pmol/L, p = 0.013) and 3 months after transplantation (34.3 vs 22.7 pmol/L, p = 0.007). Both groups showed a decline in serum PTH concentrations after kidney transplantation. In the PTx group this was statistically significant at 6 months after transplantation (p = 0.012), but this was not observed at 1 year post transplantation. In the cinacalcet group here was a statistically significant decline of PTH concentrations after KT at all time points (p = < 0.001 at all time points). In the PTx group 10.3% of patients used cinacalcet 1 year after transplantation. In total, 34.5% of patients in the PTx group used vitamin D analogs 1 year after transplantation, whereas 14.1% of patients in the cinacalcet group used vitamin D analogs.

Parathyroidectomy

Characteristics of the patients who underwent PTx are listed in table 3. Median age at time of PTx was 54.5 years, 66.7% of patients were classified as ASA III. Twelve patients (40%) underwent a PTx in the first year and 18 underwent (60%) PTx in the second or third year after KT. Subtotal parathyroidectomy was performed in 83.3% of patients. Re-exploration due to persistent tHPT was performed in 3 (10%) patients. Two patients required a second operation within the first postoperative month and one 10 months after initial surgery due to persistent HPT. There were no recurrent laryngeal nerve injuries, no postoperative cardiovascular events and there was no postoperative mortality. Postoperative hypocalcemia was apparent in 40% of patients.

Laboratory values before and after PTx are listed in table 4. Serum calcium concentrations declined significantly after PTx, no patients were hypercalcaemic one year after PTx. PTH concentrations declined significantly after PTx and were in the reference range. Vitamin D analogs were used in 42.9% of patients 1 year after PTx. One patient used cinacalcet (3.6%) after PTx. A total of 40% of patients used calcium supplementation at 6 months after surgery.

DISCUSSION

This study describes a cohort of patients treated for tHPT, either by PTx or cinacalcet. After PTx patients were normocalcaemic and PTH concentrations normalized. Treatment with cinacalcet resulted in normocalcaemia but not in normalization of PTH concentrations. After kidney transplantation the PTH concentrations declined in both groups, but were higher in the group of patients that would still undergo PTx. Median PTH concentrations in both groups remained above the upper limit of normal (7.3 pmol/L) up to 12 months after transplantation. In the cinacalcet group the serum calcium concentrations

Table 3. PTx characteristics

Characteristic	PTx group
Age at parathyroidectomy (years)	54.5 (36.8 – 59.3)
ASA classification	
- II	10 (33.3)
- III	20 (66.7)
Pre-operative imaging	
- No imaging	18 (62.1)
- Ultrasound	4 (13.8)
- MIBI-scan	3 (10.3)
- Ultrasound and MIBI-scan	4 (13.8)
Type of PTx	
- Total parathyroidectomy	3 (10.0)
- Subtotal parathyroidectomy	25 (83.3)
- Other	2 (6.7)
Complications	
- Postoperative hypocalcaemia	12 (40)
- Recurrent laryngeal nerve damage	0 (0)
- Surgical site infection	1 (3.3)
- Pneumonia	1 (3.3)
- ICU admission	1 (3.3)
- Mortality	0 (0)
- Re-exploration	3 (10)
Weight of parathyroid glands (grams)	1.9 (1.2 – 3.0)

Data are expressed as median (interquartile range) or *n* (%)
PTx: Parathyroidectomy

remained normal, whereas patients who would undergo PTx became hypercalcemic. After parathyroidectomy both serum calcium concentrations and PTH concentrations were in the normal range.

These findings raise questions about the efficacy of off-label use of cinacalcet in the treatment of tertiary hyperparathyroidism. Adequate control of PTH in the post-transplant period is paramount given the increased risk of allograft dysfunction, allograft loss[13,14], all-cause mortality[30], fractures and osteoporosis[15,16]. These reservations concerning the treatment of tHPT with cinacalcet are also supported by a study of Cruzado and colleagues[28].

Patients with ESRD are fragile as shown from high ASA-scores, and it is therefore understandable that there is some reluctance to refer patients for surgical treatment[31]. Still, in

Table 4. PTx Outcomes

	PTx group	*p*-Value^
Corrected calcium, mmol-L		
- Pre-operative	2.76 (2.62 – 3.04)	
- 3 months	2.30 (2.23 – 2.43)	<0.001
- 6 months	2.31 (2.16 – 2.37)	<0.001
- 1 year	2.34 (2.14 – 2.41)	<0.001
PTH, pmol/L		
- Pre-operative	35.5 (20.3 – 62.8)	
- 3 months	9.0 (4.7 – 20.8)	0.001
- 6 months	9.5 (3.3 – 22.6)	0.009
- 1 year	3.7 (1.2 – 9.3)	0.012
Creatinine, µmmol/L		
- Pre-operative	122 (104 – 173)	NS
- 3 months	141 (107 – 177)	0.015
- 6 months	147 (121 – 214)	NS
- 1 year	140 (107 – 214)	NS
Use of Vitamin D		
- 3 months	14 (50.0)	
- 6 months	15 (53.6)	
- 1 year	12 (42.9)	
Use of Cinacalcet		
- 3 months	1 (3.6)	
- 6 months	1 (3.6)	
- 1 year	1 (3.6)	

Data are expressed as median (interquartile range) or *n* (%)
^ *p*-value: compared with pre-operative measurements
PTx: Parathyroidectomy

this study surgical complications after PTx were rare. Cardiovascular events and recurrent laryngeal nerve injuries did not occur and only one patient developed pneumonia. This is comparable with the results of another large Dutch study[31]. The rate of postoperative hypocalcaemia in this study was 40% at six months. This was higher than expected in view of results from older studies[32,33]. However, patients in our PTx group were mainly hypercalcemic patients, who more frequently have hungry bone syndrome and require longer calcium supplementation. Overall, PTx is a safe procedure, even in this fragile population[22,31,33,34].

In our study, both total and subtotal parathyroidectomies were performed, which are both safe and effective procedures[23]. A randomized controlled trial comparing these

procedures in sHPT found similar results for both techniques with a slightly higher rate of recurrence after subtotal parathyroidectomy[32]. Such a study has not been performed for tHPT[35]. However, favorable results have been reported concerning subtotal parathyroidectomy for tHPT, albeit not in an RCT[22,28]. Considering that the underlying metabolic disorders responsible for the occurrence of HPT have been corrected after successful transplantation, we prefer subtotal parathyroidectomy. This procedure is associated with a lower risk of postoperative hypocalcemia and persistent hypoparathyroidism whilst recurrences are unlikely due to the metabolic changes.

This study was not designed to evaluate cost-effectiveness and therefore we cannot report on this. To date, no studies evaluating cost-effectiveness in tertiary HPT have been published. However, for sHPT is was demonstrated that uncontrolled HPT increases the economic burden due to higher medication and hospitalization costs[36], and PTx is more cost-effective than treatment with cinacalcet after 15 months of treatment[37]. Considering the increasing survival of kidney transplant patients, one could assume PTx to be even more cost-effective in patients with tHPT, especially when considering that in dialysis patients the cinacalcet costs for one QALY exceed $ 100,000[38].

Some limitations of this study should to be addressed. First, the retrospective design makes this study susceptible to bias as demonstrated by the difference at baseline between our groups. There is no clear guideline on indications for PTx, so indications may differ between participating centers. The PTx group was younger and had higher PTH levels at baseline. But though the baseline PTH levels were higher in the PTx group, the effect was more profound than compared with the cinacalcet group.

Second, in the Netherlands KT patients are followed in the transplant center in the first year after transplantation. If uneventful, follow-up will then be performed at the referring hospital, with only annual follow-up at the transplant center. Thus some outcome data after the first post-transplant year was incomplete. Only the short-term outcomes of the first post-transplant year have therefore been reported.

Third, outcomes in this study are primarily of biochemical nature. Comparison of clinical outcome parameters (e.g. cardiovascular disease or bone mineral density values and fracture risks) was not possible due to lack of BMD measurements and lack of follow-up at our centers.

A minority of patients in our cohort received vitamin D supplementation, recommended in the KDIGO guideline CKD-MBD as a first line treatment for HPT since 2003[6]. However, our cohort encompasses over 20 years of treatment, including the years up to 2003.

This is not applicable for the group of patients treated with cinacalcet, as cinacalcet was registered after the first KDIGO guideline. This under treatment with vitamin D might have resulted in overtreatment with cinacalcet in the cinacalcet group.

Lastly, in the present study side effects of cinacalcet were not reported. These outcomes are often not reported in patient charts, although reporting has been reliable in the EVOLVE trial. In this RCT 46% of the subjects reported side-effects and 18.1% of patients discontinued the treatment[25]. In other studies with cinacalcet, the rate of side effects was unfortunately not reported[39,40].

In conclusion, treatment with cinacalcet in patients with tHPT normalized serum calcium concentrations , but did not lead to normalization of PTH concentration. After parathyroidectomy both calcium and PTH normalized in the PTx group. Due to the heterogeneity of the two study groups and the retrospective design of this study, definitive recommendations for daily practice cannot be made. Given the effects of high PTH concentrations on renal allograft survival we favour PTx in all patients with tHPT. Future prospective randomized studies with long term follow-up are needed to define the role of surgery in patients with tHPT considering clinical outcomes and economic benefits.

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Chapter 8

Undetectable postoperative parathyroid hormone levels predict long term hypoparathyroidism after total thyroidectomy

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In preparation

ABSTRACT

Introduction

Surgical treatment of both benign and malignant thyroid diseases often necessitates total thyroidectomy. This procedure is considered safe, but has some specific postoperative complications such as hypoparathyroidism. This recovers in 90-95% of the patients, but the remaining patients require lifelong calcium supplementation. It is not yet possible to predict in which patient hypoparathyroidism will recover. Identification of high risk patients for persistent hypoparathyroidism can tailor treatment of individual patients. In this study we explore whether PTH levels measured within 24 hours after surgery are able to identify patients with a high risk for persistent hypoparathyroidism 1 year after thyroidectomy.

Methods

This is a prospective multicentre study, where patients undergoing total or completion thyroidectomy are included. PTH levels are measured on the day of surgery and on the first postoperative day. Patients with unmeasurable PTH levels postoperatively (PTH-UM) were compared to those with measurable PTH levels (PTH-M).

Results

A total of 110 patients are included of which PTH levels on the first postoperative day were available in 100 patients. Group PTH-UM consisted of 16 patients, group PTH-M of 84. Persistent hypoparathyroidism occurred in 60% and 10.4% of patients in group PTH-UM and PTH-M, respectively. This is a statistically significant difference. Patients with persistent hypoparathyroidism more frequently underwent a cervical lymph node dissection and had a longer hospital stay. A PTH level under the limit of detection on the first postoperative day is an risk factor for persistent hypoparathyroidism, with an odds ratio of 13,8.

Conclusion

A postoperative PTH level under the limit of detection on the first day after total or completion thyroidectomy is a predictive factor for persistent hypoparathyroidism.

INTRODUCTION

Surgical treatment of both benign and malignant thyroid diseases often necessitates total thyroidectomy. This procedure is considered safe, but has some specific postoperative complications such as hypoparathyroidism. In this situation, parathyroid glands are unable to maintain calcium homeostasis due to no or insufficient parathyroid hormone secretion. This can be due to surgery related factors such as inadvertent devascularisation, bruising or accidental removal of one or more parathyroid glands. Clinical signs of hypocalcaemia are perioral numbness, paraesthesia and muscle cramps. Severe hypocalcaemia can cause seizures, spasms and cardiac arrhythmias. Patients are therefore routinely monitored for clinical signs and symptoms of hypocalcaemia and serum calcium levels are measured at set times. Postoperative hypocalcaemia is treated with oral or intravenous calcium supplementation, and in some cases additional vitamin D supplementation[1]. In most cases parathyroid function will recover within weeks and calcium levels will normalize[2,3].However, up to 5 - 10% of the patients develop persistent hypoparathyroidism (defined as persistent need for calcium supplementation 1 year after surgery) and require lifelong calcium supplementation[4,5]. This number may even be higher, when considering the survey performed by the Thyroid Cancer Alliance[6]. The rate of persistent hypoparathyroidism in this survey was 13,8%. The risk for persistent hypoparathyroidism may be higher than generally published.

Persistent hypoparathyroidism impairs quality of life[7] of an otherwise relatively healthy population and poses a burden of disease[8]. Therefore, early identification of high risk patients allows clinicians not only to inform patients, but also schedule personalised postoperative outpatient follow-up visits. Patient with low risk for persistent hypoparathyroidism can be offered less visits and blood withdrawals and early reduction of calcium supplementation, being favourable from both patient and costs-effectiveness perspective. Current predictive factors for (persistent) hypoparathyroidism include perioperative calcium and parathyroid hormone (PTH) levels as well as surgical factors[9,10]. Serum PTH concentration obtained 4-24 hours postoperatively is currently the best parameter to predict direct postoperative hypocalcaemia[11-15]. However, evidence to predict persistent hypoparathyroidism is scarce. Nowadays, to our knowledge, the only known determinant for persistent hypoparathyroidism is an undetectable PTH level one month after surgery[3]. It is the ambition of this study to assess whether postoperative PTH levels obtained within 24 hours after surgery are able to predict the risk for persistent hypoparathyroidism. In this prospective multi-centre study we explored whether PTH levels measured within 24 hours after surgery are able to identify patients with a high risk for persistent hypoparathyroidism 1 year after thyroidectomy.

METHODS

This prospective study includes patients of 18 years and older undergoing a total thyroidectomy or a completion thyroidectomy. Patients are recruited at one university medical centre (Erasmus MC, Rotterdam) and one peripheral hospital (Reinier de Graaf Gasthuis, Delft). Recruitment took place from March 2014 until March 2016. Approval is obtained from the local Medical Ethical committee.

Exclusion criteria are: unable or unwilling to provide informed consent and pre-operative disorders in calcium homeostasis. Patients undergoing concurrent cervical lymph node dissection during thyroidectomy are not excluded. General data such as gender, age, preoperative diagnosis and baseline blood values are obtained at the outpatient clinic. Following surgery patient's blood is sampled around 18:00 PM on day of surgery and around 08:00 AM on the first postoperative day. Values assessed are: calcium, albumin, phosphate and PTH levels. Primary outcome measurement for the analysis is the PTH level the morning after surgery. This enables relatively easy implementation in daily practice and is shown to accurately predict direct postoperative hypocalcaemia[2,16]. Standard study follow-up including laboratory screening is performed at two weeks and one year postoperatively. Other outpatient visits are scheduled according to the discretion of the treating medical specialist.

Serum calcium levels are adjusted for albumin levels according to the formula: adjusted total calcium (mmol/L) = measured calcium (mmol/L) + (0.025 * 40 – [albumin (g/L)])). The reference interval for calcium is 2.20 – 2.65 mmol/L. The reference interval for PTH is 1.4 – 7.3 pmol/L. Hypocalcaemia is treated according to the local calcium supplementation protocol with calcium carbonate and alfacalcidol. A corrected calcium level lower than 2.20 mmol/L warrants calcium supplementation and a persistent hypocalcemia after two days warrants supplementation with active vitamin D.

To assess which change in PTH levels is clinically relevant we used the continuously updated data for clinically important quantities by Ricos et al[17]. The index of individuality for PTH (ratio of the intra- and inter- individual biological variation coefficients) is 0.4 and therefore the reference interval is not well suited to interpret clinical changes in PTH levels. The reference change value for PTH (an objective tool for assessment of the significance of differences in serial results from an individual based on intra-individual biological and methodological variation coefficient), one-sided with 95% probability and statistical power > 0.9 is 100%. Therefore, all patients in this study with a serial PTH level change of ≥100% (PTH below the limit of detection) are named group "PTH-UM", the others group "PTH-M". In other words, only undetectable PTH levels may be con-

sidered to represent true changes of PTH levels and not represent biological variations within the individual.

Primary outcome of the study is the difference in proportion of patients with persistent hypoparathyroidism when comparing the group with unmeasurable PTH levels postoperatively (group "PTH-UM") versus measurable PTH levels (group "PTH-M"). Secondary outcomes are direct postoperative PTH kinetics, calcium and vitamin D supplementation percentages and risk factors for persistent hypoparathyroidism.

Statistical analysis

Sample size was estimated a priori using G*Power software (University of Kiel, Germany, Version 3.1), using an alpha of 0.05 and a power of 0.96. At least 12 patients with persistent hypoparathyroidism ("the cases") are required. Assuming a case percentage rate of around 10% in our study population and approximately 70 eligible patients per year, we set the first accrual period on 2 years. Inclusion would continue during the year of follow-up of this cohort. If the "12 case scenario" is not met, patients included in this extra year will be included in the study and follow-up in continued another year. If the "12 case scenario" is met, these patients are not included in the study. Data were assessed for near-Gaussian distribution using the Shapiro-Wilk test and for equal distributions using the Kolmogorov-Smirnov test. Descriptives were used to express continuous variables as mean ± SD or median with interquartile range, categorical variables were described as counts (*n*) and percentages (%). Differences between groups were analysed using the independent samples Welch's t-test or the Wilcoxon-Mann-Whitney test for continuous variables and the Pearson Chi-squared rest or Fisher's exact test for categorical variables. Two-tailed p-values < 0.05 were considered statistically significant. Univariate and multivariate logistic regression analyses were performed. Statistical analyses were performed using SPSS (IBM, version 21) software.

RESULTS

Study population and baseline characteristics

A total of 110 patients were included in this study between April 2014 and April 2016 out of 172 patients assessed for eligibility (Figure 1). An additional 36 patients were included after this period, but where excluded from this study after meeting the primary number of cases required in the power analysis. The primary outcome parameter (PTH value obtained around 08:00 AM the day after surgery) was available for 100 patients. This cohort is used for the analysis of the primary outcome. All other analyses are performed with the complete cohort of 110 patients, unless otherwise specified. Baseline

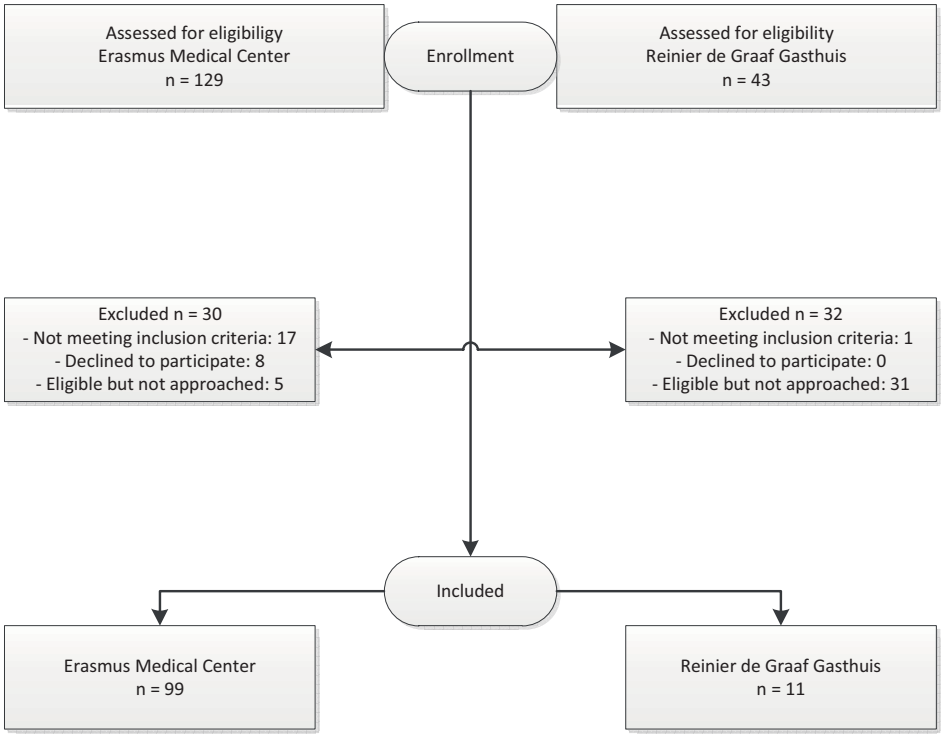

Figure 1. Flowchart of patient selection

characteristics of the total study cohort are listed in Table 1. A total of 72% of patients is female, 24% of all patients underwent a completion thyroidectomy, 33% underwent a concomitant cervical lymph node dissection. Of this cohort, 41% was treated for benign thyroid disease, Graves disease in 13.6% of patients, 20.0% for multinodular goiter, and 7.3% for other indications.

Unmeasurable PTH levels and risk of persistent hypoparathyroidism (n=100)

Sixteen patients have PTH levels under the limit of detection on the first postoperative day (group PTH-UM) The other 84 patients have PTH levels above the limit of detection (group PTH-M). Baseline characteristics are summarized in Table 2. There were no statistical significant differences at baseline between groups PTH-UM and PTH-M.

Patients in group PTH-UM had significantly lower postoperative corrected serum calcium levels when compared to PTH-M patients (2.06 vs 2.14 mmol/L, p = 0.033). By definition, PTH levels in the PTH-UM group where not detectable, whereas median postoperative day 1 PTH levels in group PTH-M are 2.05 pmol/L (range: 0.4 – 5.1 pmol/L, reference interval 1.4 – 7.3 pmol/L). The percentage of patients with persistent hypoparathyroidism was 60% in group PTH-UM versus 10.4% in group PTH-M (Figure 2). This is a statistically

Table 1. Baseline characteristics

Characteristic	Total cohort n = 110
Age (median 25/75)	53.5 (39.8-66.0)
Female (n + %)	79 (71.8%)
ASA-classification	1 –27 (24.5%)
	2 – 74 (67.3%)
	3 – 9 (8.2%)
Calcium preoperative (mean +/ SD)	2.26 (± 0.08)
PTH preoperative (median 25/75)	4.6 (3.5-5.5)
Vit D preoperative (median 25/75)	49 (32-68)
Surgical procedure	
Total thyroidectomy	86 (78.2%)
Completion thyroidectomy	24 (21.8%)
CLND	36 (32.7%)
CCLND	35 (32.7%)
LLCLND	13 (11.8%)
RLCLND	18 (16.4%)
Benign disease	45 (40.9%)

Cervical lymph node dissection = CLND
CCLND = central CLND (level VI)
LLCLND = Left lateral CLND (level II-IV)
RLCLND = Right lateral CLND (level II-IV)

significant difference (p-value < 0.001). In the multivariate analysis, a PTH level under the limit of detection on the first postoperative day is an independent risk factor for persistent hypoparathyroidism, with an odds ratio of 13,8 (95% confidence interval 3.4 – 55.4). A postoperative PTH level under the limit of detection at the day of surgery was also an independent risk factor for persistent hypoparathyroidism, with an odds ratio of 10.8(95% confidence interval 2.4 – 49.8).

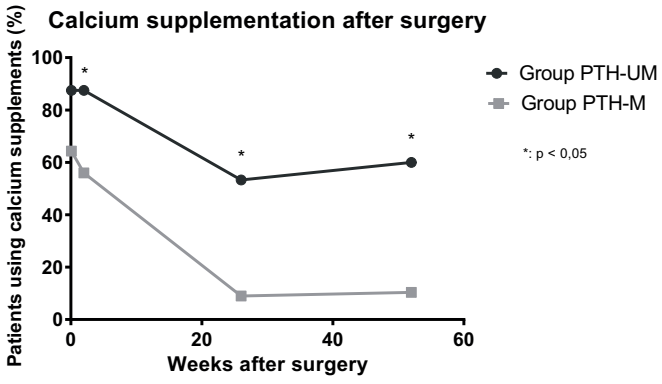

Figure 2. Calcium supplementation after thyroidectomy

Table 2. Baseline characteristics

Characteristic	PTH-UM n=16	PTH-M n=84	*p*
Age (median 25/75)	56.5 (45.8-65.0)	53.0 (35.8-65.8)	NS
Female (n + %)	9 (56%)	63 (75%)	NS
ASA-classification	1 – 3 (18.8%)	1 – 23 (27.4%)	NS
	2 – 12 (75.0%)	2 – 55 (65.6%)	
	3 – 1 (6.3%)	3 – 6 (7.1%)	
Calcium preoperative (mean +/ SD)	2.28 (± 0.09)	2.25 (± 0.08)	NS
PTH preoperative (median 25/75)	5.1 (3.4-6.0)	4.6 (3.5-5.6)	NS
Vit D preoperative (median 25/75)	56 (43-73)	48 (30-67)	NS
Surgical procedure			
Total thyroidectomy	13 (81.3%)	65 (77.4%)	NS
Completion thyroidectomy	3 (18.8%)	19(22.6%)	NS
CLND	8 (50.0%)	25 (29.8%)	NS
CCLND	8 (50.0%)	24 (28.6%)	NS
LLCLND	2 (12.5%)	9 (10.7%)	NS
RLCLND	5 (31.3%)	12 (14.3%)	NS
Benign disease	7 (43.8%)	32 (38.1%)	NS

Cervical lymph node dissection = CLND
CCLND = central CLND (level VI)
LLCLND = Left lateral CLND (level II-IV)
RLCLND = Right lateral CLND (level II-IV)

Unmeasurable PTH levels and follow-up data regarding PTH kinetics and treatment for hypocalcaemia (n=100)

There were six patients in group PTH-UM (38%) that had measurable PTH levels the day of surgery and unmeasurable levels on the first postoperative day. In contrast, four patients had unmeasurable PTH levels the day of surgery, and measurable levels the day after surgery. In other words, 29% of the patients with undetectable PTH levels on the day of surgery, had detectable PTH levels within 24 hours after surgery. Of these patients 7 (50%) developed persistent hypoparathyroidism. Figure 3a shows PTH kinetics during follow-up of PTH-UM vs PTH-M groups. Both short term (2 weeks) and long term (1 year) PTH levels are significantly lower in the PTH-UM group vs the PTH-M group. Two weeks after surgery 66.7% of the PTH-UM group had measurable PTH levels, indicative of (partial) restoration of parathyroid function. Of these patients 70% were in need of calcium supplementation after 1 year. After 1 year, only 1 patient of the PTH-UM group had unmeasurable PTH levels, and was supplemented with calcium. The other 14 patients of the PTH-UM group had measurable PTH levels after 1 year, of these 8 patients (57.1%) was supplemented with calcium. Only 1 patient in the PTH-M group, had unmeasurable PTH levels 2 weeks after surgery and developed persistent hypoparathyroidism.

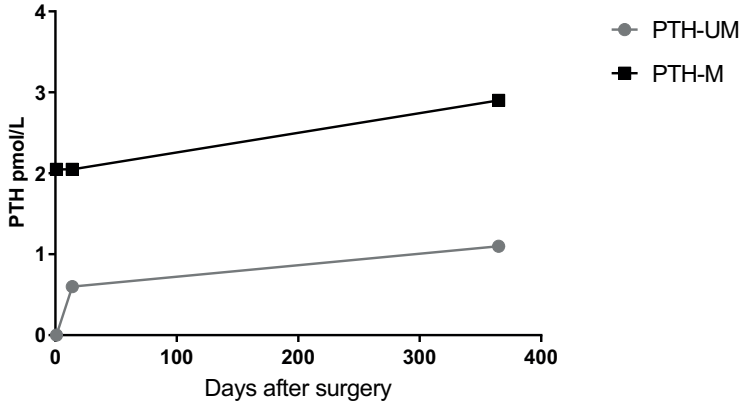

Figure 3a. Postoperative PTH levels after thyroidectomy

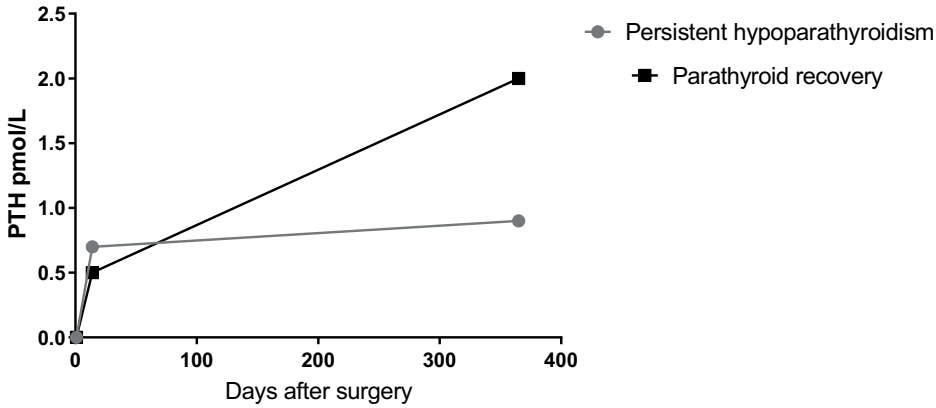

Figure 3b. PTH levels after thyroidectomt. PTH-UP group

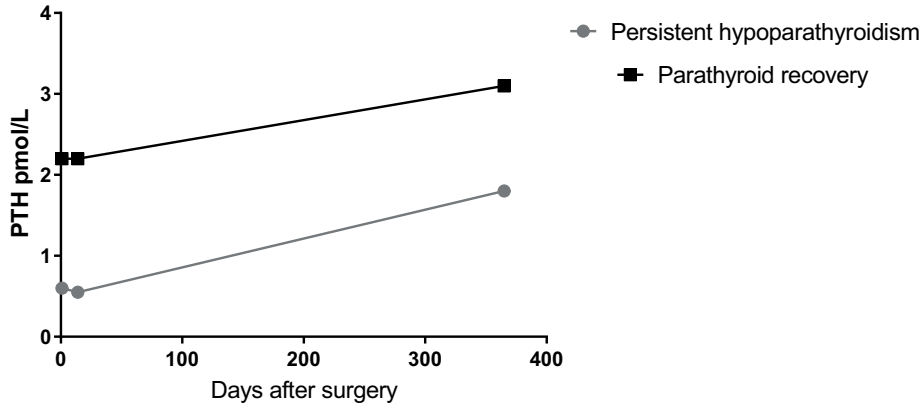

Figure 3c. PTH levels after thyroidectomy; PTH-M group

Figures 3b and 3c show PTH kinetics stratified for PTH-UM, PTH-M and need for calcium supplementation after one year. Calcium and vitamin D supplementation is summarised in Table 3. Three patients (18%) of group PTH-UM were discharged on day 2 or 3 after surgery without the need for calcium and/or vitamin D supplementation. Only 1 of them had a measurable PTH level after 2 weeks.

Tabel 3.

Day of surgery			
Characteristic	**PTH-UM n=16**	**PTH-M n=84**	*p*
- Serum calcium	2.17 (±0.13)	2.18 (± 0.10)	NS
- Serum PTH	0.00 (0.00 – 0.40)	2.10 (1.10 – 3.45)	***p < 0.001***
- Oral calcium supplementation	5 (31.3%)	15 (17.9%)	NS
- IV calcium supplementation	4 (25.0%)	13 (15.5%)	NS
First postoperative day			
Characteristic	**PTH-UM n=16**	**PTH-M n=84**	*p*
- Serum calcium	2.06 (± 0.17)	2.14 (± 0.14)	***p = 0.033***
- Serum PTH	0.00 (0.00 – 0.00)	2.05 (1.00 – 3.18)	***p < 0.001***
- Oral calcium supplementation	14 (87.5%)	54 (64.3%)	NS
- IV calcium supplementation	5 (31.3%)	13 (15.5%)	NS
- Vitamin D supplementation	7 (43.8%)	26 (31.0%)	NS
Discharge			
Characteristic	**PTH-UM n=16**	**PTH-M n=84**	*p*
- Calcium supplementation	13 (81.3%)	58 (69.0%)	NS
- Vitamin D supplementation	7 (43.8%)	26 (31%)	NS
2 after weeks surgery			
Characteristic	**PTH-UM n=16**	**PTH-M n=84**	*p*
Serum calcium (mean)	2.21 (.21)	2.28 (±0.11)	NS
Serum PTH (median)	0.60 (0.00 – 0.80)	2.05 (1.40 – 4.28)	***p < 0.001***
Calcium supplementation	14 (87.5%)	47 (56.0%)	***p = 0.024***
Vitamin D supplementation	9 (56.3%)	20 (23.8%)	***p = 0.015***
6 months after surgery			
Characteristic	**PTH-UM n=15**	**PTH-M n=77**	*p*
Serum calcium (mean)	2.11 (±0.15)	2.19 (±0.11)	***p = 0.04***
Calcium supplementation	9 (60.0%)	13 (16.7%)	***p < 0.001***
Vitamin D supplementation	8 (53.3%)	7 (9.0%)	***p < 0.001***
1 year after surgery			
Characteristic	**PTH-UM n=15**	**PTH-M n=77**	*p*
Persistent hypoparathyroidism	9 (60.0%)	8 (10.4%)	***p < 0.001***
Serum calcium (mean)	2.15 (± 0.17)	2.22 (± 0.12)	NS
Serum PTH (median)	1.1 (0.85 – 2.45)	2.9 (2.33 – 4.90)	***p < 0.001***
Calcium supplementation	9 (60%)	8 (10.4%)	***p < 0.001***
Vitamin D supplementation	8 (53.3%)	5 (6.5%)	***p < 0.001***

Total study cohort follow-up (N=102)

As mentioned earlier the total study cohort is comprised of 110 patients of which baseline characteristics are mentioned in Table 1. A total of 8 patients were excluded during follow-up, 1 patient in the PTH-M group and 7 patients in the PTH-UM group. Six patients were excluded due to additional cervical surgical procedures. The other 2 patients retracted their informed consent, and no additional study follow-up was performed after that moment.

Four patients underwent a reoperation due to postoperative hematoma (no immediate surgery due to airway compromise was necessary). Three patients had underwent total thyroidectomy, one had underwent total thyroidectomy with cervical lymph node dissection. Five patients were treated with oral antibiotics in the outpatient setting for possible wound infection, where no re-operations or interventions were needed.

Of all patients, 68% receives calcium supplementation on the first postoperative day and six start calcium supplementation after the first postoperative day. At discharge 71% of patients used calcium supplementation and 33% of patients used vitamin D supplementation. 61% received calcium supplementation at 2 weeks after surgery, 23.9% at 6 months, and 18.5% of patients required supplementation one year after surgery (= persistent hypoparathyroidism). The dosage of oral calcium supplementation one year after surgery varied from 500 to 4000 mg daily. Of all patients with persistent hypoparathyroidism PTH levels were under the lower limit of the reference interval on the first postoperative day. Of all patients with a PTH level below the lower limit of the reference interval on the first postoperative day, 60.5% of patients did not have persistent hypoparathyroidism. Patients with persistent hypoparathyroidism had a postoperative PTH < 25% of baseline value, in patients without persistent hypoparathyroidism the postoperative PTH levels were 0 – 130% of baseline value.

Multivariate analysis regarding risk factors for persistent hypoparathyroidism

Of our cohort of 110 patients follow-up data one year after surgery were available in 102 patients. A total of 18 patients (17.6%) had persistent hypoparathyroidism one year after surgery, 84 had no persistent hypoparathyroidism. Characteristics of these patients are listed in Table 4. After univariate analysis the following variables were associated with persistent hypoparathyroidism: Undergoing additional lymph node dissection, unmeasurable PTH levels on the day of surgery, need for intravenous calcium supplementation, post-operative serum calcium levels and unmeasurable PTH levels on the day after surgery. After multivariate analysis only unmeasurable PTH levels on the day of surgery and unmeasurable PTH levels on the day after surgery were independent risk factors for persistent hypoparathyroid-

Tabel 4. Baseline characteristics

Characteristic	Persistent hypoparathyroidism	No persistent hypoparathyroidism	*p*
N	18	84	
Age (median 25/75)	60 (46.5 – 69.25)	51 (38.25 – 64.75)	NS
Female (n + %)	10 (55.6%)	64 (76.2%)	NS
ASA-classification	1 – 6 (33.3%)	1 – 19 (22.6%)	NS
	2 – 11 (61.1%)	2 – 58 (69.0%)	
	3 – 1 (5.6%)	3 – 7 (8.3%)	
Calcium preoperative (mean +/ SD)	2.23 (± 0.09)	2.26 (± 0.08)	NS
PTH preoperative (median 25/75)	5.15 (3.95 – 6.13)	4.55 (3.35 – 5.30)	NS
Vit D preoperative (median 25/75)	40 (22-49)	55 (33-72)	***p = 0.040***
Surgical procedure			NS
- Total thyroidectomy	15 (83.3%)	66 (78.6%)	
- Totalizing thyroidectomy	3 (16.7%)	18 (21.4%)	
CLND	11 (61.1%)	23 (27.4%)	***p = 0.011***
CCLND	11 (61.1%)	22 (26.2%)	NS
LLCLND	3 (16.7%)	8 (9.5%)	NS
RLCLND	6 (33.3%)	11 (13.1%)	NS
Length of stay (median)	6 (4 – 9.25)	3 (3 – 4)	***p < 0.001***
Benign disease	5 (27.8%)	38 (45.2%)	NS
No complications	13 (72.2%)	78 (92.9%)	
- Rebleeding	1 (5.6%)	3 (3.6%)	
- Wound infection	2 (11.1%)	3 (3.6%)	
- Other	2 (11.1%)	1 (1.2%)	
Day of surgery			
Serum calcium	2.13 (± 0.12)	2.18 (± 0.10)	***p = 0.025***
Serum PTH	0.20 (0.00-0.60)	2.05 (1.03 – 3.30)	***p < 0.001***
Oral calcium supplementation	8 (44.4%)	13 (15.5%)	***p = 0.010***
IV calcium supplementation	8 (44.4%)	10 (11.9%)	***p = 0.003***
First postoperative day			
Serum Calcium	2.02 (± 0.12)	2.15 (± 0.14)	***p < 0.001***
Serum PTH	0.00 (0.00 – 0.60)	2.00 (1.00 – 3.10)	***p < 0.001***
Oral calcium supplementation	18 (100%)	52 (61.9%)	***p = 0.001***
IV calcium supplementation	5 (27.8%)	12 (14.3%)	NS
Vitamin D supplementation	2 (11.1%)	7 (8.3%)	NS
Discharge			
Calcium supplementation	18 (100%)	56 (66.7%)	***p =0.003***
Vitamin D supplementation	12 (66.7%)	23 (27.4%)	***p =0.002***

Tabel 4. Baseline characteristics (continued)

Characteristic	Persistent hypoparathyroidism	No persistent hypoparathyroidism	*p*
2 weeks			
Serum calcium	2.19 (± 0.21)	2.29 (± 0.15)	***p = 0.018***
Serum PTH	0.65 (0.43 – 0.88)	2.10 (1.30 – 4.30)	***p < 0.001***
Calcium supplementation	18 (100%)	44 (52.4%)	***p < 0.001***
Vitamin D supplementation	15 (83.3%)	16 (19.0%)	***p < 0.001***
6 months			
Serum calcium	2.08 (± 0.11)	2.21 (± 0.10)	***p < 0.001***
Calcium supplementation	17 (94.4%)	6 (7.2%)	***p < 0.001***
Vitamin D supplementation	14 (77.8%)	2 (2.4%)	***p < 0.001***
1 year			***p < 0.001***
Serum calcium	2.09 (± 0.14)	2.25 (± 0.10)	***p < 0.001***
Serum PTH	1.10 (0.88 – 2.48)	3.20 (2.50 – 5.60)	***p < 0.001***
Calcium supplementation	18 (100%)	0 (0%)	***p < 0.001***
Vitamin D supplementation	14 (77.8%)	0 (0%)	***p < 0.001***

CLND = Cervical lymph node dissection
CCLND = central CLND (level VI)
LLCLND = Left lateral CLND (level II-IV)
RLCLND = Right lateral CLND (level II-IV)

ism had a lower pre-operative vitamin D, with 4 patients having a vitamin D level < 30 nmol/L (indicative of severe deficiency, reference value > 50 nmol/L). There were no other pre-operative differences between the groups. A cervical lymph node dissection was performed more frequently in patients with persistent hypoparathyroidism and they had a longer hospital stay.

DISCUSSION

This study evaluates the value of PTH levels obtained the morning after total or completion thyroidectomy in predicting the risk for persistent hypoparathyroidism one year after surgery. It shows that patients with PTH levels under the limit of detection have a 60% chance of persistent hypoparathyroidism after thyroidectomy. Unmeasurable PTH levels are an independent risk factor for persistent hypoparathyroidism with an odds ratio of 13.8.

This is, to the best of our knowledge, the first study with adequate statistical power to evaluate the value of postoperative PTH levels in predicting persistent hypoparathy-

roidism after thyroidectomy, without being biased by intra-individual normal biological variations in PTH levels.

Our results are supported by other studies showing that low PTH levels are likely to predict persistent hypoparathyroidism, although one must realize that these studies are not adequately powered. Hermann et al. evaluated 402 patients undergoing a total or completion thyroidectomy[18]. Six cases (1,5%) had persistent hypoparathyroidism of which all had postoperative PTH values lower than 0.63 pmol/L, well under the lower limit of normal. In contrast, only 15% of the patients with low PTH levels developed persistent hypoparathyroidism. Due to the low number of cases, no formal statistical analysis is possible. A second study of 519 patients with 10 patients with persistent hypoparathyroidism indicates that patients with a postoperative PTH less than 0.7 pmol/L have a 19.1% risk of persistent hypoparathyroidism (calcium supplementation one year after surgery)[19]. In addition, Seo et al. show that postoperative PTH levels less than 0.5 pmol/L have a sensitivity of 73.9% and a specificity of 68.6% for predicting persistent hypoparathyroidism defined as subnormal PTH and need for calcium supplementation one year after surgery[20]. This was studied in 349 patients of which 46 (13.2%) developed persistent hypoparathyroidism. Although not adequately powered, the former studies indicate that using low but measurable PTH levels as cut-off point is more subject to bias and therefore has a lower predictive value for clinical use. The results of Sitges-Serra and colleagues support this[3]. They measured PTH levels in patients with hypocalcaemia one months after thyroidectomy. Of those with low PTH levels, 90% recovered to normal parathyroid function, compared with 62% of patients with undetectable PTH levels. Unfortunately, the study did not measure PTH levels directly after surgery so no direct comparison with our results could be made. However, it indicates the difference between low and unmeasurable PTH levels.

93.3% of our patients in the PTH-UM group had measurable PTH levels and restoration of parathyroid hormone production after one year, although clinically 60% had persistent hypoparathyroidism. This is in contrast to the results of Al-Dhahri et al . They evaluate PTH recovery by repeated PTH measured measurements in 53 patients until normalization of PTH levels or up to 6 months[21]. If PTH levels after surgery dropped by more than 88% compared with baseline measurements, the patient only had a chance of 10% of recovery PTH levels within 6 months. However, the use of calcium supplementation is not reported in this study, so the clinical implication remains unknown.

The strengths of our study are the adequately powered design, the reduced bias of biological variation in intra-individual PTH levels, the low number of lost to follow-up and the use of one hypocalcaemia treatment algorithm. Prior to describing the limitations of

our study, we would like to provide a framework in which our seemingly above average persistent hypoparathyroidism rate should be interpreted. First of all, we used a clinical definition of persistent hypoparathyroidism, namely the use of calcium supplementation one year after surgery. We are currently performing a case-by-case assessment to check whether all cases are truly in need of calcium supplementation. Until then, all the above described results are based on our current clinical endpoint. Secondly, the hypocalcaemia treatment protocol is quite defensive and warrants calcium supplementation even if calcium levels are just below normal and patients are without complaints. We are currently investigating a more liberal protocol based on the study from Cayo et al. and Raffaelli et al. who only supplement calcium in case of clinical symptoms[22,23]. This shows the influence of a strict calcium supplementation protocol on the primary endpoint. A more liberal protocol would lower the amount of patients with persistent hypoparathyroidism. Thirdly, we perceive our patient population as a selected group of patients with higher risk for postoperative hypoparathyroidism. Lastly, we question ourselves whether we really know the true incidence of persistent hypoparathyroidism. Is there a possible publication bias? Most articles report persistent hypoparathyroidism rates below 5%. However, in striking contrast, in a survey from the Thyroid Cancer Alliance[6], the rate of persistent hypoparathyroidism was reported to be around 14%. This is clearly discordant with other studies[13,19,24,25]. Differences can be explained by publication bias, differences in case mix, definitions or data registration of persistent hypoparathyroidism. For example, in our study, the definition of persistent hypoparathyroidism is not based on biochemical values, but a clinical outcome. Several patients in our cohort have a PTH level within the reference interval, but receive calcium supplementation. When adjusting our case definition to calcium supplementation one year after surgery and PTH levels below the reference value, our rate of persistent hypoparathyroidism would be 10.8%. In addition, daily calcium supplementation dosages one year after surgery vary from 500 to 4000 mg per patient per day. We could discuss whether 500 mg per day supplementation represents real persistent hypoparathyroidism. Current case-by-case analysis will provide deeper insights into our cases of hypoparathyroidism. We consider our patient selection the first limitation of the study, as extrapolation of the results to non-tertiary thyroid surgeries is debatable. Unfortunately, logistics did not allow us to fully use the inclusion potential of our participating peripheral hospital, as can be seen in Figure 1. Secondly, it would have been interesting to be able to provide details about parathyroid glands preserved during surgery or found during pathology. This is currently under investigation.

As PTH measurements on day one are able to select patients with a high risk of persistent hypoparathyroidism, especially in the setting of tertiary thyroid care, we envision the following use in clinical practice. Firstly, patients with measurable PTH levels, without

complaints of hypocalcaemia should be thoroughly informed, but not subjected to regular vena punctures or outpatient visits to check calcium homeostasis. This would presumably improve efficiency in patient care as well as costs effectiveness. In addition, patients can be provided with more detailed information regarding their personal risk for persistent hypocalcaemia. Furthermore, treatment of persistent hypoparathyroidism is based on supplementation of calcium and vitamin D. The underlying hormonal imbalance, a deficit of PTH is not targeted in this schedule. An increasing number of studies report on the use of human recombinant PTH (rhPTH) for the treatment of hypoparathyroidism. Three RCTs have used intact PTH (rh-PTH(1-84)) as a treatment of hypoparathyroidism. A decrease in the dosage of calcium and vitamin D supplementation was found, although it had no effect on quality of life[26-28]. In non-randomized cohort studies evaluating treatment with rhPTH (1-84) and the N-terminal fragment rhPTH (1-34) there was a clear effect on QoL and a reduction in supplemental calcium and vitamin D requirements[29-33]. At this moment, the long-term beneficial effects have not been evaluated in RCTs and therefore the European Society of Endocrinology discourages routine use of rhPTH[34]. This view is shared by the participants of the First International Conference on the Management on Hypoparathyroidism in 2015[35]. The approval of the first commercially available rhPTH, Natpara, by the EMA in 2017 has made it widely available for further trials. This new treatment option could render it important to adequately and early identify patients at risk for persistent hypoparathyroidism, as possible interventions might be warranted to improve quality of life.

In conclusion, we show that a PTH level under the limit of detection on the first postoperative day after total or completion thyroidectomy is a predictive factor for persistent hypoparathyroidism. These data can be used to improve efficiency of postoperative follow-up, provide patients with tailored information regarding the future and aid in early identification and selection of patients who might benefit from future PTH replacement therapy.

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Chapter 9 General discussion and future perspectives

Primary hyperparathyroidism

As has been stated in this thesis, the incidence of primary hyperparathyroidism (HPT) has been rising and is expected to rise further resulting in more parathyroidectomies being performed[1,2]. There has been a large improvement in surgical treatment of primary HPT in the last two decades. A major improvement has been the introduction of the minimally invasive parathyroidectomy (MIP) in patients with successful identification of the parathyroid adenoma. The success rate of the MIP is comparable with the bilateral neck exploration but with lower complication rates, shorter operating times and better cosmetic satisfaction[3-6]. The success of the MIP also lead to the introduction of parathyroidectomy in daycare surgery. As described in this thesis, it is safe and feasible to perform the MIP in a daycare setting. However, the success of daycare MIP depends on two important features. Patients frequently experience symptoms associated with hypocalcaemia postoperatively, even if they are normocalcemic at the time of discharge. We therefore prescribe all patients prophylactic calcium supplementation after MIP, as this has been shown to be successful in a large cohort by Vasher et al[7]. The other important feature of successful daycare surgery is adequate patient selection. In both chapter 2 and 3 of this thesis there was a strict preoperative patient selection. The criteria used (including use of anti-coagulant drugs, comorbidities, ASA classification and disease specific criteria) ensured selection of healthy patients with a high propability of successful surgery and a low chance of complications.

In patients with primary HPT, the introduction of the MIP and daycare surgery has limited the amount of surgical trauma in patients. Further improvements should therefore focus not only on the surgical procedure, but also on other factors such as anaesthesia. The MIP has been performed using local anaesthesia in several cohorts but has not been implemented in daily practice[8-12]. This could be a focus of a future study, especially with attention postoperative outcomes as nausea and vomiting.

The presentation of patients with primary HPT has changed and the majority of patients present without classic symptoms[13]. The last update of the guidelines on asymptomatic primary HPT dates from the Fourth International Workshop in 2013[14]. The recommendations for future research from both this and the Third International Workshop include further studies on neurocognitive function and other non-traditional aspects of primary HPT[15]. In this thesis it has been shown that surgical treatment of primary HPT improves Quality of Life (QoL). However, the patients in this study were all patients with indications for parathyroidectomy (PTx) according the most recent guidelines. Asymptomatic patients that do not meet the criteria for treatment were not included. QoL has been assessed for this group in 3 randomized controlled trials (RCT)[16-18]. Only the study of Ambrogini et al. showed a clear improvement in QoL in these patients after PTx. This was

also the only study where the MIP was performed, whereas the other studies used the bilateral neck exploration. Future studies in asymptomatic patients should focus on two points. The burden of disease in patients not meeting the criteria should be assessed including the effect of annual monitoring of these patients. Second, a cohort of asymptomatic patients should be randomized for monitoring and surgical treatment using all improvements in parathyroid surgery, e.g. daycare surgery, the MIP and possibly the MIP under local anaesthesia.

Secondary hyperparathyroidism

Secondary HPT remains an important problem in patients with end-stage renal disease (ESRD) and contributes to renal bone disease, cardiovascular disease and a reduced QoL[19-21]. As stated in this thesis, the treatment of secondary HPT has shifted mainly from PTx to medical treatment with cinacalcet even though there are no studies directly comparing these treatment modalities. In the recent updated guideline it is stated that medical treatment is the first line of treatment in dialysis patients with secondary HPT, with either vitamin D or calcimimetics, and PTx remains a valid treatment option if medical PTH lowering options fail[22].

A PTx in a patient with secondary HPT can mean a subtotal parathyroidectomy or a total parathyroidectomy with auto-transplantation. These procedures are both effective, without significant differences in rates of persisting of recurrent disease[23]. An advantage of PTx is the reduction on the risk of cardiovascular events and mortality[24,25]. The complication rates of PTx in patients with secondary HPT are very low, despite the fragility of dialysis patients[26].

The initial studies on cinacalcet showed very promising results, with clear improvements in serum PTH, calcium and phosphate during treatment with cinacalcet[27]. The EVOLVE trial was the first large trial to evaluate the clinical outcomes of cinacalcet, and this study did not find a reduction in the risk of death of cardiovascular events[28]. A meta-analysis of RCT's with cinacalcet confirmed this finding, and cinacalcet appears to reduce only the rate of parathyroidectomy without other beneficial effects and consequently causing patients to experience hypocalcaemia and nausea[29].

The optimal treatment of secondary HPT remains therefore unclear, and should be a major focus in future studies. To date, treatment with cinacalcet has been compared in RCT's with placebo and vitamin D but not with parathyroidectomy. A future study should therefore consist of a RCT comparing treatment with cinacalcet and PTx in dialysis patients with secondary HPT.

Recently an intravenous calcimimetic has become available (etelcalcetide, Parsabiv). Two phase III trials of Block et al. were published comparing etelcalcetide with placebo and cinacalcet[30,31]. It was concluded that etelcalcetide is not inferior to cinacalcet and superior to placebo in lowering PTH levels. Adverse effects were comparable in the cinacalcet and etelcalcetide group. Studies evaluating clinical outcomes and long term effects are not yet available. Before further clinical implementation of etelcalcetide these studies should be performed. A comparative study between etelcalcetide and parathyroidectomy should be performed only after long-term data of the efficacy and safety of etelcalcetide becomes available.

There are several options for endpoints in such a study. Important aspects of secondary HPT remain the risk of cardiovascular disease, as well as the effectiveness of treatment in reducing this risk, and renal bone disease. However, as seen in the EVOLVE trial, cardiovascular morbidity and mortality as an endpoint require very large group sizes as well as long follow-up. Renal bone disease would be very interesting as an endpoint however this would require bone biopsies in all patients. The measurement of BMD using a DEXA scan in dialysis patients does not predict fracture risk as it does in the general population and is therefore not suitable as an endpoint in a trial[22].

In recent years there has been an increasing interest in patient-reported outcome measures (PROMs) such as QoL[32]. In this thesis the effect of both PTx and cinacalcet on QoL in patients with secondary HPT was compared, and a clear effect of PTx on QoL was found. However the group of patients undergoing PTx had more severe HPT, which could increase the beneficial effect on QoL and only one study on PTx included a control group. However, QoL should be considered as primary endpoint for future studies.

Patients on dialysis are fragile with high ASA scores and represent a group of patients with complex medical problems and a high morbidity and mortality rate[26]. Attempting trials in this group of patients remains a challenge. This has been seen in the EVOLVE trial, one of the largest trials ever undertaken in a dialysis population. The investigators encountered many obstacles and challenges before completing this study. Fortunately, the EVOLVE investigators published an extensive summary of the valuable lessons learned during this study, including lessons on nonadherence, outcome selection and the effect of co-interventions[33]. Before attempting a study on the treatment of secondary hyperparathyroidism in dialysis patients, these lessons should be studied extensively as this will improve the design of a future study.

Tertiary hyperparathyroidism

Successful kidney transplantation corrects the metabolic disturbances responsible for the development of secondary HPT. After transplantation the biggest decline in serum PTH concentrations occurs in the first three months, with a more gradual decline until one year after transplantation[34,35]. A further decline after this period is unlikely, and patients with persistent elevated serum calcium and PTH levels will remain elevated without therapy. Important risk factors for the persistence of hyperparathyroidism include longer duration of dialysis and higher serum PTH, calcium and phosphorus levels at the time of transplantation[36,37].

As stated in this thesis, the first line of treatment for tertiary HPT should remain a PTx. A PTx, either a subtotal parathyroidectomy or a total parathyroidectomy, has been described in many cohort studies. The only RCT including treatment with PTx in patients with tertiary HPT showed a clear advantage in treatment with PTx[38]. A clear lack in this study is that it also focussed on biochemical parameters, and clinical outcomes were not evaluated. Considering the lesson learned from the Evolve trial, biochemical parameters only are insufficient to evaluate treatment success in hyperparathyroidism.

The use of cinacalcet in tertiary HPT has been described mainly in retrospective studies, but also in two RCT's[38,39]. The primary endpoints of these studies consisted on the effect of cinacalcet on hypercalcemia, compared with either PTx or placebo. Studies focussing primarily on the safety of cinacalcet use in transplant patients have not been performed, neither on the effect of treatment with cinacalcet on clinical outcomes in transplant patients. Considering that hyperparathyroidism in patients after kidney transplantation increases the risk of graft loss and all-cause mortality, future studies should include longer follow-up periods, focus on safety of cinacalcet in transplant patients and in addition on clinical endpoints including graft survival[40].

Another important aspect in treatment of tertiary HPT is cost-effectiveness. It is known that secondary HPT increases the use costs of medical care[41]. In these patients the use of cinacalcet also adds an additional financial burden, and surgical treatment by means of PTx is finally more cost-effective[42,43]. Given the long overall and graft survival of patients with a kidney transplant, it is likely that PTx is even more cost-effectiveness in patients with tertiary HPT. In the only study evaluating cost-effectiveness in tertiary HPT it was stated that surgical treatment is more cost-effective if treatment duration with cinacalcet reached 14 months[38]. As this is the only study, cost-effectiveness should be an endpoint in future studies on the treatment of tertiary HPT.

As tertiary HPT occurs in a cohort of patients with persistence of secondary HPT, shifts in the treatment of secondary HPT are likely to also influence the development of tertiary HPT and characteristics of patients with tertiary HPT. A study comparing PTx and cinacalcet for the treatment of tertiary HPT and focussing on clinical outcome parameters, safety of cinacalcet and cost-effectiveness should therefore be performed after such a trial has been performed in patients with secondary hyperparathyroidism.

Hypoparathyroidism

Iatrogenic hypoparathyroidism remains an important complication after thyroid surgery and can occur due to accidental removal of the parathyroid glands, bruising of the parathyroid glands or devascularisation of the parathyroid glands. The resulting hypocalcaemia is frequent directly after total or completion thyroidectomy, in this thesis 71% of patients used calcium supplementation at time of discharge. However, the parathyroid function is restored in the majority of patients, but a substantial group of patients remains dependent on calcium supplementation due to persistent hypoparathyroidism. In our cohort, 17.6% of patients were treated for persistent hypoparathyroidism one year after surgery. There is a clear discrepancy with other studies reporting rates below 5%[44-48]. Possible explanations for this discrepancy can be publication bias, differences in case mix and difference in definitions of hypoparathyroidism. However, in a large international survey among patients after thyroidectomy for thyroid carcinoma, the rate of persistent hypoparathyroidism was 13.8%, in line with a study of Seo. et al[49,50]. Given the rate in this study on patient reported outcomes, we feel there might be a large publication bias on persistent hypoparathyroidism.

As demonstrated in this thesis, it is possible to select patients with a high risk of persistent hypoparathyroidism after total or completion thyroidectomy with the use of direct post-operative PTH levels. This finding can be used as a tool for more patient tailored calcium supplementation and calcium withdrawal, and should be used as a variable in studies on restraining calcium supplementation. This may help to decrease use of calcium supplementation, decrease the amount of vena punctures and limit outpatient visits to check calcium homeostasis, thereby lowering the burden on patients. The challenge in implementing such a strategy will be selecting patients that are at either at high or low risk of persistent hypoparathyroidism, to ensure that patients with severe hypocalcaemia will not be missed or even develop complications due to hypocalcaemia.

Risk assessment for persistent hypoparathyroidism by means of post-operative PTH levels also has another possible application. There are a number of studies reporting on the use of human recombinant PTH (rhPTH) in the treatment of hypoparathyroidism, including three RCT's, but in these studies the use of rhPTH only decreases the dosage

of vitamin D and calcium supplementation, but does not lead to a cessation of supplementation[51-53]. Moreover, the use of rhPTH has not yet been evaluated for long -term outcomes, and a beneficial effect on QoL has not been found to date. Therefore further studies are warranted to assess these outcomes in patients with chronic hypoparathyroidism using rhPTH [54]. Post-operative PTH levels after surgery could adequately identify patients with a high risk of persistent hypoparathyroidism who could benefit most of rhPTH

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Chapter 10 Nederlandse samenvatting & English summary

SAMENVATTING

Hoofdstuk 1 beschrijft een algemene introductie in de calcium fosfaat as en in de verschillende vormen van bijschildklierziekten. Er zijn drie belangrijke hormonen betrokken in de calcium fosfaat as; parathormoon (PTH), calcitriol en fibroblasth growth factor 23 (FGF-23). PTH zorgt voor een stijging van het serum calcium en een daling van het serum fosfaat. Calcitriol zorgt voor een stijging van zowel het serum calcium als het fosfaat en FGF-23 zorgt voor een daling van het fosfaat.

Primaire hyperparathyreoïdie (HPT) word veroorzaakt door een aandoening van de bijschildklier, in de meerderheid van patiënten een solitair bijschildklier adenoom. Historisch gezien werden patiënten gediagnosticeerd met primaire HPT als gevolg van klassieke symptomen. De introductie van routine calcium bepalingen in screenend laboratorium onderzoek heeft geleid tot de identificatie van een groep patiënten met biochemische ziekte maar geen klinische symptomen. Dit word asymptomatische primaire hyperparathyreoïdie genoemd. Hoewel deze patiënten geen klassieke symptomen vertonen, kunnen ze ook neuro psychiatrische symptomen ervaren en kan de kwaliteit van leven (QoL) verminderd zijn. Deze neuro psychiatrische symptomen zijn geen onderdeel van de behandelcriteria van asymptomatische primaire HPT. De behandeling van primaire HPT bestaat uit chirurgische excisie van de aangedane bijschildklier(en), en heeft een 95% succes percentage. De parathyreoïdectomie (PTx) is een veilige procedure, welke ook uitgevoerd kan worden in dagbehandeling.

Secundaire HPT ontstaat als reactie op metabole stoornissen, en komt frequent voor in patiënten met chronische nierziekten. De eerste stap in de behandeling bestaat uit vitamine D suppletie en fosfaat binders. De tweede stap in de behandeling bestond historisch gezien uit PTx. In 2004 is het calcimimeticum cinacalcet geïntroduceerd, en dit heeft de PTx vervangen als de tweede stap in de behandeling van secundaire HPT. De eerste studies met cinacalcet toonden veelbelovende resultaten en het is succesvol in het verlagen van de PTH, calcium en fosfaat concentraties. Echter, in de EVOLVE trial is aangetoond dat cinacalcet het risico op cardiovasculaire events en overlijden niet verlaagd. Derhalve blijft de optimale van secundaire HPT onduidelijk, aangezien cinacalcet en PTH niet direct met elkaar zijn vergeleken.

Na niertransplantatie kan HPT blijven bestaan, ondanks een succesvolle transplantatie, en dit staat bekend als tertiaire HPT. De behandeling van tertiaire HPT is parathyreoïdectomie. Cinacalcet is niet geregistreerd voor gebruik in tertiaire HPT, maar off-label gebruik hiervan neemt toe in populariteit. Tot op heden zijn deze behandeling in slechts één studie direct vergeleken.

Hypoparathyreoïdie is een andere ziekte van de bijschildklier, en dit ontstaat regelmatig na schildklier operaties. Passagere hypoparathyreoïdie treed op tot in 60% van de patiënten na een totale of totaliserende thyreoïdectomie, en persisterende hypoparathyreoïdie treed op tot in 14% van de patiënten. De behandeling van hypoparathyreoïdie bestaat uit suppletie van calcium en actief vitamine D. Het is niet mogelijk om betrouwbaar te voorspellen in welke patiënten de functie van de bijschildklier zal herstellen, en welke patiënten persisterende hypoparathyreoïdie zullen ontwikkelen. In staat zijn om te voorspellen welke patiënten een persisterende hypoparathyreoïdie zullen ontwikkelen kan helpen de behandeling per patiënt af te stemmen. Het is onderzocht of postoperatieve PTH waarden directe postoperatieve hypocalciëmie kunnen voorspellen, echter het is niet onderzocht of postoperatieve PTH waarden kunnen voorspellen welke patiënten een persisterende hypoparathyreoïdie zullen ontwikkelen.

Hoofdstuk 2 presenteert de eerste ervaringen met de parathyreoïdectomie (PTx) in dagbehandeling. De resultaten van de eerste 20 patiënten die in dagbehandeling zijn behandeld vanwege primaire HPT worden beschreven. In dit cohort waren er geen peroperatieve complicaties. Er hebben zich 5 patiënten gemeld op de spoedeisende hulp met paresthesieën, er was echter maar 1 patiënt met een milde hypocalciëmie. We bevelen aan de chirurgische behandeling van primaire HPT te verrichten in dagbehandeling, echter schrijven we bij ontslag enkele weken profylactisch calcium suppletie voor.

In hoofstuk 3 beschrijven we de ervaring met het uitvoeren van een hemithyreoïdectomie in dagbehandeling. De veiligheid van de hemithyreoïdectomie was geanalyseerd in een retrospectief cohort van 210 patiënten die een hemithyreoïdectomie hebben ondergaan. In patiënten die potentieel geschikt waren geweest traden er geen nabloedingen op, in patiënten ongeschikt voor dagbehandeling heeft 1 patiënt nog een operatie ondergaan vanwege een nabloeding. Er werd geconcludeerd dat de hemithyreoïdectomie een veilige procedure is in geselecteerde patiënten, en de dagbehandeling strategie werd ingevoerd. We beschrijven de resultaten van de eerste 18 patiënten die een hemithyreoïdectomie in dagbehandeling hebben ondergaan. Er was 1 patiënt met een passagere stemverandering en geen andere complicaties. Er waren geen heropnames of spoedeisende hulp bezoeken. De hemithyreoïdectomie in dagbehandeling is veilig en haalbaar mits er adequate patiënt selectie plaatsvind.

Hoofdstuk 4 presenteert de resultaten van een case-control studie waarin de effecten van een PTx vanwege primaire HPT op QoL zijn geëvalueerd. In deze studie hebben we 52 patiënten die een PTx hebben ondergaan vergeleken met 49 patiënten die een hemithyreoïdectomie vanwege een benigne aandoening hebben ondergaan. De QoL was gemeten met de Short-Form 36 (SF-36) vragenlijst en een vragenlijst bestaande

uit 17 symptomen die geassocieerd zijn met primaire HPT. Patiënten met primaire HPT hadden preoperatief lagere scores op de domeinen rolbeperking (fysiek probleem) en algemene gezondheidsbeleving, alsmede als op de fysieke component score. Deze verschillen verdwenen na de operatie. Patiënten met primaire HPT lieten postoperatief een significante verbetering op alle domeinen, en dit verschil persisteerde 1 jaar postoperatief in 7 domeinen. Patiënten die een hemithyreoïdectomie ondergingen lieten alleen een verbetering op het domein mentale gezondheid; de andere domeinen lieten geen verschillen zien. Patiënten met primaire HPT hadden meer klachten van dyspepsie, polydipsie en polyurie preoperatief, dit verschil tussen de groepen verdween postoperatief. In de primaire HPT groep hadden patiënten 3 maanden na operatie minder last van moeheid, spierpijn en nycturie. Deze studie laat zien dat een PTx vanwege primaire HPT leid tot een verbetering in de QoL en er moet worden overwogen om dit als aanvulling op de huidige criteria voor de behandeling van primaire HPT op te nemen.

Hoofdstuk 5 beschrijft de resultaten van een systematisch review waarin het effect van behandeling van secundaire HPT op QoL word beschreven. Er zijn vijf artikelen gevonden waarin het effect van PTx op QoL zijn beschreven, en drie artikelen die het effect van cinacalcet op QoL beschrijven. De 5 artikelen die het effect van PTx op QoL beschrijven bestaan uit vier case series en een case-control studie. In vier studies is een significante verbetering van QoL beschreven, gemeten middels de SF-36 vragenlijst. In drie studies werd een significante verbetering van symptomen gezien gemeten middels de PAS vragenlijst en een studie beschreef een significante verbetering op drie domeinen van de VAS schaal (jeuk, gewrichtspijn en spierzwakte). De drie studies die het effect van cinacalcet beschrijven bestonden uit twee klinische trials en een cohort studie. Het gebruik van cinacalcet resulteerde niet in een verbetering van de QoL zoals gemeten bij de SF-36 vragenlijst of de EQ-5D vragenlijst. Een studie liet zien dat cinacalcet een positief effect had op vier HPT gerelateerde symptomen (droge huid, botpijnen, gewrichtspijn en geheugen problemen). Dit review laat zien dat PTx een positief heeft op QoL waar cinacalcet dit niet heeft. Deze interventies zijn niet direct met elkaar vergeleken en QoL zal een eindpunt moeten zijn in toekomstige studies.

Hoofdstuk 6 presenteert de resultaten van een systematisch review waarin de uitkomsten van chirurgische en medicamenteuze behandeling van tertiaire HPT worden vergeleken. Er zijn 47 artikelen geïncludeerd in deze studie. De uitkomsten na een PTx vanwege tertiaire HPT zijn beschreven in 14 studies. Residu ziekte was aanwezig in 0% en 1,3% van de patiënten in respectievelijk een totale parathyreoïdectomie en subtotale parathyreoïdectomie. Recidief ziekte was aanwezig in 4% en 7,6% van de patiënten. Persisterende hypoparathyreoïdie kwam voor in 0,7% van de patiënten, andere complicaties waren zeldzaam.

De uitkomsten van patiënten die zijn behandeld met cinacalcet zijn beschreven in 22 studies. Normocalciëmie is bereikt in 80.8% van de patiënten. De behandeling is in 6,4% van de patiënten gestaakt vanwege bijwerkingen.

Omdat een PTx een hoger succespercentage heeft dan medicamenteuze behandeling adviseren wij chirurgische behandeling van tertiaire HPT.

In hoofdstuk 7 zijn de uitkomsten na behandeling voor tertiaire HPT geëvalueerd in twee academische centra. Een retrospectieve evaluatie van 94 patiënten, 30 na PTx en 64 na behandeling met cinacalcet, is uitgevoerd. Een PTx corrigeerde hypercalciëmie, resulteerde in een normalisatie van PTH concentraties en had weinig complicaties. Behandeling met cinacalcet resulteerde in normocalciëmie maar PTH waarden bleven verhoogd. Gezien de effecten van hoge PTH waarden op de overleving van het nier transplantaat, geven wij de voorkeur aan een PTx in alle patiënten met tertiaire HPT.

In hoofdstuk 8 word de voorspellende waarden van PTH metingen na een thyreoïdectomie voor het ontwikkelen van persisterende hypoparathyreoïdie geëvalueerd. Er zijn 102 patiënten 1 jaar na totale of totaliserende thyreoïdectomie vervolgd. In dit cohort is 71% van de patiënten postoperatief ontslagen met calcium suppletie en ontwikkelde 17,6% een persisterende hypoparathyreoïdie. Patiënten met een postoperatieve PTH waarde onder de detectielimiet hadden een 60% kans op het ontwikkelen van een persisterende hypoparathyreoïdie, terwijl patiënten met een meetbaar PTH een 10,4% kans hadden op het ontwikkelen van persisterende hypoparathyreoïdie. Alle patiënten met een persisterende hypoparathyreoïdie hadden een PTH lager dan de referentiewaarde op de eerste postoperatieve dag. Een PTH waarde onder de detectielimiet op de eerste dag na een totale of totaliserende thyreoïdectomie is een voorspellende factor voor het ontwikkelen van persisterende hypoparathyreoïdie.

ENGLISH SUMMARY

Chapter 1 provides a general introduction in the calcium and phosphate homeostasis and the different forms of parathyroid disease. There are three important hormones involved in the calcium and phosphate homeostasis; parathyroid hormone (PTH), calcitriol and fibroblast growth factor 23 (FGF-23). PTH causes a rise in serum calcium and a fall of serum phosphate concentrations. Calcitriol causes an increase in serum calcium and phosphate concentrations and FGF-23 causes serum phosphate concentrations to decrease.

Primary hyperparathyroidism (HPT) is caused due to an ailment of the parathyroid, in the majority of patients due to a single parathyroid adenoma. Historically patients were diagnosed with primary HPT due to classical symptoms. The introduction of routine calcium measurements in biochemical screening has led identification of a group of patients with biochemical disease but no clinical symptoms. This is also referred to as asymptomatic primary hyperparathyroidism. Although these patients do not experience classical symptoms, they may experience neuropsychiatric symptoms and Quality of Life (QoL) can be influenced. These neuropsychiatric symptoms are not part of the criteria for treatment of asymptomatic primary HPT. The treatment of primary HPT consists of surgical excision of the pathologic parathyroid gland(s), and has a success rate of 95%. The parathyroidectomy (PTx) is a safe procedure, which is also performed in a daycare setting in some centers.

Secondary HPT occurs as a response to metabolic abnormalities, and is frequent in patients with chronic kidney disease. The first line of treatment consists of vitamin D supplementation and phosphate binders. Second line of treatment consisted historically of PTx. In 2004 the calcimimetic drug cinacalcet was introduced, and this has replaced the PTx as second line of treatment for secondary HPT. The first studies on cinacalcet showed promising results and it successfully lowers serum PTH, calcium and phosphate concentrations. However, in the EVOLVE trial it was shown that cinacalcet does not lower the risk of cardiovascular events or death. Therefore the optimal treatment of secondary HPT remains unclear, since cinacalcet and PTH have not yet been compared directly.

After renal transplantation HPT can persist despite a successful transplantation, and this is known as tertiary HPT. The treatment for tertiary HPT is parathyroidectomy. Cinacalcet is not registered for use in patients with tertiary HPT, but the off-label use is gaining popularity. To date the comparison of these two treatment modalities has only been performed in one study.

Hypoparathyroidism is another disease of the parathyroid and frequently after thyroid surgery. Transient hypoparathyroidism occurs in up to 60% of patients after total of completion thyroidectomy, and persistent hypoparathyroidism occurs in up to 14% of patients. The treatment of hypoparathyroidism consists of supplementation of calcium and active vitamin D. It's not possible to reliably predict in which patients parathyroid function will recover, and which patients will develop persistent hypoparathyroidism. Being able to predict which patients will develop persistent hypoparathyroidism will help tailor treatment of patients. Postoperative PTH measurements have been evaluated to predict direct postoperative hypocalcemia, but it has not been evaluated if postoperative PTH concentrations can predict which patients will develop persistent hypoparathyroidism.

Chapter 2 presents our first experience of a parathyroidectomy performed in a daycare setting. The results of the first 20 patients treated for primary HPT in a daycare setting are described. In this cohort were no perioperative complications. Five patients reported with paresthesia to the emergency department, but only one patient had mild hypocalcemia. We recommend parathyroid surgery for primary HPT in a daycare setting, but we discharge patients with prophylactic calcium supplementation for a few weeks.

In Chapter 3 we describe the experience of performing a hemithyroidectomy in a daycare setting. The safety of a hemithyroidectomy was analysed in a retrospective cohort of 210 patients who underwent hemithyroidectomy. In patients who were potentially eligible for daycare surgery there were no patients with postoperative bleeding, in patients not eligible for daycare surgery there was one patient requiring reoperative surgery due to bleeding. It was concluded that a hemithyroidectomy is a safe procedure for selected patients, and the daycare strategy was implemented. We describe the results of the first 18 patients undergoing a hemithyroidectomy in a daycare setting. There was one patient with transient vocal change in this group and no other complications. There were no readmissions or emergency department visits. The daycare hemithyroidectomy is safe and feasible provided that adequate patient selection is performed.

Chapter 4 presents the results of a case-control study evaluating the effect of PTx for primary HPT on QoL. In this study we 52 compared patients undergoing PTx with 49 patients undergoing a hemithyroidectomy for benign disease. QoL was measured using the Short-Form 36 (SF-36) questionnaire and a questionnaire consisting of 17 symptoms associated with primary HPT. Patients with primary HPT had lower preoperative scores on the domains role-physical and general health as well as a lower score on the physical component score. After surgery these differences had disappeared. The patients with primary HPT showed significant improvements on all domains after surgery, and this

improvement persisted in 7 domains one year after surgery. Patients who underwent hemithyroidectomy had an improvement on the mental health domain; the other domains did not reveal any differences. Patients with primary HPT had more complaints of dyspepsia, polydipsia and polyuria before surgery, this difference between the groups disappeared after surgery. In the primary HPT group the patients had fewer complaints of fatigue, muscle aches and nycturia three months after PTx. This study showed that a PTx for primary HPT leads to an improvement on QoL and this should be considered as a supplement in the current criteria for treatment of primary HPT.

Chapter 5 describes the results of a systematic review assessing the influence of treatment for secondary HPT on QoL. A total of five articles describing the effect of PTx on QoL were found, and three articles describing the effect of cinacalcet on QoL. The five articles describing the effect of PTx on QoL consisted of four case series and one case-control study. Four studies reported a significant improvement in QoL as measured by the SF-36 questionnaire. There were three studies that showed a significant improvement in symptoms as measured by the PAS questionnaire and one study described a significant improvement on three domains of the VAS scale (skin itching, joint pain and muscle weakness). The three studies describing the effect of cinacalcet consisted of two clinical trials and one cohort study. The use of cinacalcet did not result in an improvement in QoL as measured by the SF-36 questionnaire or the EQ-5D questionnaire. In one study it was shown that cinacalcet had a positive effect on four HPT related symptoms (dry skin, ache in bones, joint pain and trouble with memory). This review showed that PTx has a positive effect on QoL whereas cinacalcet did not. These interventions have not been compared directly and QoL should be an endpoint in future studies.

Chapter 6 presents the results of a systematic review comparing the outcomes of surgical and medical treatment for tertiary HPT. A total of 47 articles were included in this study. The outcomes after PTx for tertiary HPT were described 14 studies. Persistent disease was apparent in 0% and 1.3% of patients for respectively total parathyroidectomy and subtotal parathyroidectomy. Recurrent disease was apparent in 4% and 7.6% of patients. Persistent hypoparathyroidism occurred in 0.7% of patients, other complications were rare.

The outcomes of patients treated with cinacalcet were described in 22 studies. Normocalcemia was achieved in 80.8% of patients. Treatment was discontinued in 6.4% of patients due to side-effects.

Because PTx has higher cure rates than medical therapy we recommend surgical treatment of tertiary HPT.

In Chapter 7 the outcomes after treatment for tertiary HPT were evaluated in two academic centers. A retrospective evaluation of 94 patients, 30 after PTx and 64 after treatment with cinacalcet, was performed. A PTx corrected hypercalcemia, resulted in normalization of PTH concentrations and had low complication rates. Treatment with cinacalcet resulted in normocalcemia, but PTH values remained elevated. Given the effects of high PTH concentrations on renal allograft survival, we favour PTx in all patients with tertiary HPT.

In Chapter 8 the predictive value of PTH measurements after thyroidectomy for the development of persistent hypoparathyroidism is evaluated. A total of 102 patients were followed for one year after total or completion thyroidectomy. In this cohort 71% of patients were postoperatively discharged with calcium supplementation and 17.6% of patients developed persistent hypoparathyroidism. Patients with a postoperative PTH value under the limit of detection had a 60% chance of developing persistent hypoparathyroidism, whereas patients with a postoperative PTH within the limit of detection had a 10.4% chance of developing persistent hypoparathyroidism. All patients with persistent hypoparathyroidism had a PTH under the lower limit of the reference value on the first postoperative day. A PTH level under the limit of detection on the day after total or completion thyroidectomy is a predictive factor for the development of persistent hypoparathyroidism.

Appendix

List of publications
Curriculum vitae
Dankwoord
PhD Portfolio

LIST OF PUBLICATIONS

R.R. Dulfer, T.M. van Ginhoven, W. Geilvoet, W.W. de Herder, C.H.J. van Eijck: 'Operative treatment of primary hyperparathyroidism in daycare surgery'. *Scand J Surg. 2015 Sep; 104(3): 196-199.*

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R.R. Dulfer, W. Geilvoet, A. Morks, E.M. van Lieshout, P.C. Smit, E.J. Nieveen van Dijkum, K. In 't Hof, F. van Dam, C.H.J. van Eijck, P.W. de Graaf, T.M. van Ginhoven: 'Impact of parathyroidectomy for primary hyperparathyroidism on quality of life: A case-control study using Short Form Health Survey 36'. *Head and Neck. 2016 Aug; 38(8): 1213-1220.*

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R.R. Dulfer, E.T. Massolt, P.M.M. van Haard, Y.B. de Rijke, J.W.A. Burger, P.C. Smit, F.A.L. van der Horst, R.P. Peeters, C.H.J. van Eijck, T.M. van Ginhoven. 'Undetectable postoperative parathyroid hormone levels predict long term hypoparathyroidism after total thyroidectomy'. *In preparation*

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J.S.L. Kloth, P. Hamberg, P.C. Mendelaar, R.R. Dulfer, B. van der Holt, E.A.C Wiemer, W. Kruit, S. Sleijfer, R.H.J. Mathijssen. 'Macrocytosis as a potential positive marker for survival in the treatment with tyrosine kinase inhibitors'. *European Journal of Cancer. 2016 Mar; 56: 101-106.*

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W.Y. van der Plas, R.R. Dulfer, E.Y. Koh, L. Vogt, N.M. Appelman-Dijkstra, A. Schepers, J.I. Rotmans, R.A. Pol, T.M. van Ginhoven, E.J. Hoorn, E.J.M. Nieveen van Dijkum, A.F. Engelsman, M.H. de Borst, S. Kruijff. 'Safety and efficacy of (sub)total parathyroidectomy for patients with secondary of tertiary hyperparathyroidism in the Netherlands'. *Submitted.*

CURRICULUM VITAE

Roderick Dulfer werd geboren op 12 november 1987 te Rotterdam, als oudste van 2 zoons. Hij groeide op in Mijnsheerenland en later in Goudswaard. Zijn VWO diploma werd in 2005 behaald aan de Regionale Scholen Gemeenschap in Oud-Beijerland, in datzelfde jaar startte hij met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Zijn oudste co-schap vond plaats op de afdeling oncologische chirurgie van het Erasmus MC – locatie Daniel den Hoed, waarna hij 4 maanden doorbracht op de afdeling traumachirurgie van het Groote Schuur Hospital in Kaapstad. In november 2012 behaalde hij zijn artsexamen waarna hij startte met werken als ANIOS chirurgie in het Erasmus MC. In deze periode werd er ook begonnen met promotieonderzoek onder begeleiding van prof. dr. C.H.J. van Eijck en dr. T.M. van Ginhoven. Dit onderzoek heeft uiteindelijk geleid tot dit proefschrift. Gedurende het onderzoek heeft hij ook gewerkt op de afdelingen chirurgie van het Sint Franciscus Gasthuis en het Amphia ziekenhuis. Op dit moment werkt hij op de afdeling Heelkunde van het UMCG.

DANKWOORD

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PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Roderick Rolf Dulfer	PhD period: 2013-2017
Erasmus MC Department: Surgery	Promotor(s): prof. dr. C.H.J. van Eijck
Research School: Molecular Medicine	Supervisor: dr. T.M. van Ginhoven

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2014	1.5
- OpenClinica Training	2016	0.3
- Wetenschappelijke Integriteit	2017	0.3
- CPO mini-course	2017	0.3
- Systematic literature retrieval	2017	1.0
- Biomedical English Writing Course	2017	2.0
Specific courses (e.g. Research school, Medical Training)		
-		
Seminars and workshops		
-		
Presentations		
- Operative treatment of primary hyperparathyroidism in daycare surgery, ESSR	2013	1.0
- Post-operative PTH measurements after total thyroidectomy; a study design. Wetenschapsdag RdGG (poster)	2015	0.5
- Primaire hyperparathyreoïdie heeft een negatieve invloed op de kwaliteit van leven hetgeen verbeterd word door chirurgische behandeling, een multicenter case-control studie. Chirurgendagen	2015	1.0
- Chirurgische of medicamenteuze behandeling van tertiaire hyperparathyreoïdie; een systematic review. Stafdag.	2017	1.0
- Surgical of medical treatment for tertiary hyperparathyroidism; a systematic review. ESES (poster)	2017	0.5
- Resultaten van nationale studies betreffende secundaire hyperparathyreoïdie. Chirurgendagen.	2017	1.0
- Cinacalcet vs. operatie bij dialysepatiënten. RHINO-studie. The new kids on the block meeting.	2017	1.0
- Surgical of medical treatment for tertiary hyperparathyroidism; a systematic review. ESOT	2017	1.0

(Inter)national conferences

-	ESSR-congress	2013	2.0
-	Chirurgendagen	2015	1.0
-	Chirurgendagen	2016	1.0
-	ESES meeting	2017	1.5
-	Chirurgendagen	2017	1.0
-	The new kids on the block meeting	2017	0.5
-	ESOT congress	2017	1.5
-	Thyroid symposium	2017	0.5

Other

-	Scientific committee DHSG	2015-17	3.0
-	Wetenschapsmiddag RdGG	2013	0.3
-	Wetenschapsmiddag SFG	2015	0.3
-	Renal Rounds Westen	2015	0.3
-	Stafdag Heelkunde	2015-17	1.0

2. Teaching

	Year	Workload (Hours/ECTS)
Lecturing		
-		
Supervising practicals and excursions, Tutoring		
- Examination of Basic Life Support of medical students	2013	1.0
- Supervising medical student I. Loncar	2016-17	1.0
Other		
-		