Primary hyperparathyroidism:

current strategies for imaging, surgery and follow-up

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Primary hyperparathyroidism:

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Primaire hyperparathyreoïdie: huidige inzichten betreffende de beeldvorming, chirurgische behandeling en follow-up

(met een samenvatting in het Nederlands)

Proefschrift

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Bastiaan Anne Twigt

geboren op 5 september 1976 te Elburg

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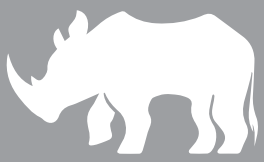
	Dr. M.R. Vriens

Aan mijn ouders

Contents

CHAPTER 1

General introduction and outline of the thesis



Theodor Kocher, chief of surgery in Bern, was at the beginning of thyroid surgery by the end of the 19th century. At the time thyroid surgery, mostly performed for the treatment of goiter, was considered a risky procedure. Some estimates put the mortality of thyroidectomy as high as 75% in 1872.[1] Indeed, the operation was believed to be one of the most dangerous operations and in France it was prohibited by the Academy of Medicine. In literature the high postoperative mortality is attributed predominantly to postoperative hemorrhage and sepsis. However, inadvertent damage or removal of the parathyroid glands might also have played an important role. Through application of modern surgical methods, such as antiseptic wound treatment, minimizing blood loss and his famous slow and precise style, Kocher managed to reduce the mortality from an already low 13% (compared to contemporary standards) to less than 0.5% by 1912. The success of Kocher's technique, especially when compared to operations performed by Theodor Billroth who was also performing thyroidectomies at that time, was described by William Stewart Halsted as follows: "I have pondered the question for many years and conclude that the explanation probably lies in the operative methods of the two illustrious surgeons. Kocher, neat and precise, operating in a relatively bloodless manner, scrupulously removed the entire thyroid gland doing little damage outside its capsule. Billroth, operating more rapidly and, as I recall, with less regard for the tissues and less concern for hemorrhage, might easily have removed the parathyroids or at least have interfered with their blood supply, and have left fragments of the thyroid."
—William Stewart Halsted.

The first descriptions of a small gland located in the vicinity of the thyroid gland appeared at the turn of the 19th/20th century,[2-4] while the first successful parathyroid operation was reported in 1925 by Mandl.[5] At the time, parathyroid surgery was done in patients with primary hyperparathyroidism (pHPT) with overt symptoms: painful bones, kidney stones, abdominal groans, psychic moans and fatigue overtones. It was not until the late 1960s that hypercalcemia could be confirmed by biochemical screening and reliable parathormone (PTH) assays became only available in the late 1980s. The ability to establish the diagnosis by routine "blood chemical analysis" resulted in a rapidly increasing number of patients diagnosed as having pHPT.[6,7]

Surgery still offers the only definitive treatment for pHPT. Historically, a conventional neck exploration was done through a Kocher's incision and an inspection of all four parathyroid glands was considered mandatory. Given an average size of a normal parathyroid gland of 2-5mm, an average weight of 35-50mg and a yellow-brown appearance - making it difficult to discern parathyroid glands from the surrounding tissue, the operation can be a defiance. Nevertheless, the reported success rate of conventional neck exploration for the treatment of pHPT is as high as 97-99%[5,8-10], and the complication rate is low. Recurrent laryngeal nerve damage and permanent postoperative hypocalcemia occur in 0-1% of the patients.

Minimally invasive surgery for pHPT was introduced in the early 1990s enabled by preoperative imaging techniques and intra-operative PTH-assessment (IOPTH). Today, in patients with non familial pHPT, parathyroid imaging is routinely done. When confirmative for a solitary adenoma a focused approach is preferred, and directed towards the abnormal parathyroid gland. In patients who undergo minimally invasive parathyroidectomy (MIP) PTH levels are commonly measured intraoperatively and a peroperative ≥ 50% drop in PTH levels is proof of surgical success. IOPTH is considered necessary to avoid surgical failures in patients with multiglandular disease.

In the last two decades MIP has replaced conventional neck exploration (CNE) as the surgical procedure of choice in patients with sporadic primary hyperparathyroidism (pHPT). MIP reduces the extent of surgical dissection, operative time, hospital stay and perioperative morbidity[11-15] while cure rates are comparable to the results of CNE.[16,17]

In our region, MIP was introduced in the late 1990s in the University Medical Center Utrecht. Preoperative imaging was preferably done by combined US and CT and a focused parathyroidectomy was done by a small incision on the anterior border of the sternocleidomastoid muscle, leaving the strap muscles medially.[18] Gradually, all regional hospitals adopted MIP, using the same operative technique, yet using different preoperative imaging strategies.

In this thesis several aspects of the work-up and treatment of patients operated for pHPT are evaluated. In addition, several issues related to special patient categories are addressed.

At present, there is on-going discussion regarding the optimal preoperative imaging strategy. In order to maximize the potential number of candidates for minimally invasive parathyroidectomy, a combination of different imaging techniques may enhance the number of visualized adenomas. In **chapter 2**, the yield of additional CT/US following a "negative" MIBI was evaluated in a prospective cohort study.

Confirmatory PTH decrease and normalization of calcium levels are commonly considered necessary proof of successful surgery. Despite the widespread use of IOPTH, the actual value of IOPTH assessment is not precisely known. The attributive value of IOPTH is studied in **chapter 3**. A prospective cohort study was done in an unselected group of patients operated for pHPT. IOPTH samples were collected while the results were not disclosed during the operative procedure.

The eventual proof of surgical success is a sustained (>6 months) normalization of the serum calcium. The response of serum calcium immediately following surgery for pHPT is poorly documented. In **chapter 4,** the course of postoperative serum calcium levels was evaluated in a prospective cohort of patients operated for pHPT.

In the era of conventional neck exploration solitary parathyroid adenomas accounted for 69-88% of the cases, while multiple adenomas and multiglandular hyperplasia (MGD) was observed in the remainder. During MIP the preoperatively identified abnormal parathyroid gland is approached directly and removed without inspection of the other glands. This surgical paradigm shift could have an effect on the observed frequencies of the causes of pHPT. In **chapter 5**, the frequency of solitary adenomas, multiple adenomas and multiglandular hyperplasia was determined in a cohort of patient who underwent a focused approach.

Lithium induced hyperparathyroidism is a rare condition. In **chapter 6A** several patients with lithium associated hyperparathyroidism encountered in our institutes are described. The aim of **chapter 6B** was to determine the prevalence of hypercalcemia in a large sample of patients treated with lithium for a bipolar disorder.

Two other less frequent types of hyperparathyroidism are part of the familial syndromes multiple endocrine neoplasia (MEN) type 1 or 2A. The major features of MEN1 are endocrine tumours of the parathyroid, pituitary, and pancreas. Minor features consists of bronchial and thymic tumours. MEN2A is associated with medullary thyroid cancer, primary hyperparathyroidism and pheochromocytoma. In both conditions parathyroidectomy is the only curative treatment that resolves symptoms and metabolic complications and thus improves quality of life. In **Chapter 7** we describe a population based cohort of patients with either sporadic, MEN1 or MEN2A related primary hyperparathyroidism. The frequency and causes (number of affected glands) as well as the differences in their clinical presentation, preoperative workup, operative strategies and follow up were determined.

In case of recurrent disease several possible causes can be distinguished: unrecognised multiglandular disease, failure to identify or entirely remove an adenoma, and very rarely parathyromatosis (the presence of small nodules of hyperfunctioning parathyroid tissue scattered in the soft tissues of the neck and/or mediastinum). Two cases of the latter condition are presented in **chapter 8**.

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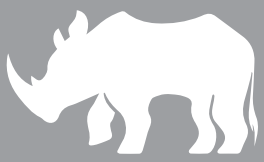
CHAPTER 2

Additional imaging following a negative sestamibi scan in primary hyperparathyroidism



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Abstract

Background: The objective of this study was to assess the additional yield of US and CT following a "negative" initial MIBI-scintigraphy (MIBI) in patients with primary hyperparathyroidism.

Methods: Prospective data were collected regarding 100 consecutive patients, preferentially undergoing a minimally invasive parathyroidectomy (MIP). MIBI was the initial imaging study for localizing a solitary adenoma, followed by US and CT (US/CT) in "MIBI-negative"-patients.

Results: Surgery led to normocalcemia in 98 patients (98%) after one operation. Overall 97 patients had solitary parathyroid disease while three patients had multiglandular disease. The sensitivity of imaging increased from 74% for MIBI alone to 92% following subsequent US/CT in "MIBI-negative"-patients. The positive predictive value of a "positive" MIBI was 96% and 76% of a positive US/CT following negative MIBI. The proportion of patients who underwent successful MIP increased from 60 to 72%.

Conclusions: MIBI and the combination of US and CT are complementary imaging studies. Additional localization studies after a negative sestamibi scan enhances the number of patients with primary hyperparathyroidism profiting from a minimally invasive approach.

Introduction

Primary hyperparathyroidism (PHPT) affects 0.3% of the general population and the incidence is 21.6 cases per 100,000 person-years.[1,2] The incidence rises with age and women are affected twice as much as men. In the last two decades minimally invasive parathyroidectomy (MIP) has gradually replaced conventional neck exploration (CNE) as the surgical procedure of choice in patients with sporadic primary hyperparathyroidism (pHPT). MIP reduces the extent of surgical dissection, operative time, hospital stay and perioperative morbidity,[3-7] while cure rates are comparable to the results of CNE.[8] Preoperative parathyroid adenoma localization and intra-operative PTH-assessment (IOPTH) both contributed to this success.[9,10]

Correct preoperative imaging of a solitary adenoma is a prerequisite for a focused surgical approach. Preoperative imaging strategies varies. Tc-99 –sestamibi scintigraphy (MIBI) is most commonly used and frequently advocated as the initial investigation.[11] Its sensitivity is reported as high as 71-93 %.[12-17] While MIBI identifies a hyperfunctional parathyroid gland (PG), ultrasonography (US) and CT-scanning (CT) of the neck detect an enlarged PG. At present single-photon emission computed tomography (SPECT) and the fusion of SPECT and CT images (SPECT/CT) is gaining importance, combining qualities that aim to detect a physiological abnormality and determine its exact anatomical localization.[18]

In order to maximize the potential number of candidates for minimally invasive parathyroidectomy we routinely use MIBI as a first investigational step, followed by CT and US (CT/US) when MIBI is “negative”, in patients with sporadic pHPT. In a prospective cohort study, the additional yield of CT/US following a “negative” MIBI was evaluated.

Methods

From January 2000 until September 2010 data were collected prospectively of all patients operated for pHPT in the Diakonessenhuis Hospital Utrecht. Patients with familial hyperparathyroidism (MEN-syndromes), patients previously operated for pHPT and lithium induced hyperparathyroidism were excluded. In all patients the diagnosis was established biochemically by: an increased serum calcium level (> 10.20 mg/dL) combined with an increased (> 70 pg/mL) or a not suppressed plasma PTH level, or an increased renal calcium excretion combined with an elevated PTH level.

Planar parathyroid scintigraphy using ^{99m}Tc-sestamibi (MIBI) was routinely done as a first investigational step for localization of a solitary adenoma. When MIBI scanning revealed no adenoma both US (13 MHz linear transducer; Acuson Antares, Siemens) and CT (16 slice; Somatom, Siemens) using a slice thickness of 3mm interval of the neck were done (CT/US). All patients were operated under general anaesthesia by the same surgeon. When at least one investigational procedure suggested a solitary adenoma a minimal invasive operation was started with a small incision that could be converted into a Kocher incision when necessary. A MIP was started as a 2-cm-long transverse incision at the medial border of the sternocleidomastoid muscle and continued as a “lateral approach”.[19] Concomitant thyroid pathology, suspicion of parathyroid malignancy and large size of a parathyroid adenoma were reasons for a unilateral exploration through a 4 cm Kocher incision, without exploration of the contralateral glands.

After removal of a preoperatively identified abnormal gland, the operation was ended, without further exploration of the neck and identifying the other parathyroid glands. When the intraoperative findings were not consistent with the preoperative imaging, MIP was converted to a CNE. IOPTH sampling was not available. Intraoperative frozen section analysis was used to confirm the parathyroid origin of excised tissue specimens. Gland weight was determined to reveal a possible relation between weight and MIBI sensitivity. Patients were cured when serum calcium and PTH levels

normalized postoperatively and remained normal at least six months after definitive surgery.

Statistical analysis

Since all imaging studies aimed to localise a solitary adenoma, a positive imaging result was defined as the visualisation of a single parathyroid abnormality. Patients were classified as having single gland disease when they were cured after removal of one abnormal PG. A contingency (2x2) table was made relating the operative findings to the preoperative predicted localization. *Sensitivity* of imaging studies aiming to detect solitary adenoma was defined as the proportion of patients with solitary gland disease (solitary adenoma and carcinoma) in whom a solitary adenoma was identified and correctly localized by preoperative imaging (no effort was made to distinguish between superior or inferior glands).

Positive predictive value (PPV) was defined as the proportion of all patients with a positive imaging study in whom the result had correctly identified and localized single gland disease.

The overall *success rate* of the preoperative imaging work-up was defined as the proportion of all patients in whom a solitary adenoma was correctly identified, i.e. in accordance with the outcome of the operation.

The *additional yield* of US/CT following a "negative" MIBI was addressed by evaluating its effect on the overall sensitivity of the preoperative imaging work-up, as well as the positive predictive value of US/CT as compared to MIBI alone and the effect on the proportion of patients who underwent successful minimal invasive surgery.

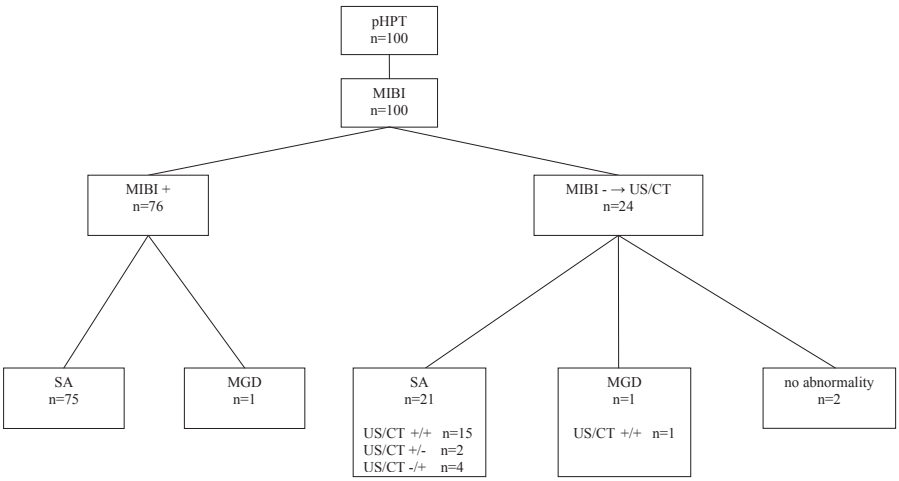
Results

One hundred consecutive patients underwent parathyroid surgery for non-familial pHPT. There were 23 men and 77 women, with a median age of 60 years (range 25-85). Patient characteristics are listed in *Table 1*.

Table 1. Characteristics of 100 patients operated for primary hyperparathyroidism

	number of patients (n=100)
male: female	23:77
median age (range)	60 (25-85)
frequency of symptoms	
fatique	55
renalstones	22
osteoporosis	41
abdominal complaints	21
psychic changes	13
mean preoperative (range)	
calcium (mg/dL)	11.92 (9.16-22.20)
PTH (pg/mL)	219 (26-1810)

Preoperative MIBI showed unilateral uptake consistent with a solitary adenoma in 75 of 100 patients (75%) (*Figure 1)*. In one patient scintigraphy suggested MGD. In the other 24 patients additional US/CT suggested the presence of a solitary adenoma in 21 patients. Overall, scintigraphy, followed by CT/US identified 96 patients with a presumed solitary adenoma.



Legend to Figure 1:
pHPT; primary hyperparathyroidism, SA; solitary adenoma, MGD; multiglandular disease, MIBI; MIBI scintigraphy, US; ultrasound, CT; CT scan.

MIP was the planned operative approach in 91 out of the 96 patients with visualized solitary gland disease. In 17 patients (18%) MIP was converted to a CNE due to insufficient exposure in eleven patients and preoperative imaging not being consistent with the intraoperative findings in six. The success rate of the first operation was 98 percent. As a result of the first operative procedure one enlarged PG was removed in 97 patients, two or more enlarged PG were found in two patients, and no adenoma was found in one patient. Hypercalcemia persisted in two patients (2%). The patient in whom no adenoma had been found was subsequently operated elsewhere where a single adenoma was retrieved (consistent with the preoperative MIBI). The other patient underwent a second operation which revealed a second (larger) adenoma. The overall incidence of solitary adenoma was 96%, multiglandular disease 3% and carcinoma 1%. Postoperative complications included one permanent recurrent laryngeal nerve damage following a MIP (1%), two transient recurrent laryngeal nerve palsy's (2%) and 2 postoperative haematomas (2%) both requiring surgical re-exploration.

The operative findings correlated with a preoperative MIBI suggesting a solitary adenoma in 72 of the 75 patients (PPV= 96%). In 16 of 21 patients who had a CT/US visualizing an assumed solitary adenoma, a single parathyroid abnormality was retrieved accordingly (PPV=76%). When US and CT unequivocally identified one parathyroid abnormality (n=16), the operative findings were consistent with these investigations in ten patients. In eleven out of 100 patients imaging did not correlate with the intraoperative findings. (*Table 2*).

The sensitivity of preoperative imaging to correctly identify a solitary adenoma increased from 74% after MIBI alone to 92% following additional CT and US. At the same time, the overall PPV decreased from 96 to 90 percent respectively. The workup success rate of our strategy was 89% and the rate of successful MIP increased from 60 to 72%.

Table 2. Summary of patients in whom imaging did not correlate with operative findings (n=11).

n	imaging result	imaging studies		intraoperative findings
4	SA	MIBI + MIBI-, US/CT +	n=1 n=3	all patients had a SA, but not on the predicted location n=4
3	SA	MIBI + MIBI-, US/CT +	n=2 n=1	all patients had MGD n=3
2	MGD	MIBI: MGD MIBI -, US/CT: MGD	n=1 n=1	both patients had a SA n=2
2	no abnormality	MIBI -, US/CT -	n=2	both patients had a SA n=2

(Sa; solitary adenoma, MGD; multiglandular disease, MIBI; MIBI scintigraphy, US; ultrasound, CT; CT scan)

Discussion

In the present study the additional yield of ultrasound and CT after a negative scintigraphy was evaluated. Following a "negative" MIBI scintigraphy in one quarter of the patients, subsequent US and CT suggested a solitary adenoma in the majority of them. The proportion of patients with correctly identified solitary adenomas increased from 75 to 92%, and the proportion of patients who underwent successful minimally invasive parathyroidectomy from 60 to 72%.

The strength of the present study is its prospective design and the adherence to an algorithm using MIBI-scintigraphy, neck ultrasound and CT stepwise to identify solitary adenomas in patients with pHPT. All three imaging techniques are readily available techniques.

The main weakness is the limited number of patients, making firm conclusions difficult. Then again, it does reflect the ability to achieve a good surgical success rate in a modest volume setting even in MIBI "negative" patients. The observed surgical success rate in a modest volume institution contradicts the conclusions from others to treat MIBI "negative" patients only in high volume institutions.[20] Furthermore we

did not investigate the contemporary use of SPECT or SPECT/CT, however MIBI is a readily available technique and was used in our hospital in the past decade. Lastly, the proportion of patients with multiglandular disease was low in the present study, which is in line with our recent multi-institutional study observing a significantly lower incidence of multiglandular disease than previously reported.[21]

Preoperative parathyroid adenoma localization is a prerequisite for a focused surgical approach in patients with pHPT and many imaging techniques and strategies are available and used for that purpose. MIBI-scans, ultrasonography, MRI, CT, SPECT are all used in the work-up of patients with pHPT with reported sensitivities ranging between 20 and 96%.
High cure rates in patients with primary hyperparathyroidectomy and two positive imaging studies are described.[22,23] Many authors have reported on MIBI-scintigraphy in combination with neck ultrasonography.[24-28] Ultrasonography has the advantage of being a readily available, cheap, preoperative localization study without the use of radiation, but it is strongly operator depended and the resulting image is difficult to interpret by the operating surgeon. CT has the benefit of providing the exact localization (even in an ectopic localization) of the enlarged gland thereby providing a roadmap for the operating surgeon, but at the expense of radiation to a vulnerable area (thyroid gland) and higher costs. The yield of the combination of ultrasound and MIBI ranges between 48 and 94%. Then again, in many of these studies it is unclear what the contribution of the separate techniques is, and surgical success rate is commonly confused with imaging identification rate (i.e. sensitivity). In addition, different surgical approaches (bilateral, unilateral or focused) and poor description of correct identification (side or quadrant) makes comparison of results difficult.

Applying the stepwise approach described in the present study, using US and CT when MIBI is negative has two advantages. On the one hand, the increased overall sensitivity of 92% in the present study is accompanied by an increased number of patients selected for, and successfully operated by a minimally invasive procedure. On the other hand, by using US and CT only when the scintigraphy was negative, unnecessary investigations are not done in the majority of patients with a positive

MIBI. The positive predictive value of 96% when a MIBI-scan is showing unilateral uptake justifies this approach. The contemporary use of SPECT or SPECT/CT may further increase this percentage in the near future, but it is accompanied by an increase in costs and patient radiation doses.[18]

The increasing number of false positive imaging studies appears to be a disadvantage of the algorithm. The chance of a false positive investigation increases when the MIBI is negative, and even more when the subsequent US and CT show equivocal results. Awareness of this decreasing reliability of a positive imaging study is important and should be communicated with the patient. Nevertheless, our data demonstrate that there is little if no harm of an opportunistic minimally invasive exploration; it selects two-third of patients who had a “negative” MIBI who can profit from a MIP. One may argue that the conversion rate in this group was high, but these patients would have had an upfront CNE anyway if the CT/US had not been done in addition.

Pushing the limits by the stepwise use of readily available imaging techniques increases the identification rate of solitary adenomas in patients with pHPT and selects more patients for minimally invasive surgery.

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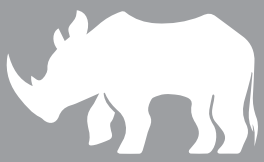
CHAPTER 3

The additional value of intraoperative parathyroid hormone assessment is marginal in patients with non familial primary hyperparathyroidism: a prospective cohort study



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Abstract

Background: The success of minimally invasive parathyroidectomy (MIP) is attributed to evolving preoperative imaging techniques and intraoperative parathyroid hormone (IOPTH) measurement. The additional value of IOPTH measurement in patients operated for primary hyperparathyroidism (pHPT) was evaluated.

Methods: Between 1999 and 2010, 119 patients underwent surgery for pHPT. In all patients, preoperative imaging was done and IOPTH samples were prospectively collected but the results were not disclosed during surgery.

Results: Postoperative calcium normalized in 114 patients (96%). The five surgical failures represented the maximum yield of IOPTH-sampling. Three of these patients would have been identified intraoperatively by an inadequate IOPTH decrease, while IOPTH decreased inaccurately in the other two. In addition, in one of these three patients no abnormal gland was found during MIP and subsequent CNE. So only two reoperations would have been prevented (1.7%).

Conclusions: IOPTH would have changed the outcome in 2 patients increasing the biochemical cure rate from 96 to 98%. We feel while it can be helpful in certain cases, it may not be necessary routinely in patients treated for pHPT.

Introduction

In recent years, minimally invasive parathyroidectomy (MIP) has replaced conventional neck exploration (CNE) as the surgical approach in patients with non hereditary, primary hyperparathyroidism (pHPT).[1,2] The advantages of MIP in comparison to CNE are shorter hospital stay and lower incidence of hypocalcemia, while cure rates are equally high. [3,4]

Preoperative parathyroid adenoma localization and intraoperative PTH assessment (IOPTH) are both associated with the success of focused, unilateral surgical exploration.[5] A positive preoperative imaging study is a prerequisite for a focused surgical exploration while a confirmatory PTH decrease following adenoma resection is considered necessary proof of success of focused surgery. Although it is used routinely in patients undergoing MIP[6-10], the actual value of IOPTH assessment is not precisely known. IOPTH-assessment will confirm surgical success, but it will not help to find a parathyroid adenoma and it is not routinely available. Furthermore its use will prolong the operation and may increase hospital costs.

A prospective study was conducted in an unselected group of patients operated for pHPT. IOPTH samples were collected while the results were not disclosed during the operative procedure. The IOPTH values were analyzed in relation to the results of surgery addressing the question to which extent IOPTH would have added to surgical success and changed intra-operative surgical strategy.

Patients and Methods

The study was done between March 1999 and August 2010. Prospective data collection of patients operated for primary hyperparathyroidism started in March 1999 at the University Medical Center Utrecht (Hospital A) and in 2006 at the affiliated Diakonessen Hospital Utrecht (Hospital B). Patients with a positive family history or a known MEN-syndrome were not included in the study: during the study

period 26 patients with known MEN-syndromes were treated in Hospital A.The study was approved in both hospitals by the medical ethical commission and patients gave preoperative informed consent.

In all patients pHPT was confirmed biochemically by an increased ionized calcium (>5.28 mg/dL) (Hospital A) and/or an increased serum calcium level (> 10.20 mg/dL) (Hospital B), combined with an increased (> 70 pg/mL) or a not suppressed plasma PTH level. In two patients calcium levels were normal but an increased renal calcium excretion combined with an elevated PTH level was affirmative for pHPT. Patient characteristics are listed in *Table 1*.

Preoperative imaging studies were done in all patients to identify and localize abnormal parathyroid gland(s). Ultrasonography (US) and CT-scanning (CT) were the preferred localizing studies in hospital A, while technetium 99m sestamibi scan (MIBI), US and CT were all used during investigational workup in hospital B. Based on the results of the preoperative localization studies, patients were selected for minimally invasive parathyroidectomy (MIP) or for a conventional neck exploration (CNE). MIP was proposed as the operative procedure if any of the performed scanning modalities visualized a focal abnormality suggesting the presence of a solitary parathyroid adenoma.[11] A true positive localizing study was defined as a preoperative imaging result consistent with the identification and removal of an enlarged parathyroid gland during surgical exploration leading to cure. Concomitant thyroid pathology, suspicion of parathyroid malignancy or (large) parathyroid size were reasons for a unilateral exploration through a 4 cm Kocher incision. In the other patients with localized solitary adenomas a lateral approach was used through a 2cm incision.[12]

Patients were operated under general anesthesia. Intraoperative venous blood samples were collected preoperatively, at the time of adenoma resection, ten minutes post resection and 24 hours postoperatively. The results of the intraoperative PTH measurements were not disclosed during or on the day of the initial procedure.

Intact PTH was determined using a solid phase two site chemiluminescent enzyme-labeled immunometric assay on the Immulite 1000 and 2000 (Siemens Healthcare Diagnostics) in Hospital A and B, respectively. A more than 50 percent drop in PTH level between the highest pre-excision and subsequent "ten minutes post resection" sample was defined as an appropriate IOPTH decrease considered affirmative for excision of all hyperfunctioning parathyroid tissue ("Miami" criteria)[13-16].

Surgery was considered successful when the level of serum calcium normalized 24 hours after surgery or when the serum calcium was decreasing one day postoperatively combined with normocalcemia measured during the first outpatient clinic visit (1-2 weeks after the operation) In addition, normocalcemia had to persist for at least 6 months postoperatively and active long-term follow-up was done in all patients. In patients presenting with preoperative calciuria and normocalcemia PTH levels were assessed postoperatively and during long-term follow-up visits too. When hypercalcemia recurred within 6 months this was considered persistent hypercalcemia and the operation was classified as "unsuccessful". An increase in calcium (or PTH) levels after 6 months was documented as recurrent disease

The additional value of IOPTH assessment was determined by analyzing the IOPTH values in relation to the result of surgery. First, the proportion of patients in whom IOPTH would have predicted surgical failure (persistent hypercalcemia combined with inadequate IOPTH decrease) was assessed and the case records were evaluated. Conversely, the proportion of successfully treated patients was assessed in whom IOPTH would have erroneously prolonged the operation (postoperative normocalcemia combined with an inappropriate IOPTH-decrease).

Results

During the study period, 119 consecutive patients underwent surgery for non hereditary pHPT. There were 30 men and 89 women, with a median age of 63 years (range 20-88). Patient characteristics are listed in Table 1.

Preoperative imaging studies visualized a solitary adenoma in 105 patients and suggested multiglandular disease (MGD) in five while no abnormality was observed in nine patients (Figure 1). One-hundred-one of the 105 patients with visualized solitary adenomas were selected for MIP through a lateral incision, while four patients were scheduled for a unilateral exploration through a midline incision due to the size of the adenoma (n=2) or thyroid pathology necessitating concomitant thyroid surgery (n=2). Intraoperatively a minimally invasive procedure had to be converted into a unilateral exploration due to insufficient exposure in seven patients. Fourteen patients were scheduled for a CNE while in an additional five patients MIP was converted into CNE because the intraoperative findings were not consistent with the preoperative imaging studies.

Table 1. Patient characteristics of 119 patients undergoing surgery for primary hyperparathyroidism at the University Medical Center Utrecht (hospital A) and the Diakonessen Hospital Utrecht (hospital B)

Characteristics	Hospital A (n = 69)	Hospital B (n = 50)	Total (n = 119)
Male:female	15:54	15:35	30:89
Median age, y (range)	67 (20–88)	60 (25–85)	63 (20–88)
Frequency of symptoms			
Lethargy	29	30	59
Renal stones	18	9	27
Osteoporosis	11	16	27
Gastrointestinal	11	14	25
Neuropsychiatric	9	8	17
Mean preoperative value (range)			
Ionized calcium, mg/dL	5.8 (5.1–7.0)		
Calcium, mg/dL		11.9 (10.0–22.0)	
PTH, pg/mL	300 (42–3,260)	265 (68–1,810)	285 (42–3,260)
Localization studies (%)			
US	69 (100)	24 (48)	93 (78)
CT	42 (61)	16 (32)	58 (49)
MIBI	33 (48)	48 (96)	81 (68)

CT = computed tomography; MIBI = technetium-99m-sestamibi scintigraphy; US = ultrasonography.
Normal ranges are as follows: ionized calcium, 4.40 to 5.28 mg/dL; serum calcium, 4.80 to 10.20 mg/dL; and PTH, <70 pg/mL.

Intraoperative findings and result of surgery

During the operation, an assumed solitary adenoma was removed in 113 patients (95%). Two or more enlarged parathyroid glands were removed in four patients. In two patients no abnormal parathyroid gland was found despite a four gland exploration In one of the latter two patients three normal glands were identified and in the other patient four normally appearing glands were identified. Postoperative complications consisted of one recurrent laryngeal nerve palsy and one postoperative hematoma requiring evacuation.

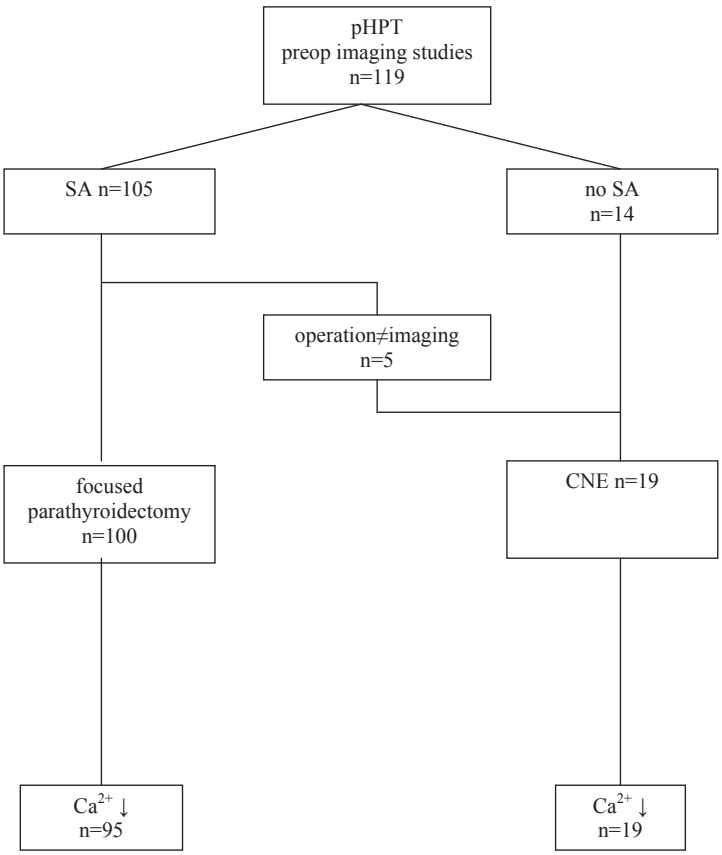

Figure 1. Biochemical results in patients operated for pHPT (n=119)
Legend to Figure 1: pHPT, primary hyperparathyroidism; SA, solitary adenoma; US, ultrasonography; CT, computed tomography; MIBI, technetium-99m-sestamibi scintigraphy.

After the operation, serum calcium normalized in 114 patients (96%), while hypercalcemia persisted in five patients. The intraoperative findings of the five "surgical failures" are outlined in Table 2. There was one of the two patients in whom no abnormal gland was found during MIP or subsequent conventional neck exploration. In another patient an assumed solitary adenoma turned out to be a lymph node. The other three patients underwent a MIP for an assumed solitary adenoma but eventually had MGD disease. In the aforementioned patient who underwent a four gland exploration serum calcium normalized and remained normal until the end of follow-up (15 months after surgery). In six of the patients with MGD preoperative imaging had suggested a solitary adenoma, while no adenoma was visualized in the other two. All patients with presumed MGD as suggested by preoperative imaging turned out to have a solitary adenoma.

Median follow-up was two years. No patient developed recurrent disease earlier than 6 months postoperatively. Combining the results of all operations pHPT was caused by single gland disease in 110 patients, MGD in 8 patients and in one patient hypercalcemia was not cured.

Potential value of IOPTH assessment in avoiding surgical failures

There were five surgical failures. In one patient no abnormality was found. In the patient in whom a lymph node was mistaken for a parathyroid adenoma, as well as in one of the three patients in whom one enlarged gland was removed during the primary operation but who eventually had MGD, IOPTH had decreased "false positively". Thus, IOPTH could have altered intraoperative decision making in two patients, i.e. 1.7% of the entire cohort and could have increased the surgical success rate from 95.7 to 97.4 percent.

Potential adverse effect of IOPTH assessment in cured patients

Conversely, analysis of the IOPTH samples of the cured patients revealed four patients in whom IOPTH had not decreased sufficiently during the operation. Hence, IOPTH measurements would have prolonged operative time and could have led to unnecessary CNE in 3.4% of the patients.

Table 2. Surgical failures (persisting postoperative hypercalcemia)

Patient	Imaging	Findings at initial procedure	IOPTH (highest pre-excision → 10 minutes postexcision value)	Reoperation	Potential role of IOPTH
Patient 1 (hospital A)	MIBI −, CT −, US+	MIP: resection of 1 adenoma	160 → 130	CNE: extirpation of a second adenoma	IOPTH helpful (MGD recognized)
Patient 2 (hospital A)	US+	MIP: resection of 1 adenoma	300 → 230	CNE: resection of 2 additional enlarged glands	IOPTH helpful (MGD recognized)
Patient 3 (hospital A)	MIBI+, CT −, US+	MIP: resection of 1 adenoma	270 → 120	CNE: resection of 2 additional enlarged glands	IOPTH not helpful (false-positive IOPTH decrease and MGD not recognized)
Patient 4 (hospital A)	MIBI+, US+	MIP: resection of an assumed solitary adenoma	110 → 20	CNE: no abnormality detected	IOPTH not helpful (false-positive IOPTH decrease)
Patient 5 (hospital B)	MIBI+	MIP → CNE: no adenoma found	90 → 100	MIP (in hospital A): extirpation of 1 adenoma	IOPTH not helpful (no adenoma found despite conversion)

According to the Miami criteria, a 50% decrease from the highest pre-excision value indicates surgical cure and predicts postoperative normocalcemia.CT = computed tomography; MIBI = technetium-99m-sestamibi scintigraphy; US = ultrasonography.

Discussion

In this prospective unselected cohort operated for non familial pHPT without using IOPTH sampling the success rate of the first operation was 96 percent. IOPTH would have altered intraoperative decision making in only two patients and could have increased the success rate from 95.7 to 97.4 percent.

To our knowledge, the present study is the only one to assess the value of the IOPTH measurements prospectively by collecting intraoperative samples but not disclosing IOPTH values during surgery. In addition, the present cohort did not represent a selection of patients with preoperatively localised adenomas. The surgical failure rate of the first operative procedure was 4%, reflecting the "maximum margin" to be obtained by IOPTH-sampling. The actual additional value however was only 1.7%, since IOPTH had no effect in a patient in whom the adenoma was not found and did "falsely" decrease in two others. Thus, the number of patients needed to treat to select one who would benefit from IOPTH assessments would have been 60. Furthermore, there was a small proportion of cured patients (3.4%) in whom the IOPTH concentration decreased insufficiently. We cannot prove that these patients would have been harmed by these "false negative" results, but IOPTH sampling would have prolonged operation time and could have extended operative treatment.

A weakness of our study is the inclusion of patients from two hospitals particularly since different imaging strategies were used. Four out of five failures were in the hospital with the more sober imaging strategy. Another important limitation is inherent to drawing only one postexcision sample. Others propose a drop of 50% from baseline AND a drop into the normal PTH range.[17,18] Subsequent 20- and 30-minutes samples could have been of help in patients with an inadequate decrease at 10 minutes. Then again, when applying the latter criteria, 19 patients (16%) would not have had an adequate IOPTH decrease 10 minutes after excision and awaiting the results of another sample at 20 minutes would have prolonged general anesthesia. Furthermore, it would not have altered decision making in those patients in whom surgical failure was accompanied by an inaccurate, "false-positive" IOPTH decrease.

Others have expressed doubts about the additional value of IOPTH as well.[19-24] Particularly when two preoperative imaging studies indicate a solitary adenoma, IOPTH measurements hardly offers any benefit over surgery alone.[25] Nevertheless, we do not argue that there are circumstances under which IOPTH-measurements are useful. In patients with recurrent disease,[26] in patients with proven or suspected multiglandular disease,[27] as well as in patients with inconsistent preoperative imaging, the use of IOPTH is considered to be of additional value. [25] Of course, IOPTH may serve as a very early confirmation of success, both convenient to patient and surgeon, realizing that serum calcium values may fluctuate substantially and return to normal only after a number of days.

Conventional neck exploration for pHPT has historical success rate as high as 97-99%.[4,28-31] However, the last two decades, MIP has become the surgical procedure of choice for patients with pHPT. Combining preoperative imaging with IOPTH measurements has led to surgical success rates comparable to CNE. Image-guided, minimally invasive parathyroidectomy is very effective. In this study IOPTH would have changed the outcome in 2 patients increasing the biochemical cure rate from 96 to 98%. We feel while it can be helpful in certain cases, it may not be necessary routinely in patients treated surgically for pHPT.

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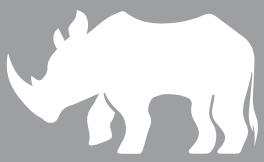
CHAPTER 4

Clinical relevance of direct postoperative serum calcium measurements in primary hyperparathyroidism



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Submitted

Abstract

Background: The proof of surgical success after a minimally invasive parathyroidectomy (MIP) is a sustained (>6 months) normalization of the serum calcium. Regrettably, serum calcium levels don't respond as quickly as parathormone levels. The response of serum calcium, during the first 24 hours, however is poorly documented.

Method: From January 2000 until July 2009 data were collected prospectively of all patients (n=83) who were operated for pHPT in our hospital. The course of postoperative serum calcium levels was analyzed and related to preoperative levels and final outcome.

Results: In 81 successfully operated patients the mean postoperative serum calcium level was 2.43 mmol/L (SD 0.20) and 2.33 mmol/L (SD 0.17) twelve and 24 hours postoperatively and the mean definitive calcium level was 2.34 mmol/L. Postoperative calcium values were normal in 63 (78%) and 74 patients (91%) twelve and twenty-four hours after parathyroidectomy. In two unsuccessfully operated patients the calcium level also normalized postoperatively. In both hypercalcemia relapsed. There were six patients with transient postoperative asymptomatic hypocalcemia. Calcium levels normalized in all six within one week and no patient received oral calcium supplements.

Conclusions: Given the limited proportion of patients in whom calcium normalizes within 24 hrs, the rareness of hypocalcemia as a clinically relevant issue, as well as the observed false positive normalization of serum calcium in unsuccessfully operated patients, the determination of serum calcium levels on the day of surgery, or the first postoperative day, does not appear to contribute to clinical decision making in patients operated for pHPT.

Introduction

Since minimally invasive parathyroidectomy (MIP) has become the routine operative treatment for patients with primary hyperparathyroidism (pHPT) and an identified solitary adenoma, intraoperative parathormone (IOPTH) assessment is commonly done to "warrant" surgical success. Parathormone (PTH) levels normalize within minutes inherent to the short half-life of the hormone that ceases to be produced excessively following removal of the enlarged gland.

The eventual proof of surgical success is a sustained (>6 months) normalization of the serum calcium. Regrettably, serum calcium levels don't respond as quickly as PTH levels to the removal of parathyroid adenomas, and fluctuate considerably in relation to fluid shifts that are not uncommon peroperatively.[1,2] The response of serum calcium following surgery for pHPT is poorly documented.

In a prospective cohort study in patients with pHPT who were treated preferably by MIP the course of postoperative serum calcium levels was evaluated.

Materials and Methods

From January 2000 until July 2009 data were collected prospectively of all patients who were operated for primary sporadic, i.e. non familial, pHPT in the Diakonessen Hospital Utrecht. In all patients the diagnosis had been established biochemically by: an increased serum calcium level (> 10.20 mg/dL) combined with an increased (> 70 pg/mL) or a non-suppressed plasma PTH level. Patients with an increased renal calcium excretion and an elevated PTH but normal serum calcium level were excluded (n=2). Renal function was normal in all patients and vitamin D status was not measured in a routine fashion.

In all patients preoperative imaging studies were done to identify abnormal parathyroid gland(s). Based on the results of these studies, patients were selected for MIP if any scanning modality demonstrated a suspected adenoma. If not, a conventional neck exploration was done. Serum calcium levels were measured preoperatively, twelve and twenty-four hours postoperatively and at least six months after the operation. Surgical success was defined as a sustained (>6 months) normalization of the serum calcium.

The course of postoperative serum total calcium values was analyzed. In successfully treated patients the proportion of patients with normalized calcium values twelve and twenty-four hours postoperatively was addressed. Furthermore, the proportional decline, defined as the proportional decline of the serum calcium in relation to the eventual decline [preoperative calcium level - six months postoperative calcium level] was calculated twelve and 24 hours postoperatively.

Calcium values were also analyzed in patients who did not undergo successful surgery.

Statistical analysis and graphical depiction of calcium course was done with SPSS software (IBM© SPSS© Statistics. Version 20).

Results

Eighty-three consecutive patients underwent parathyroid surgery for non-familial pHPT. There were 17 men and 66 women, with a median age of 68 years (range 25-85), patient characteristics are listed in Table 1. Sixty-three patients underwent MIP, while twenty patient had a CNE. Hypercalcemia persisted in two patients, while 81 patients were normocalcemic at least until six months postoperatively. The surgical success rate was 98%.

Table 1. Characteristics of 83 patients operated for primary hyperparathyroidism

	number of patients (n=83)
male: female	17:66
median age (range)	68 (25-85)
frequency of symptoms	
fatique	35
renalstones	17
osteoporosis	38
abdominal complaints	15
psychic changes	9
mean preoperative (range)	
calcium (mmol/L)	3.01 (2.29-5.55)
PTH (pmol/L)	23.12 (2.60-181)
Increased renal calcium excretion	2

In the 81 successfully operated patients mean postoperative serum calcium level was 2.43 mmol/L (SD 0.20) and 2.33 mmol/L (SD 0.17) twelve and 24 hours postoperatively respectively. The mean calcium level six months postoperative was 2.34 (SD 0.11;Figure 1). Postoperative calcium values were normal in 63 (78%) and 74 patients (91%) twelve and twenty-four hours after the operative procedure. In the patients in whom serum calcium levels were above normal 12 hour postoperatively, the preoperative values had not been significantly higher (3.12 mmol/L versus 2.97 mmol/L, p=0.25, independent sample t-test)

When compared to the absolute calcium decline as measured between the preoperative value and the 6 months postoperative value, the mean proportional decline was 90% twelve hours postoperatively and 116% 24 hours postoperatively. The preoperative calcium level correlated linearly with the absolute postoperative calcium-drop (figure 2 A and B), while the proportional decline was fairly constant and not associated with the preoperative calcium value (Figure 3 A and B).

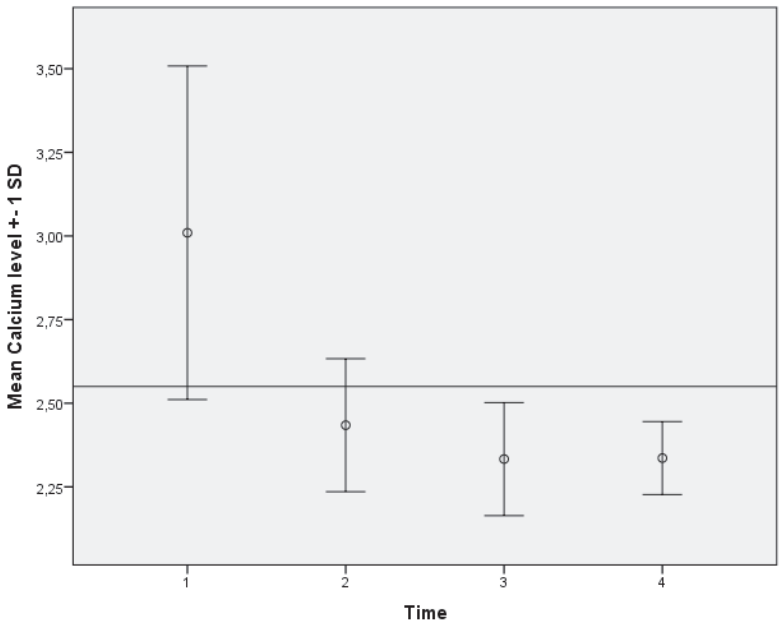
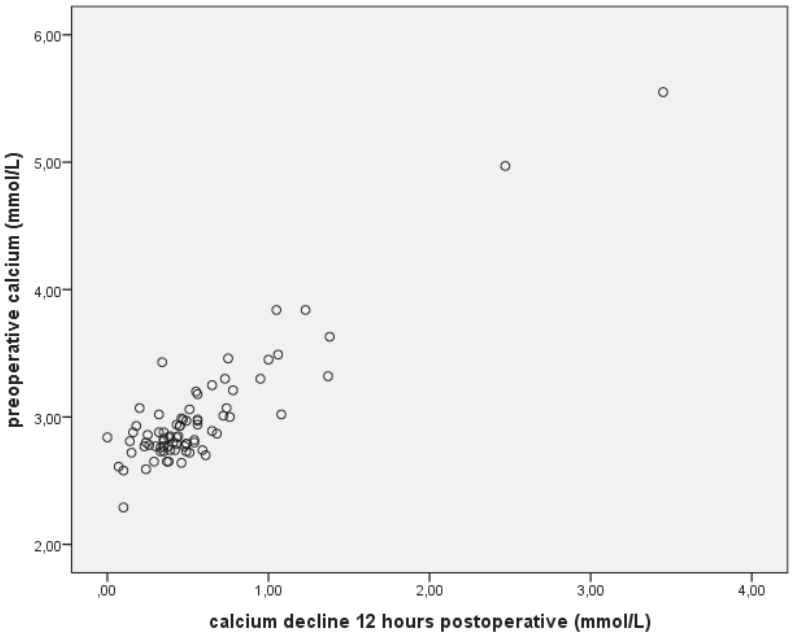


Figure 1. Mean calcium levels +/- 1 standard deviation (SD) at T1= preop; T2=twelve hours postoperatively; T3=twenty-four hours postoperatively; T4=at least six months postoperative.

There were two patients who were not successfully operated. These patients had preoperative calcium levels of 2.87 and 2.83, and the postoperative calcium was normal twelve hours postoperatively in one of them (2.38) and 24 hours postoperatively (2.50) in the other. In both patients serum hypercalcemia relapsed one week after surgery with calcium levels of 2.63 and 2.64 respectively. Both patients underwent a second operation to achieve normocalcemia.

There were six patients with transient postoperative asymptomatic hypocalcemia (range 1.94 – 2.05). The mean preoperative calcium value in this group of patients was significant higher (3.43 vs. 2.97, p=0.031). Three of these six underwent a CNE. Calcium levels normalized in all six within one week and no patient received oral calcium supplements.



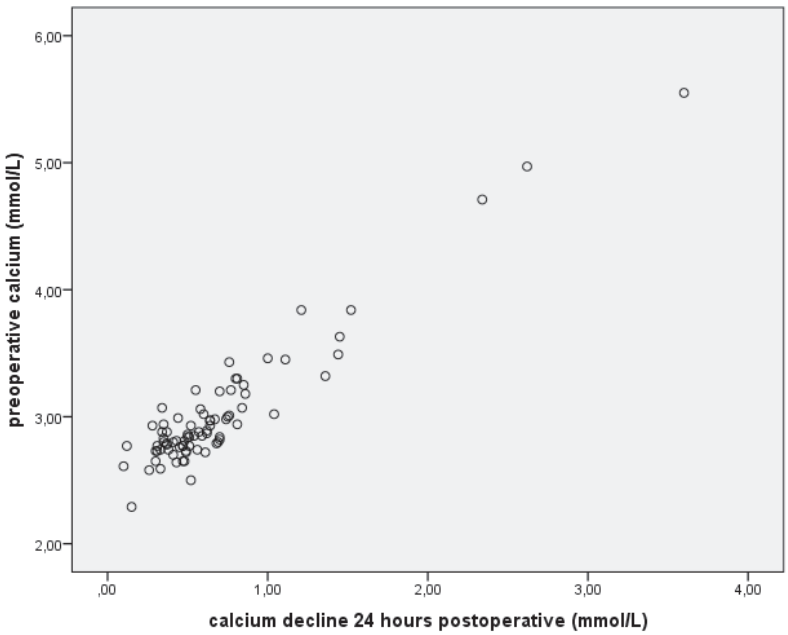
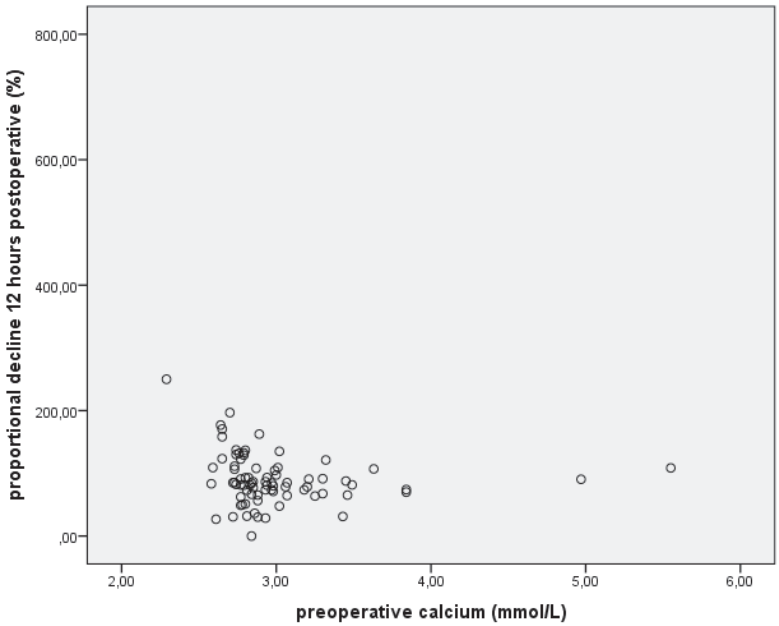


Figure 2 A and B: Relation between the extent of preoperatieve calcium elevation compared to the degree of decline, respectively twelve and twenty-four hours postoperatively.



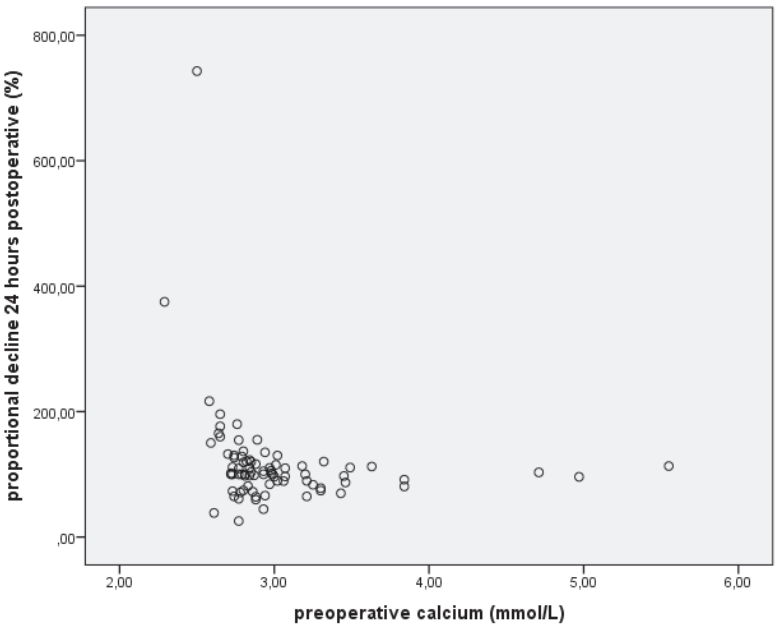


Figure 3 A and B: proportional decline of the serum calcium was fairly constant in relation to the preoperative extent of hypercalcemia

Discussion

In patients operated for pHPT calcium levels normalized on the day of surgery in 78% of the patients and 24 hours postoperatively in 91% of the patients. While the absolute postoperative serum calcium drop correlated with the extent of the preoperative hypercalcemia, the proportional drop was fairly constant. Approximately 90% of the eventual calcium decline occurs on the day of surgery.

This prospective cohort study is analyzing postoperative changes in serum calcium levels. The study has several limitations. Most importantly, since the data do reflect the postoperative calcium levels in successfully operated patients no discrimination regarding eventual success can be made based on these results, mainly because there are not enough unsuccessfully operated patients to evaluate the postoperative calcium course in them. Another limitation is the use of total calcium as a parameter, various authors advocating assessment of ionized calcium levels.[3-5] Lastly, the size of the patient cohort remains modest.

In the present study we observed that ninety percent of the absolute eventual postoperative calcium drop took place within the first twelve hours postoperatively, and 91 percent of the patients have normal calcium values 24 hours postoperatively. Many studies have addressed the course of PTH following parathyroidectomy, surprisingly little is known about the immediate postoperative course of serum calcium. Only a few studies have looked into intraoperative calcium measurements as a substitute for IOPTH measurements in predicting operative success; the results were equivocal.[6,7] Most other studies mention the course of postoperative calcium levels by reporting on the value at one week, 6 months or even one year, the immediate postoperative decline in these studies was not reported.[8-11] Whether the observed nine percent of not fully normalized calcium levels one day postoperatively deviates from other series is unclear. Then again, the observed 78% normalized calcium rate suggests a very limited role for calcium assessment in determining surgical success.

Until recently, a reason to monitor postoperative serum calcium levels was the early recognition of profound postoperative hypocalcemia. In the era of conventional neck exploration up to 31 percent of patients suffered from this complication[12] and persistent postoperative hypocalcemia occurred in 0.3-1 percent of patients.[13,14] Since the introduction of MIP (transient) postoperative hypocalcemia seems very rare and none of the patients in the present series experienced postoperative hypocalcemia that necessitated oral calcium supplements. In addition, in the two patients in whom surgery was unsuccessful a decline in postoperative calcium levels was observed too. This might be explained by the administration of perioperative fluids and a subsequent dilution and renal excretion of calcium.[15] The same pathophysiological mechanism may well explain the proportional decline of 116% twenty-four hours postoperative compared to the six months postoperative value.

Many studies have been focussing on intraoperative PTH measurements as early predictors of postoperative success.[10,16-18] Indeed, PTH measurements are a powerful diagnostic. Even PTH measurements show signs of variation and despite low false negative and false positive rates it may not be necessary as a routine measurement in patients with unequivocal preoperative imaging localizing a solitary parathyroid adenoma.[19-28]

Given the limited proportion (91%) of patients in whom calcium normalizes within 24 hrs, the rareness of hypocalcemia as a clinically relevant issue following parathyroidectomy in the age of minimally invasive surgery, as well as the observed false positive normalization of serum calcium in unsuccessfully operated patients, the determination of serum calcium levels on the day of surgery, or the first postoperative day, does not appear to contribute to clinical decision making in patients operated for sporadic primary hyperparathyroidism. We suggest determining the serum calcium only preceding the first outpatient clinic visit (one week postoperative) to confirm surgical success.

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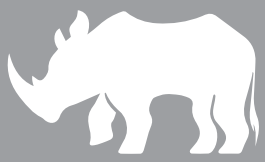
CHAPTER 5

Shifting incidence of solitary adenomas in the era of minimally invasive parathyroidectomy. A multi-institutional study



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Abstract

Background: Previously, when a conventional neck exploration (CNE) without preceding diagnostic imaging was the surgical treatment for patients with primary hyperparathyroidism (pHPT) solitary adenomas were observed in 69-88 % of patients. The advent of minimally invasive parathyroidectomy (MIP), aiming at a preoperatively identified parathyroid abnormality may be associated with a different incidence of solitary and multiglandular parathyroid disease.

Methods: In a cohort of 467 patients with sporadic pHPT who preferentially underwent MIP in four hospitals in the same geographical region, the incidence of solitary adenomas, multiple adenomas and multiglandular hyperplasia was evaluated.

Results: Three hundred sixty-seven patients were scheduled for MIP, one hundred patients underwent a planned CNE. The overall surgical success rate of the first operation was 93 percent and the cumulative success rate, including a second operative procedure, was 99 percent. Normocalcemia resulted from removing one abnormal PG in 426 patients (91%) and more than one abnormal gland in 35 patients (8%). A parathyroid carcinoma was diagnosed in four of the 426 patients with a single abnormal gland. Four gland hyperplasia was observed in one patient. In hospitals where diagnostic work-up usually consisted of US and CT the incidence of solitary adenomas was 88 percent, compared to 96 percent in hospitals where MIBI, US and CT were used preoperatively (P=0.007).

Conclusions: A higher frequency of solitary adenomas was observed than historically reported. The extent of the preoperative workup influences the number of observed solitary adenomas.

Introduction

Previously, when a conventional neck operation (CNE) was the surgical standard of care for patients with primary hyperparathyroidism (pHPT) solitary parathyroid adenomas reportedly accounted for 69-88 percent of the cases, while multiple adenomas and multiglandular hyperplasia (MGD) was observed in the remainder. [1-6] The diagnosis of solitary or multiglandular disease was merely based on the judgment of the surgeon who explored the neck for all parathyroid glands and removed the parathyroid glands that appeared enlarged.

Preoperative imaging has revolutionized the surgical treatment of primary hyperparathyroidism. Minimally invasive parathyroidectomy (MIP), has replaced CNE as the routine operation for patients with pHPT. Instead of exploring the neck for all four glands, a preoperatively identified abnormal parathyroid gland is directly approached, and the operation is terminated when abnormal parathyroid gland is removed. MIP is usually combined with an intraoperative confirmation of success by means of an adequate decrease of serum PTH levels (IOPTH). Today, CNE is reserved for cases when preoperative imaging suggests multiglandular disease or fails to detect an abnormal parathyroid gland. [7]

Hence, instead of assessing all four glands for being normal or abnormal, today the effect of removing an identified abnormality is awaited. This surgical paradigm shift could have an effect on the observed frequencies of the causes of pHPT. In a population based cohort of patients who preferentially underwent a focused parathyroidectomy following preoperative imaging, we evaluated the frequency of solitary adenomas, multiple adenomas and multiglandular hyperplasia.

Patients and methods

Data were collected regarding patients operated for pHPT in four hospitals in one geographical region in the Netherlands: the University Medical Center Utrecht (Hospital A), the Meander Medical Center Amersfoort (Hospital B), the Diakonessen Hospital Utrecht (Hospital C) and the Mesos Medical Center Utrecht (Hospital D). In these hospitals MIP was introduced as an alternative for CNE between 1994 and 2002. All patients who were treated surgically from the time of introduction in the different hospitals until 31 December 2009 were included (n=542). In hospitals A and C data were collected prospectively, and retrospectively in hospitals B and D. Patients with MEN related syndromes (n=57), unsuccessful previous surgery elsewhere (n=13), concomitant thyroid malignancy (n=4) and isolated familial PTH (n=1) were excluded. Hence, the study cohort consisted of 467 patients.

The diagnosis pHPT was established biochemically by an increased serum calcium level (> 10.20 mg/dL) combined with an increased (> 65 pg/mL) or not suppressed plasma PTH level. In a few patients calcium levels were normal but an increased renal calcium excretion combined with an elevated PTH level was affirmative for pHPT.

Imaging strategies differed between the four hospitals. All patients underwent at least one preoperative localizing study: ultrasonography (US), computed tomography (CT) or technetium-99m-sestamibi-scintigraphy (MIBI), and usually a combination of techniques. In Hospital A and B, both US and CT were most commonly done as investigational work-up. In the other two hospitals MIBI was the first investigational procedure and in the absence of abnormalities on MIBI-scanning, CT and/or US were additionally performed. In all hospitals patients were scheduled for MIP if at least one of the studies was indicative of a solitary adenoma; if not a CNE was done.

In hospitals A and B where US and CT were preferably used, the location of an identified abnormal parathyroid gland was preoperatively marked by US to guide the placement of the skin incision. In the other hospitals, where MIBI was the investigation study of first choice, US was not used to mark the skin incision. Instead, a minimal invasive operation was started with a small incision at one of the lateral edges of

a “Kocher incision” that was marked on the skin. A MIP was performed through a 2-cm-long transverse incision at the medial border of the sternocleidomastoid muscle and a lateral approach was uniformly used. [8] After identification and removal of the preoperatively identified abnormal gland, the operation was ended, without further exploration for normal parathyroid glands. When the intraoperative findings were not consistent with the preoperative imaging, MIP was converted to a CNE. The “minimal invasive” incision then would be extended over the midline to create a symmetrical “Kocher incision” in the skin lines. In patients with an assumed and preoperatively marked cranially localized adenoma a “Kocher incision” would be made as a separate/second incision. Equivocal results of the preoperative imaging studies, concurrent thyroid pathology, suspicion of multiple adenomas or the absence of abnormal parathyroid gland on preoperative imaging investigations were reasons to choose for an upfront conventional neck exploration.

The use of IOPTH –assessments and intraoperative frozen section analysis of removed glands varied between the different hospitals. IOPTH assessments were used in two hospitals (A and B). In the other hospitals frozen section analysis was done following removal of an assumed parathyroid adenoma. An inadequate IOPTH-decrease or an intraoperative frozen section result that did not confirm the parathyroid origin of an assumed adenoma was reason to convert to CNE as well.

Surgery was considered successful when normocalcemia was achieved and persisted postoperatively. Persisting hypercalcemia or hypercalcemia recurring within the first six months after surgery was considered indicative of surgical failure. After an unsuccessful first operation additional imaging studies were done and patients were advised to undergo a second operation.

The findings of all operations necessary to achieve normocalcemia were taken into account when determining the cause of pHPT. Extirpation of a single enlarged parathyroid gland with subsequent normalization of serum calcium was defined as single gland disease. Retrieval of more than one enlarged parathyroid gland leading to normocalcemia was defined as multiglandular disease. Multiglandular hyperplasia was defined as the situation when all four glands appeared abnormal.

We evaluated the proportions of the different explanatory causes of pHPT: solitary adenoma, multiple adenomas, carcinoma and multiglandular hyperplasia. Furthermore we explored the relation between the observed frequencies and the extent of the preoperative work-up by comparing the two hospitals that commonly did CT and US to the hospitals that used all three imaging modalities opportunistically. Associations between the various causes of pHPT and the aforementioned factors were evaluated by Chi-square analysis.

Results

The median age of the 467 patients was 63 (range 20-88) years; there were 357 women (76%). Patient characteristics are summarized in Table 1. There were differences in the number and type of preoperative imaging studies between the hospitals, reflecting the different preoperative work-up strategies employed in daily practice (Table 2). In hospital C and D 42 percent of patients underwent three imaging modalities compared tot 14 percent of patients in hospital A and B (P<0.001). In total, preoperative imaging studies identified a solitary adenoma in 367 patients (79%).

Table 1. Characteristics of 467 patients operated on for nonfamilial primary hyperparathyroidism

Characteristics	Total
Male: female	110:357
Median age (range)	63 (20–88)
Frequency of symptoms (%)	
Lethargy	188 (40)
Renal stones	115 (25)
Osteoporosis	73 (16)
Gastrointestinal symptoms	67 (14)
Neuropsychiatric	42 (9)
Mean preoperative (range)	
Ionized calcium (mg/dl)	6.76 (4.60–7.40)
Calcium (mg/dl)	11.56 (10.12–22.20)
PTH (pg/ml)	219 (10–3097)

Table 2. Preoperative imaging studies in patients with sporadic pHPT (n = 467) according to institutional differences

Imaging modality	Institutional policy: preferably US and CT* n = 335	Institutional policy: MIBI, US, and CT* n = 132	Total n = 467
US	319 (95)	80 (61)	399 (85)
CT	237 (71)	80 (61)	317 (68)
MIBI	86 (26)	120 (91)	206 (44)

P < 0.001
Values in parentheses are percentages
pHPT primary hyperparathyroidism, US ultrasonography, CT computed tomography, MIBI technetium-99m-sestamibi scintigraphy
* See "Patients and Methods" section for explanation of the institutional differences regarding the diagnostic workup

As a consequence 367 patients were scheduled for a MIP. The remaining 100 patients underwent a planned CNE. The proportion of MIP procedures differed between the hospitals: 76 percent in hospital A and B and 94 percent in hospital C and D (P=0.006). In 39 patients a MIP procedure was intraoperatively converted to a CNE. In eighteen patients the minimal invasive approach provided insufficient exposure to enucleate a correctly localized adenoma. In one patient the adenoma was not found. In the other twenty patients the preoperative imaging was not consistent with the intraoperative findings. The conversion rate differed statistically between the two groups (3% in the US/CT group vs. 7% in the MIBI/US/CT group; *P* =0.037).

The surgical success rate after a first operation was 93 percent (Figure 1); normocalcemia was not achieved after the first operation in 31 patients. In 20 patients no adenoma was found during the first operation, in eleven patients hypercalcemia persisted despite the removal of an enlarged parathyroid gland. The cumulative surgical success rate including the early second operative procedure was 99 percent (n=461).

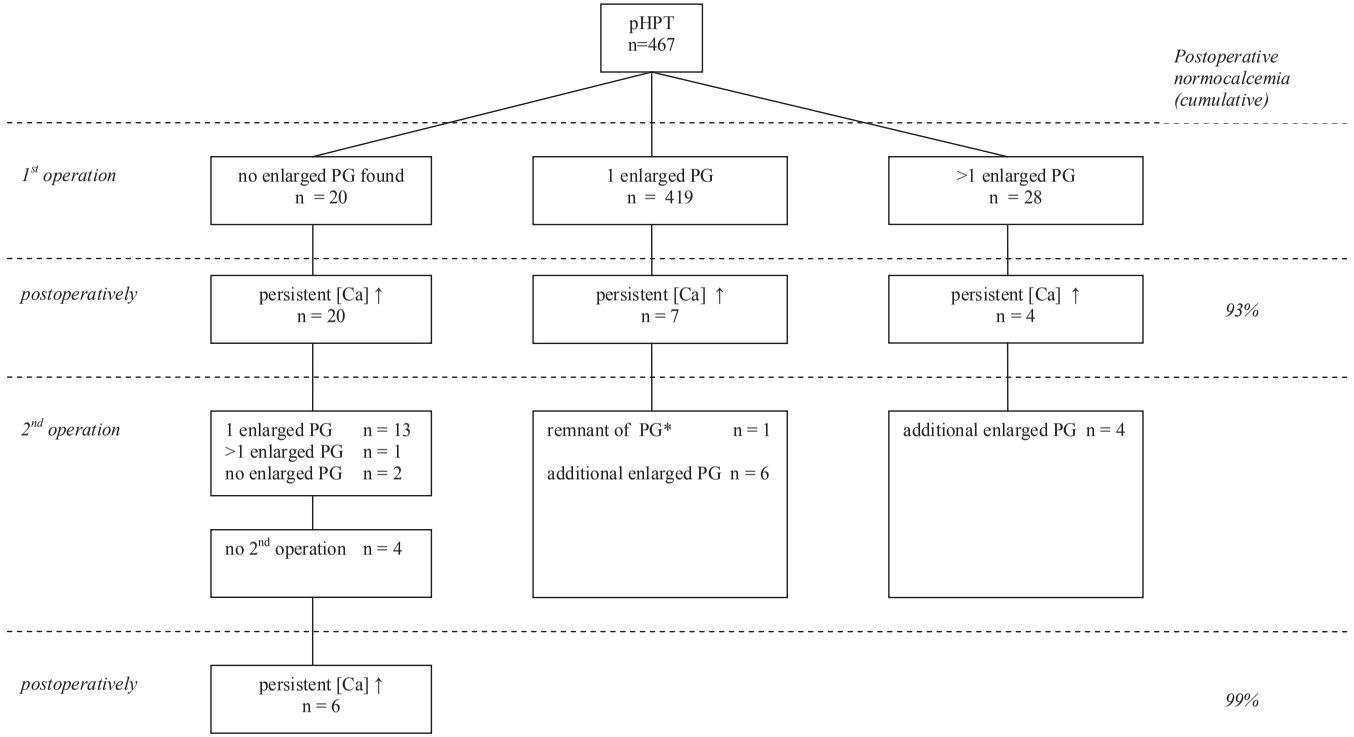

Figure 1. Outcome of surgical treatment in patients preferably treated by MIP for sporadic pHPT (n = 467). * See text results for explanation. MIP minimally invasive parathyroidectomy; [Ca] calcium level; PG parathyroid gland; pHPT primary hyperparathyroidism

Normocalcemia resulted from removing one abnormal PG in 426 patients (91%), and a parathyroid carcinoma was diagnosed in four of them (Table 3). Two or more abnormal glands were removed in 35 patients, while four gland hyperplasia was the observed cause of pHPT in only one patient. In six patients no abnormal parathyroid gland was retrieved. Apart from the patients with persistent hypercalcemia (n=6), no patient developed recurrent hypercalcemia during the first six months postoperatively. The observed frequencies of explanatory causes of pHPT were associated with the extent of the preoperative diagnostic work-up (Table 4). In the two hospitals where more imaging studies were done not only was the preoperative work-up more often indicative of a solitary adenoma (94% vs. 73%; P<0.001), but the incidence of a solitary adenoma as the observed explanatory cause of pHPT was significantly higher as well (96% vs. 88%; P=0.007).

Table 3. Observed parathyroid gland abnormalities in patients with primary hyperparathyroidism (n = 467)

Cause of pHPT	Frequency, n (%)
No adenoma found	6 (1)
1 enlarged gland	426 (91)
Solitary adenoma	422
Carcinoma	4
>1 enlarged glands	35 (7)
2 enlarged glands	26
3 enlarged glands	8
>3 enlarged glands/hyperplasia	1

Table 4. Observed causes of pHPT in relation to the extent of preoperative diagnostic workup (n = 467)

	Institutional diagnostic work-up US and CT* n = 335	Institutional diagnostic workup MIBI, US, and CT* n = 132	P
Preoperative imaging studies indicative of a solitary adenoma	243 (73)	124 (94)	<0.001
Observed PG aberrancies			0.007
Solitary adenoma	295 (88)	127 (96)	
>1 enlarged gland	32 (10)	3 (2)	
2 enlarged glands	24	2	
3 enlarged glands	8	0	
>3 enlarged glands/hyperplasia	0	1	
Carcinoma	3 (1)	1 (1)	
No adenoma	5 (2)	1 (1)	

Values in parentheses are percentages
pHPT primary hyperparathyroidism, PG parathyroid gland, US ultrasonography, CT computed tomography, MIBI technetium-99m-sestamibi scintigraphy
* See text "Patients and Methods" section for description of institutional differences regarding the diagnostic workup

Discussion

In a population based cohort of 467 patients that preferentially underwent focused parathyroidectomy a higher incidence of solitary adenomas was observed than historically reported. Taking all operations to achieve a surgical success rate of 99 percent into account, the frequency of solitary enlarged glands was 91 percent, while parathyroid hyperplasia was seen in less than one percent of the patients. In addition, the frequency of solitary adenomas was even higher when more imaging modalities were used as part of the preoperative work-up.

The main strengths of the present study are the size of the patient cohort and the population based nature of the study. Other patient series usually originate from tertiary referral centers [2,4,6] whereas in the present study patients were treated in three community hospitals and one university hospital, all four in the same

geographical area and only the latter being a regional referral center. Furthermore, since all patients referred for surgical treatment of pHPT were included, the role of selection bias was minimized.

Paradoxically the multicenter design of the study is a weakness of the study as well. The preoperative work-up, the indication for minimal invasive parathyroidectomy, and the use of IOPTH assessment were different in the four hospitals. Particularly, the significant differences in the average number of preoperative imaging studies were accompanied by different rates of preoperatively identified single gland disease. Then again, the observed differences were in line with the hypothesized effect of performing focused parathyroidectomies, i.e. a higher rate of single gland disease.

The overall frequency of single gland disease was 91 percent and as high as 97 percent in the hospitals where all three imaging modalities (MIBI, US and CT instead of merely US and CT) were used complementarily. Conversely, multiglandular disease was observed in less than ten percent of the patients and multiglandular hyperplasia was considered the cause of pHPT in less then one percent in the present series of patients with sporadic pHPT. The apparent vanishing of the clinical entity “four gland hyperplasia” in patients with non-familial pHPT was observed in all participating hospitals.

Historically, in cohorts of patients that underwent “conventional” neck exploration and identification of all four parathyroid glands therapeutically as well as diagnostically, the surgical success rates were as high as 99 percent and the reported frequency of solitary adenomas 69-88 percent. [1-6] Historical data from our country are not available, but there is no reason to assume that the frequency would diverge substantially. Since the introduction of focused parathyroidectomy the frequency of solitary adenoma has been reported as high as 87 to 95 percent with a concomitant surgical success of about 97 percent. [2,6,9,10] These series originate from tertiary referral centers. The present study describes a heterogeneous unselected group of patients and confirms the higher frequency of solitary adenomas and the rarer incidence of four gland hyperplasia than reported in the aforementioned studies.

Hence, the present data corroborates the hypothesized higher incidence of solitary parathyroid adenoma in the era of focused minimally invasive parathyroidectomy.

There are a number of possible explanations for this “shifting incidence”. Patient selection may play a role. The absence of an abnormality on preoperative imaging in patients with borderline increased calcium values may be a reason for physicians not to refer patients for surgical treatment. Furthermore, patients with familial hyperparathyroidism may have been included in historical series, being responsible for the higher rate of multiglandular hyperplasia in those series. Then again, the rarity of MEN-syndromes cannot explain for historical rates of multiglandular disease that have been reported to be as high as 20 to 30 percent. [13-16]

Others have suggested that the proportions of solitary adenoma, multiple adenoma and multiglandular hyperplasia appear to be a function of operative approach. [6] We partly agree with these authors, but consider these proportions rather as a function of the preoperative work-up. Historically, the four parathyroid glands were identified and assessed for their respective size or weight during a conventional neck exploration. Size of normal and abnormal parathyroid glands varies considerably, as illustrated by the absence of a linear relation between size of a parathyroid adenoma and the associated biochemical changes.[16] Furthermore, pathology distinction between normal and abnormal parathyroid tissue on histology maybe problematic.

In the era of conventional neck exploration not preceded by diagnostic imaging it is conceivable that normal functioning parathyroid glands may have been mistaken for parathyroid adenomas and consequently removed.[13-15] Probably, glands that appeared enlarged were not always the ones that were dysfunctional. Today, imaging studies are used direct the surgeon in the majority of cases to a localized abnormal parathyroid gland and the effect of removing this gland is awaited and the surgical success is confirmed quickly by IOPTH measurements. As the present data demonstrate, doing preoperative imaging leads to fewer removed parathyroid glands and, maybe most remarkably, to the mere “disappearance” of four gland hyperplasia as a clinical entity in patients with non familial pHPT. Hence, more extensive work-up

more often identifies a solitary abnormality, and its subsequent removal is nearly always successful.

This study was not designed to evaluate the yield of different work-up strategies; then again two important observations were made. First, MIBI appears important to optimize the identification rate of solitary adenomas. Second, based on the observed lower rate of conversions in the group where ultrasonography was used preoperatively to guide the skin incision, it is advised to use ultrasonography for that purpose.

In conclusion, the frequency of solitary adenomas as the cause of pHPT is higher than previously reported and amounts to more than 90% of the patients. Since the extent of the preoperative workup influences the rate of the detected solitary adenomas, we consider it in the patient's interest to extend the work-up in order to detect the abnormal parathyroid gland by using all available imaging modalities if necessary.

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CHAPTER 6A

Lithium-induced hyperparathyroidism

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Ladies and gentlemen,

For over 60 years lithium is the treatment of choice in several psychiatric disorders, especially bipolar disorder.[1] Its success as a mood stabilizer, particularly if used continuously for a longer period, comes with the downside of complications such as renal impairment and hypothyroidism. A less well known complication, described for the first time in 1973, and previously in this journal, is lithium-induced hyperparathyroidism (LIH).[2,3] Because symptoms of LIH are hard to recognize, a considerable doctor's delay may occur, as will be illustrated in the next three cases.[4]

Patient A, a 51-year-old woman, presented herself on our outpatient clinic with long-standing complaints of fatigue and apathy. She was using lithium for approximately ten years because she was diagnosed with bipolar disorder (type 1). During this time her disease was stable. Additional investigations showed an elevated serum creatinine of 135 umol/l (reference 44-80), a serum calcium of 2.71 mmol/l (reference 2.10-2.55) and a parathormone (PTH) of 17.2 pmol/l (reference <9). Other laboratory results, such as vitamin D, were not outside their normal range. It was concluded that the clinical picture could match a primary hyperparathyroidism. First, a wait and see policy was initiated, because the patient was reluctant to undergo surgery. However complaints persisted and after four years patient was referred to a surgeon. Ultrasound showed an abnormality suspicious for a solitary adenoma. Shortly after, she underwent a minimally invasive parathyroidectomy, after which calcium and parathormone levels normalized. Pathological examination confirmed the successful removal of a parathyroid adenoma. Two years later, calcium levels were still normal and the patient free of symptoms.

Patient B, a 47-year old woman, with an extensive psychiatric history, presented herself on the outdoor psychiatric department with complaints of fatigue, apathy, excessive sleeping and loss of libido. She was diagnosed, at the age of 31, with bipolar disorder (type 1) and was using lithium from than onwards. The apathy disappeared after addition of an antidepressant, however the sleeping disorder persisted. Laboratory investigations revealed a hypercalcemia, ionized calcium was 1.49 mmol/l (reference 1.24-1.34 mmol/l) and an elevated parathormone (13.0

pmol/l). In retrospect, hypercalcemia already was present for two years. Lithium dose had always been within therapeutic limits (therapeutic range: 0.6-1.0 mmol/l) and vitamin D levels and kidney function were normal. Patient was referred to the internal medicine department by her psychiater. Localizing imaging studies showed increased uptake of technetium retrosternally, possibly due to a thyroid adenoma. A parathyroid adenoma was not identified. Additional CT could not confirm this. Because of this discrepancy there was a certain reluctance with respect to surgical intervention. Instead, patient was treated with calcimimetics. Serum calcium levels reduced quickly (2.34 mmol/l) after six weeks of treatment. Patient experienced also a decrease in symptoms. Imaging will be repeated in a year.

Patient C, a 56- year old woman, was treated for a schizoaffective disorder with lithium for over a decade. Because of decreased creatinine clearance she was referred by her psychiater to the internal medicine department for diagnostic work up and treatment advice. The decline of renal function was possibly due to chronically exposure to lithium. Except for a polyuria (6-8 liters per day) patient had no other complaints. Creatinine levels were gradually decreased to 115 umol/l (reference: 70-100 umol/l) over the past years. Further laboratory testing also revealed a hypercalcemia (2.65 mmol/l) and an elevated PTH (53.6 pmol/l). The internist ruled out a secondary hyperparathyroidism because of the only mildly elevated creatinine levels. The polyuria was interpreted as a nefrogenic diabetic insipidus, a known side effect of chronic lithium use. Vitamin D levels were not aberrant. The most probable diagnosis was therefore lithium-induced hyperparathyroidism. Technetium-99m-sestamibi(MIBI)-scintigraphy showed a presumably solitary adenoma, which was resected during subsequent minimally invasive parathyroidectomy. Calcium levels normalized postoperatively. Unfortunately, one year later, at routine follow-up, calcium levels were elevated again (2.70 mmol/l). CT showed another lesion suspicious for a parathyroid adenoma at the contralateral side. It was concluded that there was recurrent disease caused by continuous use of lithium. This time a conventional neck exploration was conducted and another adenoma was resected. Because of patient's ongoing dependence of lithium treatment, it was aimed to remove all normal parathyroid glands and re-implant some parathyroid tissue in the

musculus brachioradialis, in order to prevent future recurrence as well as permanent hypoparathyroidism. Reimplantation would make future explorations easier and prevent possible recurrent laryngeal nerve damage. However, normal parathyroid glands were not found during conventional neck exploration. Postoperative calcium levels normalized quickly. Renal function has not worsened yet, however when this occur in the future, discontinuation of lithium has to be reconsidered.

Discussion

Prolonged use of lithium can cause a range of side effects. In chronic lithium users 5-35% of patients develops a hypothyroidism.[5] This side effect is relatively easy to diagnose based on symptoms such as increased sensitivity to cold, weight gain, fatigue, muscle weakness and depression. Further more long-lasting lithium treatment may cause severe renal impairment , occasionally even leading to renal failure. Polyuria (15-40%), as illustrated in patient C, and polydipsia (38-70%) are signs of lithium-induced nefrogenic diabetic insipidus. All together these side effects and symptoms are not hard to diagnose. However, a less well known side effect is the occurrence of lithium-induced hyperparathyroidism (LIH), which subsequent causes hypercalcemia.[1-5] The prevalence of LIH varies from ten till more than thirty percent.[6,7] Furthermore, this clinical entity is hard to recognize since symptoms, described in the mnemonic; groans, moans, bones, stones and psychiatric overtones, are often subtle.[4] Especially, the latter symptoms are hard to identify in a patient population already suffering from some kind of psychiatric illness. Moreover symptoms are rather assigned to a possible hypothyroidism and are therefore easily over looked. Timely recognition is also hampered by the relative unfamiliarity of this condition by family physicians, surgeons, psychiatrists and endocrinologists. On the other hand LIH can be easily diagnosed by simple laboratory tests, like is illustrated in patient C. It is therefore crucial that, besides renal and thyroid function, calcium levels are measured in a routine fashion in patients on prolonged lithium treatment. This is now recommended in the latest Dutch guideline on “Bipolar Disorders”.[5]

Pathofysiology

Primary hyperparathyroidism occurs as the result of a proliferation of parathyroid tissue. This might result in a solitary adenoma or, in rare cases, multiglandular hyperplasia or a malignancy. Secondary hyperparathyroidism is caused by renal impairment or a chronic vitamin D deficiency. The pathological mechanism behind the onset of LIH however, is still unknown. Discontinuation of lithium therapy rarely reverses hypercalcemia. This implies that LIH is not a direct effect of the lithium itself. Although, renal dysfunction caused by lithium might influence calcium metabolism, in many patients on lithium therapy renal function is not decreased. Lithium might shift the set point of the parathyroid glands for blood calcium levels. Subsequently, the inhibition of PTH is reduced, unmasking a pre-existent subclinical primary hyperparathyroidism or inducing a novel hyperparathyroidism. In LIH, one parathyroid adenoma can be involved as well as hyperplasia of all four glands. More research in the future will have to shine light on the exact pathofysiology.[6]

Treatment

In primary hyperparathyroidism surgical therapy is the only curative option and therefore treatment of choice.[8] With respect to LIH consensus is lacking regarding the ideal treatment. Possible therapeutic options are minimally invasive parathyroidectomy, conventional exploration with subtotal parathyroidectomy or removal of all glands combined with autotransplantation. Furthermore, in patients not suitable for surgical intervention, treatment with calcimimetics are an alternative.[9] In case of minimally invasive surgery, localizing studies are necessary to identify the affected gland and the extent of the involvement of the other glands. Ultrasound and MIBI are typically used, followed by CT or MRI in case of discordant imaging or ectopic localizations.[7]

Especially the extent in which all four gland are affected by lithium is one of the topics which remains controversial. Chronic use of lithium is described to cause solitary adenomas as well as multiglandular hyperplasia. In comparison with primary hyperparathyroidism, where multiglandular disease is rare, the described incidence of multiglandular disease in patients on lithium varies widely.[4,6,7] Multiglandular disease necessitates a different surgical approach with resection of all affected

parathyroid tissue to prevent recurrences and re-operations, as is illustrated in patient C.[7,10] Because the exact etiology has to be elucidated yet, evidence is lacking to support one surgical strategy, whether that is minimally invasive and selective or a conventional neck exploration and subtotal parathyroidectomy with or without auto-transplantation. Possibly a more extensive primary operation could have prevented the recurrence in patient C. Additional research will be required to address the question which surgical approach is best in these patients.

Ladies and gentlemen,

Lithium-induced hyperparathyroidism is hard to recognize and therefore easily overlooked. The most important symptoms, as fatigue, apathy and depression, are quite similar to the underlying psychiatric illness for which lithium therapy was initiated or symptoms are attributed to a presumed lithium-induced hypothyroidism. Prevalence of LIH varies among studies from 10 to 30%. There is still no consensus about optimal treatment. Despite a recent adaptation of the guideline with respect to follow-up and laboratory investigations in patient on lithium treatment, LIH lacks sufficient awareness. In order to prevent these patients suffering from a significant doctor's delay, regular screening for elevations of their serum calcium levels is mandatory. This enables early detection and treatment of LIH.

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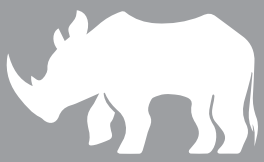
CHAPTER 6B

Hypercalcemia in patients with bipolar disorder treated with lithium: a cross-sectional study



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Abstract

Objective: Lithium-induced hyperparathyroidism (LIH) is a relative unknown complication of long-term lithium treatment. Hypercalcemia may be the first, but often overlooked, sign of lithium-induced hyperparathyroidism (LIH). Symptoms of LIH can be similar to the underlying psychiatric illness, which may cause a significant doctors delay in diagnosing LIH. The aim of this study was to determine the prevalence of hypercalcemia.

Methods: In this cross-sectional study we collected data from 314 patients treated with lithium in an outpatient clinic for bipolar disorder. Patient characteristics and laboratory results were collected, during the period of June 2010 till June 2011.

Results: The mean serum calcium level was 2.49 (SD 0.11) mmol/l. The point prevalence of hypercalcemia (> 2.60 mmol/l) was 15.6%. In a comparable group of psychiatric patients not on lithium the mean serum calcium level was 2.37 mmol/l, and none of these patients had hypercalcemia (p 0.001). Duration of lithium treatment was the only significant predictor for the development of hypercalcemia (p 0.002).

Conclusion: The prevalence of hypercalcemia in lithium-treated patients was significantly higher than in non-lithium treated controls. We recommend that serum calcium levels should be routinely tested in lithium-treated patients to avoid doctors delay in diagnosing LIH.

Introduction

Lithium is used effectively in the treatment of bipolar disorder over the last 60 years, and despite the availability of many pharmacotherapeutic options it remains the cornerstone of long-term prophylaxis.[1] Hypercalcemia associated with lithium-induced hyperparathyroidism (LIH) is a common, but underrecognized, complication of lithium treatment. Monitoring of serum calcium levels is therefore recommended in the International Society for Bipolar disorders (ISBD) consensus guidelines for safety monitoring of bipolar disorder treatments.[2] The first case of lithium-induced-hyperparathyroidism (LIH) was published in 1973.[3] The reported prevalence of hypercalcemia in patients on lithium therapy varies among studies from 15-60%.[4-11]

Since symptoms of LIH such as fatigue, weakness and depression are quite similar to symptoms of the mood disorder for which lithium therapy was initiated, this may cause a significant doctors delay in the diagnosis of LIH when misinterpreted.[11-13] The exact pathophysiology, by which LIH develops is still unknown. Lithium may induce LIH directly or only unmask or accelerate a previously unnoticed hyperparathyroidism.[14-19] There are no clear predictors to determine which patients are at risk for LIH. Furthermore, the way in which these patients should be treated is still a matter of debate. Discontinuation of lithium treatment, if possible, has been proven unsuccessfully in most patients that have been using lithium for longer periods.[3,12] Different surgical approaches have been described, but calcimimetics or a "wait and see policy" might be an alternative to surgery.[4-12,20-22]

Given the unfamiliarity with this condition – periodical monitoring of serum calcium has only recently been implemented in psychiatric guidelines and is still less well-known in comparison to other well-known complications regarding thyroid and kidney function.[2,23] We therefore assume that LIH is both underdiagnosed and undertreated.

Aims of the study

The aim of this study was to determine the prevalence of hypercalcemia in a large sample of outpatients treated with lithium for bipolar disorder. To gain insight into which of these patients are more prone to develop LIH, we assessed which determinants were related to hypercalcemia.

Material and methods

Patients and controls

The medical records of patients with bipolar disorder who were treated with lithium between June 2010 and June of 2011 at an outpatient clinic for bipolar disorder were reviewed. Inclusion criterion was the continuous use of lithium. Outpatients with bipolar disorder from the same clinics who had never been treated with lithium and of whom serum calcium levels were available were included as controls.

Outcomes

The following data were collected from the medical records: age, gender, past medical history, medication, current lithium dose, any possible interruptions during the period that lithium was taken, and total cumulative duration of lithium treatment. The following laboratory variables were registered and analyzed by routine methods (reference values between brackets); serum levels of lithium (0.6-1.2 mmol/l), calcium (2.10-2.55 mmol/l), PTH (1.0-7.0 pmol/l), albumin (38-42 mmol/l), creatinine (74-110 µmol/l), TSH (0.35-5.00 mU/l), FT4 (9-27pmol/l), sodium (135-145 mmol/l) and potassium (3.5-5.0 mmol/l). Also, any medication used by the patient was registered since thiazid/chloortalidon diuretics, calcimimetics, vitamin D supplements and calcium supplements can induce increased serum calcium levels.

Data analysis

The Kolmogorov-Smirnov test was employed to test normal variance for each variable. Statistical differences were calculated by means of the Students (paired) t-test, the Mann-Whitney U-test and Fishers exact test. Correlations were calculated

as Spearman's rho. Missing data resulted in a lower n than the actual number of patients. Statistical significance was set as a two-tailed $p<0.05$. Subsequently, subgroup analysis and a multivariate linear regression analysis was performed to study possible determinants of the development of hypercalcemia.

Definitions

The point-prevalence of hypercalcemia was defined as the prevalence of elevated serum calcium levels within our cross-sectional one year timeframe. If more than one serum calcium level was available the average serum calcium level was determined. The upper-limit for serum calcium was set at 2.60 mmol/l.

Total duration of lithium use was defined as the cumulative period that lithium was taken by a patient expressed in months. If the use of lithium had been interrupted, the total duration of lithium reflects the sum of all individual periods.

Ethical committee

Approval was obtained from the medical ethics committee of the University Medical Centre Utrecht (registration protocol 10/340C).

Results

Descriptive analysis

A total of 314 patients were identified who were currently under treatment or follow-up and in which the serum calcium level was determined at least once. The control group consisted of 15 patients with bipolar disorder who had never used lithium and from whom a serum calcium measurement was available.

Study population

In the 314 lithium treated patients the mean age was 47 years and 61.5% were women (n=195). The mean dosage of lithium was 960 (SD 280) mg a day. The mean serum level of lithium was 0.74 (SD 0.19) mmol/l. The mean period that lithium was

taken was 117.6 (SD 91.2) months, and the point prevalence of hypercalcemia was 15.6% (n=49). None of these patients had a medical history of hyperparathyroidism, hypercalcemia or kidney failure, nor did they use any medication with hypercalcemia as a possible side effect.

Controls

In the control group the mean serum calcium level was 2.37 (SD 0.10) mmol/l, which was significantly lower than in the lithium-treated patients (2.49 (SD 0.11) mmol/l, p 0.001) (Table 1). None of these patients had a serum calcium level above 2.60 (mmol/l). The calcium levels in the lithium-treated patients were generally higher with a possible higher set-point than the non lithium-users who were more in line with the general population (Figure 1).

Table 1. Gender, age and laboratory variables in lithium users compared to non lithium users.

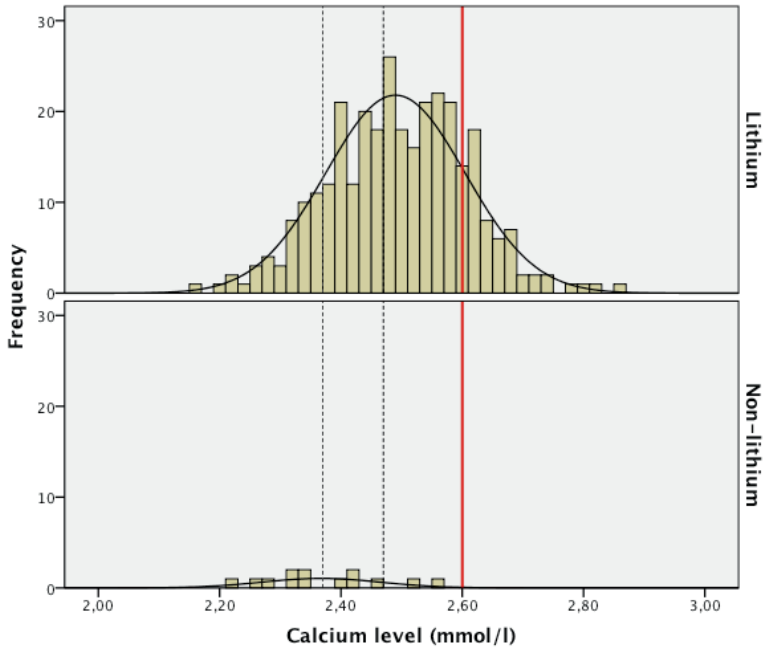
	Lithium users (n=314)	Non lithium users (n=15)	P
Gender (% Female)	61.5	66.7	0.692
Age (years)	47 (13)	40 (9)	0.036
Creatinine (µmol/l)	77.59 (18.9)	68.45 (14.8)	0.113
TSH (mU/l)	2.7 (3.6)	1.9 (0.7)	0.462
Sodium (mmol/l)	140.5 (2.26)	140.9 (1.30)	0.552
Potassium (mmol/l)	4.5 (0.35)	4.3 (0.26)	0.140
Calcium serum level (mmol/l)	2.49 (0.11)	2.37 (0.10)	0.001

Subgroup analysis

Subgroup analysis showed that the cumulative duration of lithium use (i.e. the total time that a patient had used lithium regardless of any possible interruptions) was the only predictor for the development of hypercalcemia. The mean cumulative duration of lithium use was 165 months in hypercalcemic patients versus 109 months in patients with normal calciumlevels (p 0.002).

In addition, we calculated a hypothetical lifetime lithium dose by multiplying the cumulative duration of lithium use. This was significantly different between both groups (p 0.004)(Table 2).

All other factors such as gender (p 0.425), current lithium dose (p 0.759), serum lithium level (p 0.379), age (p 0.174) serum creatinine (p 0.091) and thyroid function (p 0.176) did not differ significantly (Table 2).



Hypercalcemic patients

Of the 49 patients with calcium levels above 2.60 mmol/l, 3 patients were referred to an endocrine physician or surgeon to reveal the cause of hypercalemia. Two of these patients with serum calcium levels of 2.71 and 2.65 mmol/l and elevated PTH levels of 17.2 and 53.6 pmol/l respectively (reference value 1.3-9.3 pmol/l) underwent minimally invasive parathyroidectomy after preoperative workup confirmed the diagnosis of LIH. The third patient was treated with cinacalcet since the preoperative workup showed inconsistent results regarding the presence and location of any adenoma. The other 46 patients remained under strict control but were at the time of this cross-sectional study not referred for further analysis. Follow-up is currently conducted to obtain better insight into the clinical course of these patients.

Table 2. Gender, age, laboratory variables and lithium exposure in lithium users with normal serum calcium levels compared to hypercalcemia lithium users with hypercalcemia

	Lithium users with serum calcium level <= 2.60 (mmol/l)(n=265)	Lithium users with serum calcium level > 2.60 (mmol/l)(n=49)	p
Gender (% Female)	60.4	67.3	0.425
Age (years)	47 (13)	50 (13)	0.174
Lithium recent dosage (mg dd)	960 (270)	970 (330)	0.759
Creatinine (µmol/l)	76.82 (17.00)	81.91 (26.89)	0.091
TSH (mU/l)	2.8 (3.8)	2.0 (1.8)	0.176
Sodium (mmol/l)	140.5 (2.20)	140.7 (2.61)	0.610
Potassium (mmol/l)	4.5 (0.34)	4.5 (0.37)	0.349
Lithium serum level (mmol/l)	0.74 (0.19)	0.77 (0.18)	0.379
Lithium period (months)	109 (84)	165 (111)	0.002
Lifetime dosage quotient	$1.03 .10^5$ ($8.3 . 10^4$)	$1.63 .10^5$ ($1.3 . 10^5$)	0.004

Cohort of lithium users (n=314) divided according to the measurement of the serum calcium level in which an upper limit of 2.60 (mmol/L) was uphold. (Mean, SD))

Discussion

Main findings

In this cross-sectional study we found a significant higher prevalence of hypercalcemia in patients using lithium compared to a control group of patients without a current and previous history of lithium treatment (p 0.001). In addition, the development of hypercalcemia was correlated to the cumulative time lithium was taken regardless whether this was continuously or with one or more interruptions of various durations.

Strengths and weaknesses

This study is the first to determine the prevalence of hypercalcemia in a major cohort of psychiatric patients. Our results regarding the prevalence corroborates with previous studies.[4-9,20,26-27] However, compared to previous studies, in our study we included a large number of patients and selection bias is less likely because we used a predefined search for patients that were currently treated in a large, non-academic psychiatric outpatient clinic. Patients attending this clinic reflect a regular sample of

bipolar outpatients of varying severity and duration of illness. In most other studies, patients were selected from an endocrine surgery database instead of a psychiatric cohort. As a consequence, these cohorts included a highly selected subgroup of lithium-treated patients since the outcome, i.e., hyperparathyroidism, was already present.

In our study, patients were identified based upon their bipolar disorder, and calcium levels were measured as part of a routine monitoring schedule. In addition, using an upper limit for serum calcium levels of 2.60 mmol/L compared to various lower upper limits uphold among different hospitals, psychiatric facilities and laboratories, it is unlikely that our results overestimate the prevalence of hypercalcemia.
Furthermore, our sample consists of a relatively homogeneous group of patients, being treated at the same psychiatric hospital by a small team of psychiatrists. All other factors such as a complete medical history, use of other medication besides lithium and possibly previous surgery were taken into account. None of these showed a significant difference that could distort our results.

Although our control group of lithium-naïve patients was very small compared to the group of lithium users, reflecting the widespread use of lithium for bipolar disorder in the Netherlands, the range from low to high calcium levels seems to be higher in lithium users than in the control patients. This may be an indication that the set-point of serum calcium is higher in lithium users implicating that serum calcium is also higher in all lithium users, and leading to hypercalcemia in approximately 15%. Our control group was small (n=15) and therefore such conclusions remain preliminary. Nonetheless, this cross-sectional study is the first including a control group of psychiatric patients, in this perspective. Because lithium is the mainstay for the long-term treatment of bipolar disorder it is very difficult to identify a larger cohort of control patients (Table 1).

Whether lithium shifts the calcium set-point to the right or that it uncovers a pre-existing hyperparathyroidism remains the question. Because of the absence of parathormone (PTH) measurements, calcium in 24-hour urine specimens and proper

imaging of patients with suspected LIH we were unable to investigate this in our sample, which poses a limitation of our study.

Conclusion

The present study clearly established that the prevalence of hypercalcemia is significantly higher in patients using lithium. Furthermore, our subgroup analysis showed that the total duration of lithium treatment was significantly longer in the hypercalcemia group, regardless of any possible interruptions or discontinuation of lithium treatment.

Our results underscore that it is mandatory to perform regular monitoring of serum calcium as well as PTH levels.

LIH cannot be diagnosed based upon signs and symptoms alone, since these are easily misinterpreted in the context of mood disorders. Hypercalcemia may be caused by a higher set-point of serum calcium in lithium-treated patients. With the growing awareness of LIH, future research should focus on how to treat these patients.

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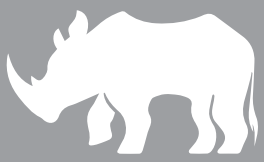
CHAPTER 7

Differences between sporadic and MEN-related primary hyperparathyroidism; clinical expression, preoperative workup, operative strategy and follow-up



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Abstract

Background: Primary hyperparathyroidism (PHPT) is most commonly sporadic (sPHPT). However, sometimes PHPT develops as part of multiple endocrine neoplasia (MEN) type 1 or 2A. In all, parathyroidectomy is the only curative treatment. Nevertheless, there are important differences in clinical expression and treatment.

Methods: We analyzed a consecutive cohort of patients treated for sporadic, MEN1-related, and MEN2A-related PHPT and compared them regarding clinical and biochemical parameters, differences in preoperative workup, operative strategies, findings, and outcome.

Results: A total of 467 patients with sPHPT, 52 with MEN1- and 16 with MEN2A-related PHPT were analyzed. Patients with sPHPT were older, more often female and had higher preoperative calcium and parathyroid hormone levels, when compared with MEN1 and MEN2A patients. Minimally invasive parathyroidectomy (MIP) was performed in 367 of 467 sPHPT patients (79%). One abnormal parathyroid was found in 426 patients (91%). Two or more in 35 patients (7%). In six patients (1%) no abnormal parathyroid gland was retrieved. Of 52 MEN1 patients, eight (15%) underwent a MIP and 44 patients (85%) underwent conventional neck exploration (CNE); with resection of fewer than 3½ enlarged glands in 21 patients (40%), subtotal parathyroidectomy (SPTX, 3-3½ glands) in seventeen (33%) and total parathyroidectomy with autotransplantation (TPTX) in six (12%). Eleven patients (21%) had persistent disease, 29 (56%) recurrent PHPT and nine (17%) permanent hypoparathyroidism, mostly after TPTX. Of 16 MEN2A patients, six (38%) underwent MIP, four (25%) CNE and six (38%) selective resection of the enlarged gland(s) during total thyroidectomy. Three patients (19%) suffered from persistent PHPT and two (13%) developed recurrent disease.

Conclusions: Sporadic PHPT, MEN1- and MEN2A-related PHPT are three distinct entities as is reflected preoperatively by differences in gender, age at diagnosis and calcium and PTH levels.
MEN2A patients are very similar to sPHPT with respect to operative approach and findings. MIP is the treatment of choice for both. MIP has low rates of persistent and recurrent PHPT and a low complication rate. The percentage of multiglandular disease and recurrences are significantly higher in MEN1 patients, demonstrating the need for a different approach. We advocate treating these patients with CNE and SPTX.

Background

The etiology of primary hyperparathyroidism (PHPT), a common endocrine disease, is most frequently sporadic and non-familial (sPHPT).[1] A significant proportion of patients, however, develop PHPT as part of the familial syndromes multiple endocrine neoplasia (MEN) type 1 or 2A [2,3]. Major features of MEN1 are endocrine tumors of the parathyroid, pituitary, and pancreas. Minor features consists of bronchial and thymic tumors.[4,5] MEN2A is associated with medullary thyroid cancer, PHPT, and pheochromocytoma.[6] In all cases of PHPT, parathyroidectomy is the only curative treatment that resolves symptoms and metabolic complications and thus improves quality of life, in both symptomatic and asymptomatic patients.

Clinical features that differentiate between patients with sporadic PHPT and MEN-related PHPT are: age of onset, female to male ratio, severity of bone involvement, family history and related endocrine neoplasias.[7-9] Once PHPT and its setting are diagnosed, the course of the disease and its treatment will change the perspective for both surgeon and patient considerably.

However, most of the current literature analyzes data on surgical treatment of PHPT without making any such distinction to this profound difference in etiology.[9-11] Although hypercalcemia might be the first clinical parameter to be discovered in all three, we strongly believe, these are very distinct and different entities, requiring a different approach.
In a population based cohort of patients treated for PHPT, we evaluated the frequency and causes (number of affected glands) of sporadic, MEN1- and MEN2A-related PHPT, as well as the differences in their clinical presentation, preoperative workup and operative strategies, findings and outcome. We sought to determine whether, with optimal surgical strategies for each subgroup, a comparable outcome (low persistent and recurrence rates) with equally low complication rates (hypoparathyroidism and recurrent laryngeal nerve injury) could be obtained.

Patient and methods

We retrospectively analyzed the records of a consecutive cohort of patients treated for sPHPT in one geographical region of The Netherlands between 1994 and 2009, comprising one academic center and three affiliated hospitals. All patients were symptomatic. The diagnosis PHPT was established biochemically by a serum calcium level greater than 10.20 mg/dL (>2.55 mmol/L) and/or a serum ionized calcium greater than 5.28 mg/dL (>1.32 mmol/L) combined with an increased, greater than 65 pg/mL (>6.5 pmol/L), or not suppressed plasma parathyroid hormone (PTH) level. In a few patients calcium levels were normal, but an increased renal calcium excretion combined with an elevated PTH level was affirmative for PHPT.[12-14] In addition, all patients with PHPT from the MEN1 and MEN2 database at the University Medical Center Utrecht (UMCU), The Netherlands were analyzed. The MEN1 database includes patients diagnosed with PHPT between 1967 and 2009. Patients were included in the MEN1 database if they had genetically proven MEN1, or three out of five manifestations of MEN1 or one out of five manifestations and a first-degree family member. Gene testing (mutation analysis) was performed in very young patients with PHPT, PHPT in combination with possible MEN1 manifestations, or a MEN- positive family history.[15] From the MEN2 database, patients diagnosed with PHPT between 1979 and 2009 were selected. MEN2A was defined in case of a MEN2A germline mutation. Patients with MEN1 and MEN2A were included if they had biochemical evidence of PHPT as stated above or enlarged parathyroid glands while undergoing a total thyroidectomy. Since the UMCU is a tertiary referral center, also patients who were initially treated at another institution and later referred to our institution were included.

Preoperative localizing studies were used in sPHPT and MEN2A patients and included ultrasonography (US), computed tomography (CT) and/or technetium-99m-sestamibi-scintigraphy (MIBI). The preoperative diagnostic work up differed between hospitals and evaluated over time. Presently, our preferential preoperative work up consists of MIBI and US. Depending on the results of the preoperative localization studies, sPHPT and MEN2A patients were subsequently operated in a preferentially

minimally invasive approach.[16] MIP was defined as a small (3cm) incision over the suspected adenoma as guided by preoperative localization (two concordant preoperative imaging techniques), whereas a unilateral approach involves a larger incision and exposure plus systematic exploration of the entire area of interest on one side (based on one positive preoperative imaging). Both inferior and superior parathyroid glands will have to be identified using this approach. In case of no visualization of an enlarged gland or discordant imaging techniques a conventional neck exploration (CNE) was performed. Preoperative imaging for MEN1 patients is not part of our policy, although many patients underwent preoperative imaging studies prior to referral to our surgical department. In subtotal parathyroidectomy (SPTX), 3–3½ parathyroid glands were resected during a CNE after identification of all parathyroid glands. In total parathyroidectomy (TPTX), four glands were resected and one (partial) gland was used as a graft for autotransplantation into the brachioradialis muscle of the nondominant forearm. The autotransplantation was performed during the same operation, using fresh parathyroid tissue.
Intraoperative PTH measurements (IOPTH) and/or intraoperative frozen section analysis, to verify removal of aberrant parathyroid tissue, were carried out in a routine fashion whenever a minimally invasive parathyroidectomy (MIP) was performed. A significant drop of more than 50% from the highest of either preoperative baseline or preexcision level at 10 minutes after hyperfunctioning parathyroid gland(s) excision indicates surgical cure and predicts postoperative normocalcemia.[17,18]

Surgical cure was defined as a normalization of serum (ionized) calcium and PTH levels for a period of at least six months after the surgical procedure. Persisting hypercalcemia or renewed hypercalcemia within the first six months after surgery was considered indicative of surgical failure. Hypercalcemia after a period of six month of postoperative normocalcemia was defined as recurrent disease. The findings of all operations necessary to achieve normocalcemia were taken into account when determining the cause of PHPT. Extirpation of a single enlarged parathyroid gland with subsequent normalization of serum calcium was defined as single gland disease. Retrieval of more than one enlarged parathyroid gland leading to normocalcemia was defined as multiglandular disease (MGD). Multiglandular hyperplasia was defined as

the situation when all four glands appeared abnormal. Hypoparathyroidism and nerve damage were considered complications of surgery. Permanent hypoparathyroidism was defined as a serum ionized calcium of less than 4.60 mg/dL (<1.15 mmol/L) and/or total calcium of less than 8.48 mg/dL (<2.12 mmol/L), persisting beyond the first six months after surgery and requiring substitution with calcium and an active form of vitamin D.

To get insight into PHPT in MEN1 and MEN2A and their difference with respect to sPHPT, we evaluated clinical and biochemical parameters, differences in preoperative workup, operative strategies, and findings.

All continuous variables were reported as median (range). Mann–Whitney U test and Independent-Samples T Test were used for two-group comparison of continuous variables and Chi squared test for analysis of categorical data. Statistical analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL). Statistical significance was established at $p<0.05$.

Results

A total of 535 patients were analyzed. The cohort consists of 467 patients with sPHPT, 52 with MEN1- and 16 with MEN2A-related PHPT. Patient characteristics are summarized in Table 1. Gender, age, preoperative calcium and PTH levels were significantly different among groups. In the sPHPT group, there were more females, patients were older and preoperative calcium and PTH levels were higher compared with the MEN1 and MEN2A patients ($p<0.001$ Chi^2, $p<0.001$ Independent-Samples T Test and $p=0.012$ Mann–Whitney U test, respectively). Clinical complaints as lethargy and renal stones were not significantly different between sPHPT patients and MEN1 and MEN2A patients ($p=0.184$ and $p=0.06$ versus $p=0.22$ and $p=0.59$ Chi^2, respectively).

Table 1. Characteristics of Primary Hyperparathyroidism in Sporadic, MEN1 and MEN2A Patients

Characteristics	Sporadic pHPT, n = 467	MEN1-pHPT, n = 52	MEN2A-pHPT, n = 16
Female, n	357 (76%)	33 (63%)	9 (56%)
Age, y, median (range)	63 (20 to 88)	33 (11 to 62)	39 (20 to 66)
Symptoms at first presentation, n	467 (100%)	42 (81%)	12 (75%)
Fatigue	188 (40%)	16 (31%)	4 (25%)
Renal stones	115 (25%)	14 (27%)	3 (19%)
Osteoporosis	73 (16%)	0	4 (25%)
Gastrointestinal symptoms	67 (14%)	7 (14%)	0
Neuropsychiatric	42 (9%)	7 (14%)	1 (6%)
Preoperative serum level, mean (range)			
Ionized calcium, mg/dL	6.76 (4.60 to 7.40)	5.56 (4.44 to 6.44)	5.4 (5.32 to 5.68)
Calcium, mg/dL	11.56 (10.12 to 22.20)	-	-
Parathyroid hormone, pg/mL	219 (10 to 3097)	78 (16 to 191)	89 (52 to 249)
Imaging modality, n			
Ultrasonography	399 (85%)	30 (57%)	10 (63%)
Computed tomography	317 (68%)	13 (25%)	8 (50%)
Technetium-99m-sestamibi-scintigraphy	206 (44%)	12 (23%)	8 (50%)
Number of used imaging modalities, mean	1.97	1.06	1.63

Abbreviations: pHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A.

The average number of preoperative imaging was similar in the sPHPT and MEN2A group (mean number of used imaging modalities 1.97 and 1.63 respectively), but higher when compared with MEN1 patients (mean number of used imaging modalities 1.06).

The operative findings and postoperative course, as well as the complications for each group are described in Tables 2 and 3.

Table 2. Surgery for Primary Hyperparathyroidism in Sporadic, MEN1 and MEN2A

Characteristics	Sporadic pHPT, n = 467	MEN1-pHPT, n = 52	MEN2A-pHPT, n = 16
Initial operation, n			
Minimally invasive parathyroidectomy	328 (70%)	5 (10%)	6 (38%)
Minimally invasive parathyroidectomy converted to conventional neck exploration	39 (8%)	3 (6%)	0
Conventional neck exploration	100 (21%)	44 (84%)	10 (62%)
Subtotal parathyroidectomy, n	-	38 (73%)	-
Total parathyroidectomy, n	-	6 (12%)	-
Number of operations, n			
One procedure	435 (93%)	26 (50%)	13 (81%)
Two procedures	31 (7%)	17 (33%)	1 (6%)
Three or more procedures	1 (<1%)	9 (17%)	2 (13%)
Mean number of operations	1.07	1.85	1.29
Cumulative operative findings, n			
No adenoma found	6 (1%)	-	1 (6%)
1 enlarged gland	426 (91%)	17 (33%)	13 (81%)
Solitary (adenoma, hyperplasia)	422 (90%)	17 (33%)	13 (81%)
Carcinoma	4 (1%)	-	-
> 1 enlarged glands	35 (7%)	35 (56%)	2 (13%)
2 enlarged glands	26 (6%)	12 (23%)	2 (13%)
3 enlarged glands	8 (2%)	17 (33%)	-
> 3 enlarged glands or hyperplasia	1 (<1%)	6 (12%)	-

Abbreviations: pHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A. Subtotal parathyroidectomy; (less than) SPTX. Total parathyroidectomy; TPTX.

Table 3. Outcome of Surgery for Primary Hyperparathyroidism in Sporadic, MEN1 and MEN2A

Characteristics	Sporadic pHPT, n = 467	MEN1-pHPT, n = 52	MEN2A-pHPT, n = 16
Persistent disease, n			
After first procedure	31 (7%)	11 (21%)	3 (19%)
After second procedure	6 (1%)	4 (8%)	1 (6%)
Recurrent disease, n			
After first procedure	3 (<1%)	28 (54%)	2 (13%)
After second procedure	-	12 (24%)	1 (6%)
Complications, n			
Recurrent laryngeal nerve injury	3 (<1%)	1 (2%)	1 (6%)
Hypocalcemia	1 (<1%)	10 (19%)	2 (13%)

Abbreviations: pHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A.

sPHPT

Of 467 patients with sPHPT, treated in the UMCU or in one of three regional teaching hospitals, 367 patients (79%) were scheduled for a MIP. The remaining 100 patients underwent a planned CNE. In 39 patients (8%) a MIP procedure was intraoperatively converted to a CNE. In 18 of these patients, the minimal invasive approach provided insufficient exposure to enucleate a correctly localized adenoma. In one patient the adenoma was not found. In the other 20 patients, the preoperative imaging was not consistent with the intraoperative findings. The surgical success rate after primary surgery was 93% (n=435). Hypercalcemia persisted after the first operation in 31 patients (7%). The persistence rate in patients with IOPTH measurement was 4%. The cumulative surgical success rate, including an early second operative procedure, was 99% (n=461). Normocalcemia resulted from removing one abnormal parathyroid gland in 426 patients (91%). Two or more abnormal glands were removed in 35 patients (7%), while four gland hyperplasia was the observed cause of PHPT in one patient. In six patients (1%) no abnormal parathyroid gland was retrieved and thus hypercalcemia persisted. Four patients developed recurrent hypercalcemia. Parathyroid carcinoma was diagnosed in four patients. The median follow-up was two years (range 1–15 years). Three patients sustained permanent recurrent laryngeal nerve damage and one patient became permanent hypocalcemic.

MEN1

Fifty-two patients underwent primary surgery for PHPT either at the UMCU (n=36) or another affiliated hospital (n=16). Eight patients (15%) underwent a MIP, twenty-one underwent less than SPTX (<SPTX), seventeen underwent SPTX and six underwent TPTX. In three patients a MIP procedure was intraoperatively converted to a CNE and TPTX due to inadequate drop of IOPTH levels. Eleven patients (21%) had persistent disease; nine patients after <SPTX (31%), one after SPTX (7%) and one after TPTX (17%). Twenty-eight patients (54%) developed recurrent PHPT, after a median time to recurrence of 8.0 years after <SPTX (56%), and after a median time of 13.0 years after SPTX (65%). None of the patients who underwent TPTX had recurrence. After primary surgery, ten patients (19%) developed permanent hypoparathyroidism; 7% after <SPTX, 25% after SPTX and 67% of the patients who underwent TPTX. One patient had a permanent recurrent laryngeal nerve injury, after multiple operations for persistent and recurrent PHPT.

MEN2A

Sixteen MEN2A patients underwent primary surgery for parathyroid disease between 1979 and 2010. Eleven operations were carried out at the UMCU and five in affiliated hospitals. Ten patients were operated in varying years after a previous total thyroidectomy. Six patients of these underwent MIP and four patients underwent CNE (n=3 one gland resected, n=1 two glands resected). In the other six patients selective resection of the enlarged gland(s) was performed during total thyroidectomy for medullary thyroid carcinoma (n=1 no glands resected because none were found, n=4 one gland resected, n=1 two glands resected). None of our MEN2 patients underwent a parathyroidectomy before they underwent a thyroidectomy. Thirteen patients were initially cured after the primary operation. Three patients suffered from persistent PHPT, two patients developed recurrent disease. The mean overall follow-up after primary surgery was 9 years (range 5–27 years). After MIP, one patient had persistent PHPT, but no one developed recurrent PHPT during five years of follow-up. Five patients had hypoparathyroidism, due to inadvertent damage to parathyroid glands during total thyroidectomy.

The percentage of operations started as a minimally invasive operation was higher in the sPHPT group when compared with the MEN populations ($p < 0.001$, chi^2). The average number of operations was higher in MEN patients when compared with the sPHPT population ($p<0.001$, chi^2); between MEN1 and MEN2A we could not demonstrate a significant difference. The number of patients with MGD was the highest in the MEN1 group ($p<0.001$, chi^2).

Conclusions

Main findings

According to our study and previous literature, sporadic PHPT, MEN1- and MEN2A-related PHPT are three distinct entities as is reflected preoperatively by differences in gender, age at diagnosis, and preoperative calcium and PTH levels.[7-9] Clearly this leads to a distinct algorithm regarding the preoperative workup and operative strategy (Figure 1). We found no difference in the prevalence of clinical symptoms, in agreement with previous studies.[9,19]

Figure 1 Treatment algorithm for patient with PHPT. PHPT primary hyperparathyroidism, MEN1 multiple endocrine neoplasia type 1, MEN2A multiple endocrine neoplasia type 2A, sPHPT sporadic primary hyperparathyroidism, MIBI technetium-99m-sestamibi-scintigraphy, US ultrasound, MIP minimally invasive parathyroidectomy, NE neck exploration, CNE conventional neck exploration.

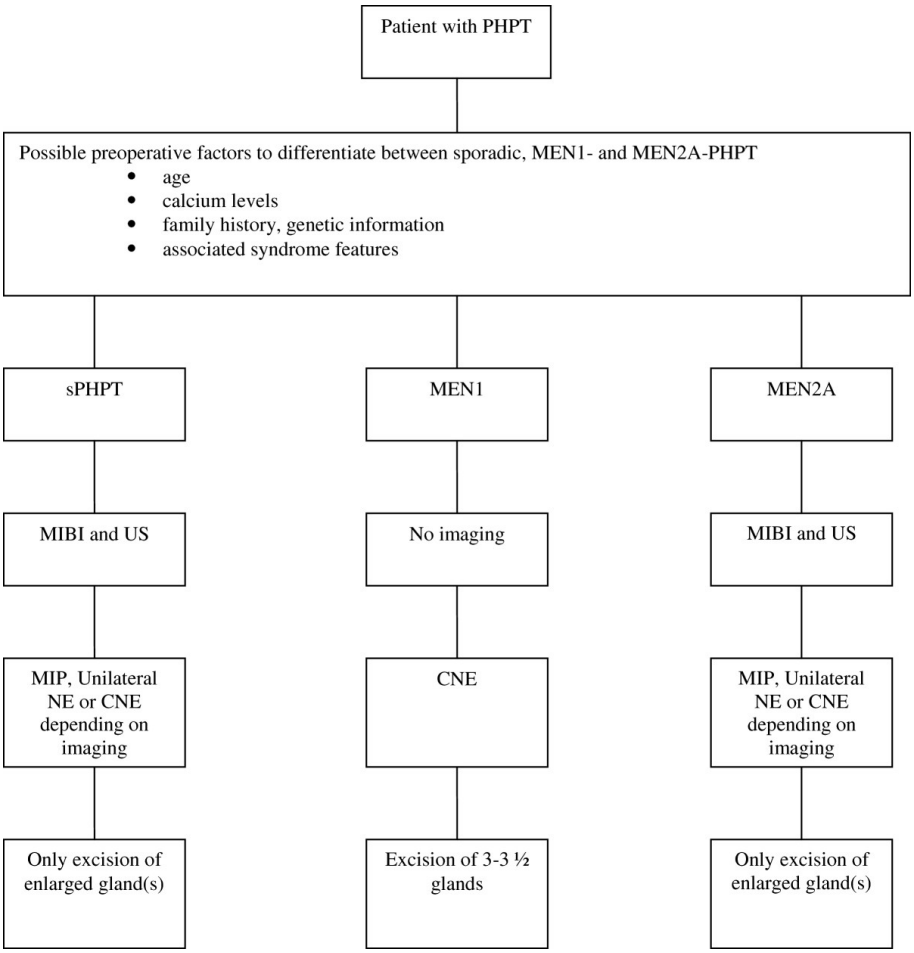

Figure 1. Treatment algorithm for patients with PHPT
Abbreviatons: PHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A; sPHPT, sporadic primary hyperparathyroidism; MIBI, technetium-99m-sestamibi-scintigraphy; US, ultrasound; MIP, minimally invasive parathyroidectomy; NE, neck exploration; CNE, conventional neck exploration.

Our data compared with the literature

sPHPT

As others have demonstrated operative findings may be a function of the operative approach; a CNE leads to removal of more parathyroid glands and thus a higher percentage of multiglandular disease.[20,21] In our series the frequency of solitary

adenomas observed is higher than historically reported.[22] The extent of the preoperative workup influences the number of observed solitary adenomas. In case of two concordant imaging studies we advocate to perform a MIP, if there is only one positive study a unilateral exploration and if all imaging studies are negative or contradictive an upfront CNE. The use of IOPTH remains controversial and we advise not to use it in a routine fashion.[23-29] Others, however, do show benefits of IOPTH measurement.[30-32] Especially, in patients with recurrent disease, in patients with proven or suspected multiglandular disease, as well as in patients with inconsistent preoperative imaging, IOPTH can add to decision making and improve outcome.[33-35] We included some patients with a normal calcium level. One might argue whether in these patients PHPT can be diagnosed. However, pathology examination confirmed the diagnosis. Part of these patients might only be intermittent normocalcemic or become asymptomatic patients later. Furthermore there is some evidence for a generalized target-tissue resistance to parathyroid hormone and as a result a renal tubular resistance to the action of PTH and thus increased renal calcium excretion.[12-14]

MEN1

The percentage of MGD is significantly higher in MEN1 patients, this demonstrates the need for a different approach in this category of patients. Ninety-five percent of MEN1 patients were treated with a CNE. Some advocate to perform a TPTX.[36-38] Based on the data presented by the DutchMEN1 Study Group, who reported a genotype-phenotype correlation in MEN1-related PHPT, we have changed our surgical strategy over the last years. Part of the patients in the present study was included in the patient cohort of a previous study. Recurrence after <SPTX, in this cohort, was significantly lower in patients with nonsense or frameshift mutations in exon 2,9, and 10. This indicates that cure primarily depends on the amount of parathyroid tissue removed. As these results have to be confirmed in an independent patient population, we have not repeated this analysis in the present cohort.[5] Because TPTX frequently results in hypoparathyroidism[38-45], SPTX combined with bilateral transcervical thymectomy is now the preferred procedure in our institution, providing the best balance between cure and postoperative hypoparathyroidism.[5,46]

When taken the high number of CNE into account we found the number of used imaging modalities in the MEN1 group rather high. A plausible cause might be the unawareness of referring physicians with the possibility of MEN-related PHPT and the inability to localize a solitary gland at first presentation causing more extensive preoperative imaging.

MEN2A

Despite different patient characteristics, MEN2A patients are very similar to patients with sPHPT with respect to their operative approach and intraoperative findings. A focused MIP is therefore the treatment of choice for PHPT in MEN2A patients.[47] MIP has low rates of persistent and recurrent PHPT and the complications are minimal. Especially patients treated in more recent years have equal rates of solitary and multiglandular disease.

Weaknesses and strengths

Weaknesses of our study are the fairly large differences in the number of sporadic, MEN1- and MEN2A-related PHPT patients and the time period in which they were treated. Unfortunately, due to the rarity of MEN syndromes these differences are inevitable. Furthermore, treatment of all three categories has gradually changed over the years due to more refined preoperative localization techniques, IOPTH measurement and the growing awareness and understanding of their differences in pathophysiology and genotype. This implies a heterogeneous case mix. On the other hand, this does reflect the clinical practice over the past decades in many hospitals and countries. A potential confounding factor is the location of treatment. The majority of MEN patients were treated in a tertiary referral center, whereas (50%) of the sPHPT patients were treated in an affiliated hospital. However, preoperative imaging and a preferentially minimally invasive approach was the standard of care in all four hospitals. Many studies have focused on patients with sporadic and MEN-related PHPT separately. The strength of this study is the description of both phenotype, preoperative work up and surgical strategy in all three categories; offering a complete overview and a treatment algorithm.

Conclusion

We performed a descriptive case–control study in which the different outcomes for sporadic, MEN1- and MEN2A-related primary hyperparathyroidism were assessed and possible contributing confounding factors were analyzed. In light of our findings in these three categories of patients; i.e. the significant higher number of MGD, reoperation rate and percentage of recurrent disease in MEN1 patients we advocate the treatment algorithm as outlined in Figure 1. In our opinion these findings are a corroboration to concentrate and treat MEN patients in a tertiary referral center.

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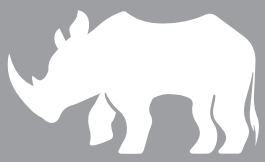
CHAPTER 8

Recurrent hyperparathyroidism caused by benign neoplastic seeding: Two cases of parathyromatosis and a review of the literature



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Abstract

Background: Parathyromatosis is defined as small nodules of hyperfunctioning parathyroid tissue scattered in the soft tissues of the neck and/or mediastinum. Parathyromatosis may be primary, it may be aimed for when autotransplanting parathyroid tissue in secondary hyperparathyroidism, and it may occur after surgery for primary hyperparathyroidism (pHPT). In the latter cases parathyromatosis poses a diagnostic and therapeutic challenge.

Methods: To illustrate the clinical problem of parathyromatosis as a rare cause of recurrent disease after an operation for pHPT we describe two patients and performed a review of the literature for contributing factors.

Results: Two patients, previously treated for pHPT and having undergone multiple neck explorations had at their final operation numerous small nests of benign parathyroid tissue scattered thoughout connective tissue of the neck. These findings concur with various previous cases reported in the reviewed literature.

Conclusions: These cases illustrate that meticulous handling of parathyroid adenomas during surgical excision is of the utmost importance. Regardless of which operating technique is utilized, great emphasis must be placed on precautions towards ensuring the complete and above all the intact removal of the affected gland without capsular rupture. As parathymatosis is caused by seeding, which although extremely rare, it might very well result in the need for reexploration.

Introduction

Recurrent hyperparathyroidism in patients previously operated for primary hyperparathyroidism (pHPT) is attributed to various causes: unrecognized multiglandular disease, failure to identify or entirely remove an adenoma, and very rarely parathyromatosis. The latter condition is defined as the presence of small nodules of hyperfunctioning parathyroid tissue scattered in the soft tissues of the neck and/or mediastinum. Parathyromatosis poses diagnostic and therapeutic challenges to the clinician.

Since parathyromatosis implies the presence of disseminated foci of abnormal parathyroid tissue it is conceivable that the primary operation contributes to this rare condition. Meticulous surgery for the primary adenoma, removing it without spill of tissue, should prevent the developing of parathyromatosis. It is unknown whether the introduction of minimally invasive parathyroid surgery (MIP) had an influence on the incidence of parathyromatosis .

We present two patients who were treated for recurrent hyperparathyroidism due to parathyromatosis. In addition the literature was searched for factors contributing to the occurrence of this condition.

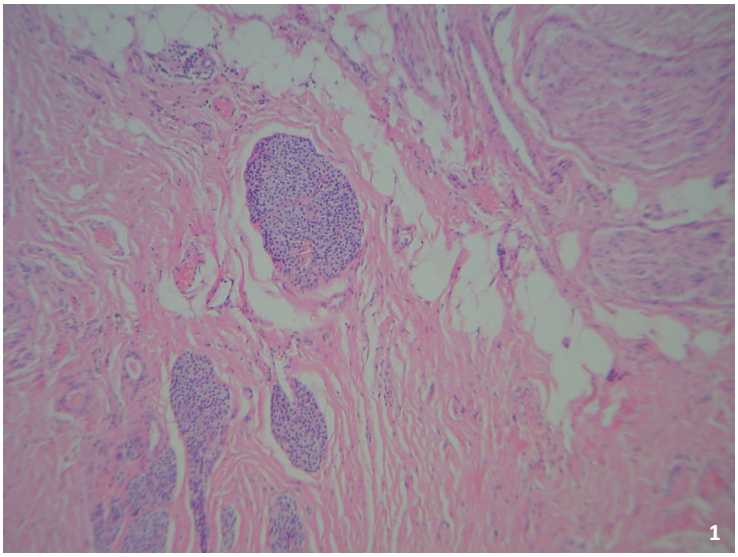
Case presentations

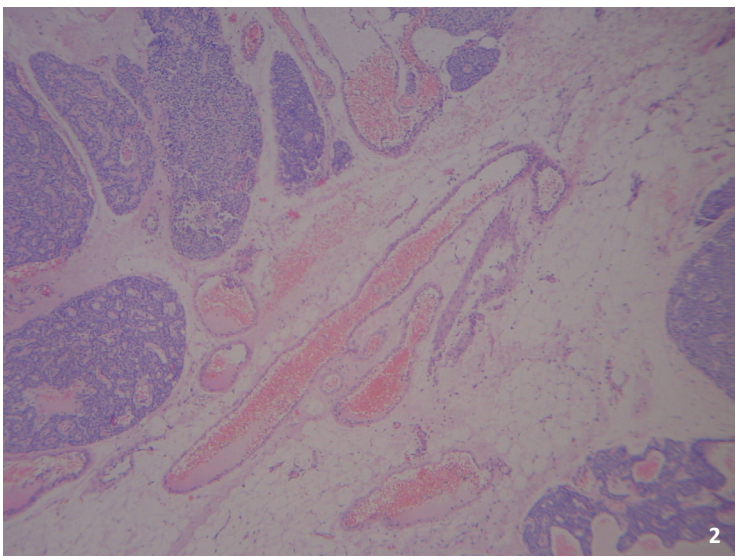
Patient A. In 1985 a 29-year-old woman presented with complaints of nausea and fatigue during pregnancy. Blood tests revealed elevated calcium and parathormone (PTH) levels. She underwent a conventional neck exploration for pHPT elsewhere. One enlarged parathyroid gland was identified inferior to the lower pole of the right thyroid lobe and subsequently resected. A normal ipsilateral parathyroid gland was not seen, while two normal parathyroid glands were identified on the contralateral side. Pathologic examination confirmed the diagnosis of a solitary parathyroid adenoma and postoperative calciumlevels were normal. Seven years later the patient

had complaints of fatigue and renal stones. Calcium and PTH levels were elevated again confirming the diagnosis of recurrent hyperparathyroidism. Preoperative technetium99- sestamibi scan (MIBI), ultrasound and venous sampling showed a right-sided parathyroid abnormality. A right-sided neck exploration was performed. During the operation parathyroid tissue was seen at several places throughout the central neck compartment. No clear adenoma was found. The parathyroid origin of the spicules was confirmed by pathologic examination. All visible parathyroid tissue was excised en-bloc with part of the right thyroid lobe. Postoperatively patient became normocalcemic. Hyperparathyroidism (HPT) recurred once more nine years after the second operation (in 2001). Ultrasound and CT once more showed abnormal parathyroid tissue on the right side of the neck. A third (right sided) neck exploration was done clearing all tissue medial and anterior of the recurrent laryngeal nerve. Histological examination revealed two adenomas. Calcium levels returned to normal one day postoperative. One year later HPT recurred a third time. CT and venous sampling of the neck showed four possible localizations of ectopic parathyroid tissue on the right side of the neck. Again all right-sided paratracheal tissue was excised. Histological examination confirmed the clinical diagnosis parathyromatosis (Figure 1). Until now patient remains normocalcemic and without symptoms. She has normal vocal cord function.

Patient B. An 81-year-old woman underwent a bilateral neck exploration for pHPT elsewhere in 1974. At the time a retrosternal adenoma had been excised. When reviewing the original operation report it was noticed that at the primary operation the excised adenoma had been defragmented. The patient had become normocalcemic postoperatively. Twenty-nine years after the first operation she developed recurrent HPT. After establishing the diagnosis biochemically, MIBI scan showed a marked increase in uptake at the right side and a CT showed a paratracheal mass measuring 3.8 by 0.9 cm suggestive of an adenoma. A conventional neck exploration was performed. At the right side adenomatous tissue was found scattered all along the paratracheal groove. A macroscopic complete resection of all right-sided abnormal paratracheal tissue was done with great precaution not to injure the recurrent laryngeal nerve. Intraoperative PTH levels dropped more than

50% proving success of the operation. Histological examination (Figure 2) showed connective tissue containing multiple nodules of parathyroid tissue. Postoperatively there was no vocal cord paresis and she became and remained normocalcemic.





Legend to Figures
Histological findings of Patient A (Figure 1) and Patient B (Figure 2); Nodules of parathyroid tissue are clearly demonstrated throughout the resection specimens.

Discussion

Parathyromatosis is a benign condition, defined as the presence of small nodules of hyperfunctioning parathyroid tissue scattered in the soft tissues of the neck and mediastinum. Two etiologies are described. Primary parathyromatosis is a clinical entity due to hyperplasia of embryologic parathyroid rests (ontogenesis) and usually occurs in patients with multiple endocrine neoplasia, especially MEN type 1.[1] Secondary parathyromatosis is caused by seeding of parathyroid cells during surgical excision.

Seeding of parathyroid tissue, the assumed pathophysiologic basis of secondary parathyromatosis, may occur following excision of normal as well as adenomatous parathyroid tissue. Fragments of parathyroid tissue survive in surrounding tissue, grow and regain endocrine function. Parathyromatosis is even aimed for when autotransplanting parathyroid tissue after subtotal parathyroidectomy. In patients with secondary hyperparathyroidism cases have been reported where these auto grafts caused relapsing secondary HPT which is in itself not surprising since the cause that was related to the development of secondary HPT remained.[2] Secondary parathyromatosis may also occur after surgical treatment of pHPT.

Patients with secondary parathyromatosis following treatment for pHPT present with recurrent HPT. Yet, even when not taking patients with missed multiglandular disease into consideration, recurrent HPT following surgical treatment of pHPT more often will be caused by the adenomatous change of a hitherto normal parathyroid gland then by parathyromatosis. The former is the case in MEN type I patients whose parathyroid glands are all at risk as well as in patients operated for pHPT who develop sporadic adenomas in one of the remaining parathyroid glands. The incidence of MEN syndrome in relation to sporadic pHPT is reportedly 1-5%.[3] However the reported risk of developing a recurrence in 11-50% of (especially MEN1) patients is almost tenfold when compared to a recurrence rate of 0.5-4% in non-familial pHPT.[4-11]

Literature Search

A review of the literature was done. Pub Med was searched with the MESH term "parathyromatosis", which revealed 29 hits. The articles were reviewed focusing on patients who had developed parathyromatosis after surgical treatment for pHPT. About 50 cases of parathyromatosis have been described since the original report from Palmer et al. in 1975.[12] Most described cases concerning patients with secondary hyperparathyroidism. When excluding reports describing patients with parathyromatosis following treatment for secondary HPT there were seven 7 articles describing a total of 16 cases operated for primary hyperparathyroidism (Table 1). One patient had had a minimally invasive procedure as the initial treatment for primary HPT, the others underwent a conventional neck exploration. The average interval between primary surgery and occurrence of secondary parathyromatosis was eight years (range 1-18years). In four patients there seemed to be primary parathyromatosis. The localization of the parathyromatosis in relation to the primary identified cause of the initial pHPT was on the ipsilateral side in 15 of the 16 patients.

Given the very low incidence of parathyromatosis it is not surprising that a preoperative diagnosis is seldom established. In one of the larger series reported by Matsuoka et al. 10 patients from a cohort of 1932 patients with renal HPT had developed parathyromatosis and in only four the diagnosis was considered preoperatively.[13] Awareness of this condition is conditional to arouse suspicion. In addition imaging studies suggesting recurrence at the same location as the primary disease in patients formerly treated for sporadic pHPT should be indicative too. When there is any suspicion on MIBI additional ultrasonography may be helpful, showing marked multiple hypoechoic to isoechoic nodules.[14] Fine-needle aspiration (FNA) may be used to confirm the diagnosis.[15] Fear of spreading parathyroid particles by FNA has proved unnecessary.[16]

Table 1. Review of the literature (Pub Med; MESH term "parathyromatosis"; 29 hits of which only relevant articles describing patients with secondary parathyromatosis are displayed).

Author, Year	Journal	Nr. of patients with parathyromatosis (n=)	Nr. of patients with primary pHPT (n=)
Fernandez 2007	Cancer	13	7
Tublin 2007	J Ultrasound Med	2	1
Koukouraki 2007	Hell J Nucl Med	1	0
Unbehaun 2007	Clin Nephrol	1	0
Carpenter 2007	Ear Nose Throat J	0	0
Matsuoka 2007	World J Surg	10	0
Bisceglia 2006	Pathologica	0	0
Daphnis 2006	Am J Kidney Dis	1	0
Jimeno 2005	Cir Esp	1	0
Evans 2005	Hosp Med	1	1
Falvo 2003	Am Surg	5	0
Lentsch 2003	Arch Otolaryngol Head Neck Surg	1	0
Makela 2001	Duodecim	1	0
Baloch 2001	Diagn Cytopathol	1	0
Lee 2001	Endocr Pract	1	0
Kendrick 2001	Am Surg	0	0
Perez 1999	Nephrol Dial Transplant	0	0
Stehman 1996	Am J Kidney Dis	5	0
Kollmorgen 1994	Surgery	1	0
Fitko 1990	Hum Pathol	1	1
Reddick 1977	Lancet	3	3
Palmer 1975	Arch Surg	2	2
Faneyte 2009	Ned Tijdschr Geneeskd	1	1

Treatment of parathyromatosis consists of surgery. Patients often undergo multiple reexplorations and extensive resection of the complete involved area add to an increased risk of recurrent laryngeal nerve damage. Despite this, persistent or recurrent disease occurs in up to 69% of patients treated for parathyromatosis. Some therefore advocate routine cervical thymectomy especially in renal HPT; apparently parathyroid cell nests may occur in the mediastinal thymus even in the absence of previous surgery.[1,17,18] Other therapeutic options consists of local alcohol ablation and the systemic use of calcimimetics.[19,20] It may be difficult to distinguish parathyromatosis from parathyroid carcinoma. Clinically, the infiltrative and adherent

growth of parathyromatosis may mimic carcinoma. Profound hypercalcemia and the presence of a palpable neck mass are indicative for carcinoma.[21,22]

Surgical technique may well play a role in the risk of developing parathyromatosis, since seeding is likely to be associated with " tumor" spill during primary surgery and all but one of the cases occurred at the location of the primary abnormality. Emphasis needs to be on a delicate dissection and operative technique resulting in the removal of intact adenoma(s) during the first operative procedure.[23]

The effect of the contemporary use of a minimally invasive approach on the incidence of parathyromatosis is unclear but could be twofold. On the one hand minimally invasive adenomectomy could increase the risk of parathyromatosis because a smaller operation field makes intact enucleation of an adenoma more difficult. A minimally invasive videoscopic parathyroidectomy for example has the possible risk of seeding parathyroid cells in the trocar track. On the other hand, a minimal approach is associated with a smaller area at risk for dissemination of parathyroid tissue. In addition all but one of the reported cases of parathyromatosis occurred after CNE. However, since the average time span between the initial operation and development of symptoms of parathyromatosis takes approximately a decade it is too soon to conclude that MIP is associated with a lower risk of developing parathyromatosis.

The cases described in the literature are almost exclusively patients with renal HPT. Renal failure causes strong stimuli for the growth of parathyroid tissue. In renal HPT the stimuli of the parathyroid cells (hypocalcemia, phosphate retention and deficiency of active vitamin D) persist after initial subtotal (3 ½) parathyreoidectomy. Therefore parathyromatosis in renal PHT is much more frequent then in primary HPT. Only a handful of cases are described in the literature regarding patients with primary HTP.

We have described two patients with parathyromatosis causing recurrent HPT after primary HPT, respectively 7 and 29 years after their initial surgical treatment. Both recurrences were on the ipsilateral side of the neck and after conventional neck

exploration. Surgical treatment implies extensive dissection of the paratracheal area with an inherent risk of recurrent laryngeal nerve damage. Meticulous handling of parathyroid adenomas during surgical excision is imperative and future studies will tell us whether MIP is associated with an increased or decreased risk of developing this condition.

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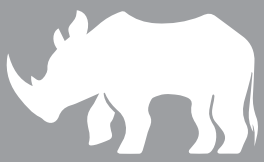
CHAPTER 9

General discussion and conclusions



Since the introduction of minimally invasive parathyroidectomy (MIP) some twenty years ago, the focused approach has gradually replaced conventional neck exploration (CNE) as the routine procedure for primary hyperparathyroidism (pHPT).[1] The rapid rise of MIP was enabled by improved preoperative localization techniques and the widespread implementation of intraoperative parathormone measurements (IOPTH). After the first successful reports of MIP in the early nineties, showing cure rates comparable to CNE combined with favourable morbidity (a lower rate of recurrent laryngeal nerve palsy and of permanent hypoparathyroidism), clinicians have readily adopted MIP. In addition, work-up has evolved and various means to increase the number of patients profiting from a minimally invasive approach have been explored.

In this thesis, patients treated for pHPT, preferably by a minimally invasive approach, were evaluated to address several issues regarding the preoperative work-up an operative treatments. Over the years (during the period that the cohort studies were conducted) some special patient groups (Lithium induced hyperparathyroidism, patients with MEN-syndromes, parathyromatosis), who may need a different preoperative workup and/or surgical approach, were identified. These particular groups have been addressed in this thesis as well.

Preoperative Work-up

MIP is only possible when a solitary adenoma is identified by preoperative imaging. Various imaging modalities are used. None of the reported techniques has a 100% sensitivity of identifying a solitary adenoma. Hence, it makes sense to combine various modalities instead of using them solely as single modalities. In **chapter 2** the additional yield of an algorithm using ultrasound and CT after a "negative" scintigraphy was evaluated. Following a "negative" MIBI scintigraphy in one quarter of the patients, subsequent US and CT suggested a solitary adenoma in the majority of the latter patients. Overall, the proportion of patients with a correctly identified solitary adenoma increased from 75 to 92%. In turn, the number of false-positive results increased also, implying that a substantial proportion of patients had imaging suggesting a solitary adenoma, while no adenoma was found at that particular site

intraoperatively. Thus, pushing the limits by the stepwise use of readily available imaging techniques increases the identification rate of solitary adenomas in patients with pHPT and selects more patients for minimally invasive surgery, yet the surgeon should be prepared to convert to CNE in patients when a solitary adenoma was identified only after the second imaging study.

Focused parathyroidectomy is based on reliable preoperative localization of suspected parathyroid pathology. Until recently, there was quite some scepticism about the necessity of preoperative imaging, as illustrated by the remark of a radiologist not that long ago (1986): "The only localizing study indicated in a patient with untreated PHTH is to localize an experienced parathyroid surgeon."[2] Despite the fact that there still lies an important truth in this allegation, the wide acceptance of MIP as the new gold standard of operative treatment of pHPT has led to a proliferation of parathyroid imaging modalities and protocols. Many surgeons may have a preference for visualization of an anatomic abnormality as a 3-dimensional representation in its relation to the surrounding/adjacent structures.

Table 1 shows the results of a PubMed search of different modalities used and their reported sensitivity. The selection of the most appropriate preoperative imaging techniques is not only a matter of accuracy of the respective techniques, but also requires knowledge of the possibilities and limitation of one's own institution. Availability, costs, local expertise of the radiology and nuclear medicine departments are all crucial considerations, as well as the patients anticipated pathology and whether it is the novo or refractory disease. In addition, effectiveness of newer techniques, such as 4DCT and SPECT/CT should be balanced against significantly higher radiation doses and costs.[3]

Which modality or which imaging strategy is the most effective remains a matter of debate. As is illustrated by the literature in Table 1 there is quite a substantial range in the reported sensitivities. Two recent meta-analyses show similar results and little difference in sensitivity and predictive value between most used algorithms.[4,5]

Hence, the choice of preoperative imaging strategy depends more on the various, institutional, economic and patient factors, all of which the surgeon should be aware of.

In our view, the imaging algorithm of choice combines MIBI and US or MIBI and SPECT. The use of SPECT-CT and 4DCT should be reserved for patients with tumours localized in the mediastinum or patients who have "unidentifiable" adenomas. In case of patients with pHPT and concordant imaging, a focused approach is at all times justified. In case of positive secondary imaging a focused approach may well be used too, but it should be readily converted to a conventional procedure. In case of negative preoperative MIBI and US one can both argue to perform an additional CT or proceed straightforward to a CNE. Although our data show that an aggressive preoperative imaging strategy allows more patients to profit from a minimally invasive approach, the historically reported success rate of CNE in experienced hands without any preoperative imaging is still as high as 97-99%.[6-9]

Table 1. Yield (sensitivity) of preoperative imaging in pHPT. Pubmed search; MESH terms: [primary hyperparathyroidism] and [imaging] and [sensitivity], English, Publication date>1989. 301 Hits. Number of patients ≥ 100. Total of 35 useful articles.

Author	Year	N	Yield[1]
MIBI			
McHenry	1996	124	81[1]
Pattou	1999	261	82[1]
Jones	2002	138	84[1]
Arici	2002	237	80[1]
Clark	2003	118	89[2]
Jacobson	2004	100	97[1]
Westerdahl	2004	103	65[2]
Saint Marc	2004	149	80[1]
Gotthard	2004	109	45[1]
Chen	2005	242	84[1]
Grant	2005	1088	86[1]
Steward	2006	103	58[2]
Barczynski	2006	121	85[1]
Carneiro	2006	519	80[2]
Nilsen	2006	100	88[3]
Solorzano	2006	226	57[2]
Prasannan	2007	131	79[1]
Lo	2007	100	89[1]
Whitson	2008	159	67[1]
Levy	2011	440	83[3]
Cummulative yield		4568	80
US			
Krubsack	1989	100	55[3]
Chapuis	1996	447	76[3]
Lumachi	2001	191	82[1]
Haber	2002	120	77[2]
Arici	2002	303	65[1]
Saint Marc	2004	149	65[1]
Grant	2005	413	61[1]
Steward	2006	106	87[2]
Barczynski	2006	121	87[1]
Solorzano	2006	226	77[2]
Prasannan	2007	131	79[1]
Lo	2007	100	57[1]
Whitson	2008	164	67[1]
Soon	2008	218	82[2]
Tublin	2009	144	74[3]

Deutmeyer	2011	136	87[1]
Untch	2011	392	87[2]
Levy	2011	440	723
Cummulative yield		3901	74
SPECT			
Civelek	2002	338	87[1]
Nichols	2008	462	87[2]
Lindqvist	2009	264	84[1]
Tublin	2009	144	58[3]
Untch	2011	506	76[2]
Cummulative yield		1714	81
US/MIBI			
Arkles	1996	121	86[1]
Steward	2006	106	93[2]
Solorzano	2006	226	90[2]
Prasannan	2007	131	94[1]
Lo	2007	100	90[1]
Whitson	2008	139	82[1]
Kwon	2013	105	94[1]
Cummulative yield		928	90
CT			
Krubsack	1989	100	68[3]
Zald	2008	223	77[2]
Cummulative yield		323	74
SPECT/CT			
Lavely	2010	110	73[1]
4DCT/US			
Kutler	2011	179	82[1]
MRI			
Krubsack	1989	100	57[3]

Yield defined as: [1] TP/(TP+FN), [2] correctly positive, confirmed by surgery, [3]unclear

Value of Intraoperative PTH assessment (IOPTH)

Apart from preoperative imaging, IOPTH is considered an important adjunct for a successful minimally invasive parathyroidectomy. Since IOPTH only confirms the successful removal of the adenoma, and does by no means help the surgeon to find the correct location, we hypothesized that IOPTH measurements added only marginally to clinical decision making. For that purpose, in **chapter 3**, a prospective

cohort of unselected patients with non familial primary HPT was operated without disclosing the results of IOPTH sampling intraoperatively. With the intraoperative knowledge of the IOPTH samples the success rate in this group of patients could have been increased at most from 95.7 to 97.4 percent. Therefore, although we don't argue that it will be certainly helpful in selected cases, we plead against the routine use of IOPTH measurements in all patients with pHPT, since the attributive value seems marginal. While our data, as well as other recent studies, favor the selective use of IOPTH,[10-19] IOPTH remains indicated under several circumstances. It is important in recurrent disease or previous unsuccessful surgery, in case of suspected MGD and in patients with negative or discordant imaging.[11,20-23] One could argue that the latter patients would be best off with a CNE just as in the years prior to the introduction of MIP, given the historical high success rate of CNE. However one should realize that the suggested selection of patients now constitutes a negative subset of patients. Therefore, IOPTH maybe worthwhile to prove the success of surgery. [24]

Definitive operative success is based on sustained normal calcium levels up to six months postoperative. While persistent hypercalcemia and recurrence rates are well described, the actual postoperative calcium drop has been poorly documented. Therefore, in **chapter 4,** we assessed postoperative calcium levels and analyzed its decline in comparison to the preoperative levels, opportunistically wondering whether calcium levels could serve as an early predictor of operative success. On the day of surgery and 24 hrs after surgery calcium levels normalized in only 78 per cent and 91 per cent of patients operated for pHPT. While the absolute postoperative serum calcium drop correlated with the extent of the preoperative hypercalcemia, the proportional drop was fairly constant. Six patients developed transient hypocalcemia one day postoperatively, but in all of these patients calcium levels returned to normal within one week. We concluded that measuring serum calcium levels on the day of surgery, or the first postoperative day, does not contribute to the early prediction of operative success. Since severe hypopararthyroidism seems non-existent in this population of minimally invasively treated patients, we suggest that determining the serum calcium level solely on the first visit in the outpatient clinic is sufficient.

Obviously, this approach necessitates a good explanation of symptoms of hypocalcemia. When MIP is performed in an outpatient setting one can consider to give temporary calcium supplementation.[25] Several factors are identified to predict the development of a hungry bones syndrome including older age, weight/volume of the resected parathyroid glands, radiological evidence of bone disease and vitamin D deficiency.[26] In another cohort, using a protocol for postoperative oral calcium suppletion, based on the following factors; elevated preoperative serum calcium >12 mg/dL, bone density T score less than -3, morbid obesity, removal of >1 parathyroid, and manipulation/biopsy of all remaining glands only 0.1% out of 6,000 patients required a visit to the emergency room for IV calcium.[27]

Incidence of multiglandular parathyroid disease

The shift from CNE to MIP seems to result in a higher frequency of observed solitary adenomas. This was confirmed, in **chapter 5**, in a population based cohort of 467 patients that preferentially underwent focused parathyroidectomy for primary non familial HPT. A higher incidence of solitary adenomas was observed than historically reported. Taking all operations to achieve a surgical success rate of 99 percent into account, the frequency of solitary parathyroid gland abnormalities was 91 percent, while parathyroid hyperplasia was seen in less than one percent of the patients. In addition, the observed frequency of solitary adenomas was even higher when more imaging modalities were used as part of the preoperative work-up. In patients who undergo MIP fewer parathyroid glands are resected than in patients operated in the 'CNE-era'. Given the absence of any evolutionary change over the last thirty years this can imply two things. Either today's rate of MGD is an underestimation or the historic rates are an overestimation. In favour of the latter explanation is the fact, that historically, the macroscopically enlarged glands were resected during a CNE following inspection of all glands while the judgement of a gland being normal or not was based on their size (>40mg). Since it is notoriously unreliable to distinguish adenoma from hyperplasia on pathology evaluation alone, and regarding size alone as a somewhat crude measure of normal function of a gland, it seems conceivable that more glands were historically resected than necessary to cure the underlying disorder. The present surgical success rates of MIP are in support of this explanation.

On the other hand, the difference in the proportion of patients with MGD can also be explained also by missed enlarged or hyperplastic parathyroids in minimally operated patients. This would result in a higher incidence of recurrent pHPT during follow-up. Indeed, there are studies reporting a higher incidence of recurrent disease following MIP, as illustrated by the Kaplan Meier plots in Figure 1.[28] This supports the former explanation.

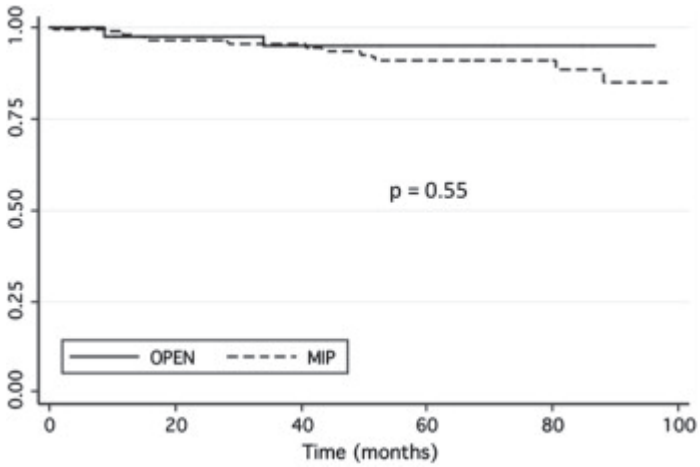


Figure 1. Recurrence. Kaplan-Meier plots for recurrent hyperparathyroidism. These plots were compared by the log-rank test with the P value indicated (Open, open parathyroidectomy; MIP, minimally invasive parathyroidectomy).

Even when MIP misses second ''borderline"- abnormal glands that eventually develop into hyperfunctioning adenomas causing recurrent disease it is questionable whether it should be reason to abandon the minimally invasive (pre)operative strategy. For some it is. Norman studied a very large cohort of 15.000 patients and reported failures 11 times more often following unilateral explorations ($p < 0.001$ vs. bilateral). Therefore rapid analysis of all 4 glands through the same 1-inch incision has been introduced in this group and they abandoned unilateral parathyroidectomy.[29]

Like the authors of Figure 5, we feel that one should not. Parathyroid reoperation remains a formidable challenge to even the most experienced endocrine surgeon and should be avoided whenever possible. Accurate intraoperative identification of abnormal parathyroid tissue in a scarred field with obliterated anatomic planes is tedious, and surgery for recurrent disease is accompanied by an increased risk for persistent hypocalcemia and/or recurrent laryngeal nerve damage and is not always successful. Yet, even if recurrence rates increased from 3% to 6% as a result of focused parathyroidectomy, this would imply that the 3% of patients who initially underwent a CNE would undergo a reoperation in an overall scarred neck, whereas the 6% who previously underwent MIP would only have the scarring only at the site where an abnormal gland had been removed during the first operation.

Special conditions: HPT in patients using lithium and in in MEN-syndromes and parathyromatosis

While a straightforward work-up and operative approach is suitable for patients with non-familial pHPT, several subgroups of patients with particular conditions require a tailored approach and/or a specific awareness.

In **chapter 6**, a cross-sectional study in patients with bipolar disorders who were using lithium medication, was conducted to determine the frequency of hyperparathyroidism. A significantly higher prevalence of hypercalcemia was found than in non-lithium treated controls. Furthermore, the presence of hypercalcemia in patients with this psychiatric condition was correlated to the cumulative time lithium was used regardless whether lithium had been taken continuously or with one or more interruptions of various duration. The observed higher incidence in this subgroup argues in favour of serum calcium and PTH levels in patients who use lithium.

There is no evidence-based consensus on the optimal surgical approach in lithium-induced hyperparathyroidism, although a number of cohort studies have been published on this subject.[30-35] The underlying pathophysiology how lithium induces hyperparathyroidism has not been elucidated, explaining why some advocate

removal of all four glands,[34,36] where others aim for a focused approach.[33,37,38] While lithium was thought to induce hyperplastic changes to all four glands (based on the idea that all glands are equally exposed) rather than causing formation of one or multiple adenomas, routine conventional neck exploration was the surgical procedure of choice for a long time.[30,39] Then again, the prevalence of multiglandular disease (MGD) in patients operated for lithium induced HPT ranged from 13 to 62 percent.[30,31,33,34,37,39] Therefore, the 'conviction' that the remaining parathyroid glands will render hyperfunctional in time lacks evidence. Some recent publications show good outcome following focused parathyroidectomy based on preoperative imaging and using IOPTH. In these studies a substantial proportion of lithium induced HPT, 38% and 68% respectively, had single adenomas and were successfully treated with unilateral surgery.[37,38] In the last few years, the development of the calcimimetics might offer an alternative in patients who are not candidates for surgery.[40,41]

Another category are patients with familial HPT, constituted by MEN1 and MEN2A patients. Preoperative differences in sex ratio, age at diagnosis, preoperative calcium and PTH levels have been reported by others.[42-44] MEN2A patients are very similar to pHPT with respect to their operative approach; a focused minimally invasive parathyroidectomy may be advocated for both PHPT and MEN2A patients. In MEN1 patients however, the percentage of multiglandular disease and recurrence rates are as high as 54% stressing the need for a different approach in the latter category. We advocate treating all these patients with a CNE and SPTX (3-3½ glands).
In light of our findings in these three categories of patients; e.g., the significantly higher number of MGD, reoperation rate and percentage recurrent disease in MEN1 patients we advocate the treatment algorithm as outlined in Figure 1, **chapter 7**.

One of the more rare causes of recurrent elevated serum calcium levels is a parathyromatosis. Parathyromatosis is a defiant condition for an endocrine surgeon. The cases described in **chapter 8** illustrate that a meticulous handling of parathyroid adenomas during primary surgical excision is of the utmost importance as the condition is thought to be the result of intraoperative "spilling" of parathyroid tissue during initial surgery. There is no evidence of the condition being more likely

to develop following CNE or MIP, but regardless of which operating technique is used for primary HPT, emphasis should be placed on removing abnormal glands in one piece. The knowledge of the existence of parathyromatosis is crucial for every (para)thyroid surgeon. Parathyromatosis, although benign, might be regarded as a malignant disease.

At various places in this thesis, the role of the operating surgeon is highlighted. The subgroups described in **chapter 6, 7 and 8** obviously underscore this statement and raise questions about current Dutch surgical practice. Approximately only 600 parathyroidectomies are performed in the Netherlands annually. Yet, in a recent questionnaire published in the Journal of the "Dutch Society of Surgery" (NVvH) only 20 percent of clinics performed more than ten parathyroid operations annually, while 86 percent of the 104 surgical practices answered affirmative on the question whether they had sufficient expertise to continue parathyroid surgery.[47]
There is evidence that a case load of >20/year (combined thyroid and parathyroid surgery) significantly decreases complication rate[45], and surgeons performing 100 or more endocrine operations yearly seem to achieve optimal results,[46] particularly in parathyroid surgery. Besides surgical experience, institutional aspects are related to patient volume as well. Interdisciplinary collaboration, dedicated endocrinologist, nuclear physicians and radiologist and off course budget for diagnostics procedures and imaging equipment are all important. While a recent interdisciplinary Dutch guideline by SONCOS (interdisciplinary collaboration between surgeons, oncologists and radiotherapists) states that twenty operations (combined thyroid and parathyroid surgery) as the minimum standard and in addition lists several requirements for the institutional endocrine infrastructure, we consider these numbers the absolute minimum threshold for (para)thyroid surgery.[48] Regional partnerships and referrals should supersede the current situation. Furthermore, all Dutch MEN patients should be operated in one or perhaps two dedicated academic hospitals.

Conclusions

The following conclusions may be drawn from the studies in this thesis.

- Pushing the limits by the stepwise use of readily available imaging techniques increases the identification rate of solitary adenomas in patients with pHPT and selects more patients for minimally invasive surgery (Chapter 2)
- The benefit of the routine use of IOPTH measurements seems marginal (Chapter 3)
- Determination of serum calcium levels on the day of surgery, or the first postoperative day, does not contribute to the early prediction of operative success (Chapter 4)
- The shift from CNE to MIP results in a higher frequency of observed solitary adenomas (Chapter 5)
- Despite current guidelines the rate of hypercalcemia in patients suffering from bipolar disorder is underestimated (Chapter 6)
- MEN1 patients require a different approach when compared to pHPT and MEN2A patients (Chapter 7)
- The handling of the parathyroids is crucial in the prevention of parathyromatosis (Chapter 8)

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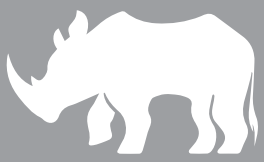
CHAPTER 10

Samenvatting



De vier bijschildklieren (parathyreoiden) zijn verantwoordelijk voor de calciumhuishouding in het lichaam. Een normale bijschildklier is slechts een paar millimeter groot en weegt ongeveer 35-50 milligram. Als één of meerdere bijschildklieren uit zichzelf te hard gaan werken, stijgt het calcium in het bloed. Men spreekt dan van een primaire hyperparathyreoïdie (pHPT). Een patiënt kan dan onder andere te maken krijgen met botontkalking, nierstenen, vermoeidheid en psychische klachten. De eerste beschrijvingen van de bijschildklier verschenen aan het eind van de 19de eeuw en de eerste succesvolle operatie werd in 1925 verricht.

Nog steeds is een operatie de enige curatieve behandeling van primaire hyperparathyreoïdie. In de afgelopen 20 jaar is de behandeling van een te snel werkende bijschildklier verschoven van een “klassieke” halsexploratie (CNE) naar een minimaal invasieve ingreep. Bij een CNE worden alle vier de bijschildklieren opgezocht en beoordeeld of ze afwijkend zijn. Bij een minimaal invasieve operatie wordt op geleide van preoperatief beeldvormend onderzoek een afwijkende bijschildklier via een kleine incisie verwijderd. Het gerapporteerde succespercentage, dat wil zeggen het correct identificeren en verwijderen van de afwijkende bijschildklier(-en) resulterend in een genormaliseerd calcium, na een CNE is 97-99% en het complicatiepercentage is laag. Een letsel van de stembandzenuw of een permanent te laag calciumniveau (hypocalciëmie) komt in slechts 0-1% van de patiënten voor. Het verwijderen van een vergrote bijschildklier door een kleine incisie wordt ook wel een minimaal invasieve parathyreoïdectomie (MIP) genoemd. Voordelen van MIP ten opzichte van CNE zijn een kleinere operatie die korter duurt, met een kortere ziekenhuisopname en minder kans op complicaties. Het succespercentage is vergelijkbaar. Het lokaliseren van een vergrote bijschildklier door preoperatief beeldvormend onderzoek is noodzakelijk om een MIP mogelijk te maken. Daarnaast is de snelle bepaling van het bijschildklierhormoon (parathormoon=PTH) een belangrijke factor geweest in de snelle introductie van MIP. Door tijdens de operatie het verloop van de bijschildklierhormoonwaarden in het bloed te bepalen (IOPTH metingen), is het mogelijk geworden om het succes van een operatie al tijdens te ingreep te beoordelen. Na verwijdering van een aangedane bijschildklier daalt het bijschildklierhormoon binnen enkele minuten naar normale waarden wat maatgevend is voor normalisering van de calciumwaarden in het bloed.

Bij patiënten met een primaire hyperparathyreoïdie is meestal slechts één bijschildklier aangedaan en vergroot, dit wordt dan een solitair adenoom genoemd. Soms gaat het echter om meerdere bijschildklieren, men spreekt dan van multiglandulaire ziekte (MGD). In de Utrechtse regio werd MIP geïntroduceerd in de jaren negentig in het UMC Utrecht en vervolgens in de regionale ziekenhuizen. In dit promotieonderzoek werden de resultaten onderzocht van bijna 500 patiënten, die volgens deze nieuwe methode geopereerd zijn, waarbij gekeken werd naar verschillende aspecten zoals de preoperatieve work-up, operatieve behandeling en follow-up.

MIP is alleen mogelijk wanneer een afwijkende bijschildklier van te voren gevisualiseerd is. De meest gebruikte beeldvormende technieken zijn echografie (US), scintigrafie met radioactief gelabeld technetium-sestamibi (MIBI), computertomografie (CT) en “single photon emission” computertomografie (SPECT). Welke beeldvormende onderzoeken of combinatie daarvan het meest effectief is, is niet duidelijk. Elke techniek heeft een beperkte gevoeligheid voor wat betreft de kans om en afwijking te vinden. Wat ons betreft wordt bij de work-up van patiënten met een primaire hyperparathyreoïdie gebruik gemaakt van een combinatie van technieken met een voorkeur voor MIBI en US of MIBI en SPECT. In het geval van een negatieve preoperatieve MIBI of US kan men een aanvullende CT maken. Ons onderzoek laat zien dat door stapsgewijs gebruik te maken van deze technieken het percentage preoperatief geïdentificeerde solitaire adenomen toeneemt en daarmee de mogelijkheid op een minimaal invasieve procedure uit te voeren.

Naast verbeterde beeldvorming is IOPTH een belangrijke factor geweest in de snelle acceptatie van MIP. IOPTH helpt uiteraard niet om een afwijkende bijschildklier te vinden. Omdat het PTH een zeer korte halfwaardetijd heeft, kan door het objectiveren van een 50% daling van het PTH 10 minuten na resectie van een bijschildklieradenoom het succes van de operatie wel worden bevestigd.
In een prospectief cohort patiënten onderzochten wij de toegevoegde waarde van IOPTH op de succeskans van de operatie en vonden een zeer beperkte toegevoegde waarde. IOPTH bepalingen werden wel gedaan, maar de uitslagen werden niet bekend gemaakt bij de operateur. Het succespercentage zou gestegen kunnen zijn

door kennis te hebben van de IOPTH-waarden van 96 naar 98%. Daartegenover staat echter een vals-negatieve uitkomst van de test in 3,4% van de patiënten waardoor een operatie onnodig langer of meer uitgebreid zou zijn geweest. Hoewel IOPTH van waarde kan zijn, zoals bijvoorbeeld bij patiënten met vermoede MGD, recidief ziekte of inconsistente preoperatieve beeldvorming, lijkt het routinematig gebruik niet zinvol.

Of een operatie definitief succesvol is, wordt pas bewezen als het calcium postoperatief normaliseert en ook zes maanden lang normaal blijft. Alhoewel het percentage niet geslaagde operaties en recidieven tamelijk goed beschreven is, is over de calciumdaling in de eerste 24 uur na een operatie weinig bekend. In een prospectief cohort blijkt dat in succesvol geopereerde patiënten 12 en 24 uur postoperatief het calcium respectievelijk 78% en 91% van de patiënten normaliseert. Daarbij komt een aantal niet succesvol geopereerde patiënten waarin het calcium in eerste instantie (vals-positief) normaliseert. We concluderen dat een postoperatieve bepaling van het calcium niet bijdraagt aan voorspellen van het succes van de operatie. Als nevenbevinding werd aangetoond dat symptomatische postoperatieve hypocalciëmie niet optrad na MIP.

Met het in toenemende mate toepassen van MIP wordt een hoger percentage van solitaire adenomen ten opzichte van MGD geobserveerd. In ons cohort van meer dan 500 patiënten was de frequentie van solitaire adenomen 91%. Daarentegen werd bijschildklierhyperplasie slechts in 1% van de patiënten gezien, wat daarmee veel lager is dan in de literatuur gerapporteerd wordt. Opvallend in ons onderzoek was het hogere percentage van solitaire adenomen hoger in de groep patiënten waarbij meer preoperatieve lokaliserende onderzoeken verricht werden. Aangezien een normale bijschildklier slechts een paar millimeter groot is en 35-50 mg weegt is het een voor de hand liggende verklaring dat het blote oog in het verleden het afwijkend zijn van bijschildklieren nogal eens heeft overschat. Dat suggereert tegelijkertijd dat er voor de minimaal invasieve operatietechniek meer bijschildklieren verwijderd werden dan strikt noodzakelijk.

Terwijl voor patiënten met sporadische primaire hyperparathyreoïdie de preoperatieve work-up en (operatieve) behandeling goed onderzocht zijn, is dat niet het geval voor een aantal speciale patiëntencategorieën, zoals patiënten met hyperparathyreoidie die lithium gebruiken, patiënten die lijden aan een MEN-syndroom (multipele endocriene neoplasie) en patiënten met een recidief hyperparthyreoïdie ten gevolge van parathyromatosis. Bij deze patiëntencategorieën is een meer specifieke aanpak nodig.

Het voorkomen van hyperparathyreoïdie onder patiënten die lithium gebruiken is onderzocht in het kader van dit proefschrift. Onder patiënten met een bipolaire stoornis die lithium gebruiken, is er een hogere prevalentie van hypercalciëmie. Het ontstaan van hypercalciëmie blijkt ook gecorreleerd aan de totale cumulatieve gebruiksduur. Of dit het gevolg is van het verschuiven van het calcium set-point, waarmee de hyperparathyreoïdie feitelijk secundair is of dat lithium een tot dan toe nog niet geopenbaarde hyperparathyreoïdie onthult, is nog onderwerp van discussie. De geobserveerde incidentie pleit in ieder geval voor een regelmatige controle van het serum calcium bij patiënten die lithium gebruiken, en dat wordt ook in de recent gewijzigde richtlijn aanbevolen. Daarnaast dient de behandelend chirurg rekening te houden met de bovengenoemde etiologische aspecten. Als de hyperparthyreoïdie beschouwd wordt als secundair, zou dat pleiten voor een klassieke halsexploratie. Welke behandeling, de minimaal invasieve (selectieve) parathyreoïdectomie of exploratie van alle vier de bijschildklieren, uiteindelijk de voorkeur geniet, zal moeten blijken uit verder onderzoek.

Er zijn verschillende types van het MEN-syndroom, waarbij op verschillende locaties hormoonproducerende tumoren kunnen ontstaan. Zowel bij MEN1 (geassocieerd met tumoren in de hypofyse, alvleesklier, bronchus en thymus) als MEN2A (geassocieerd met medullair schildkliercarcinoom en feochromocytoom) komen vergrote en te snel werkende bijschildklieren voor. Bij MEN2A patiënten, bij wie de bijschildklierafwijkingen erg lijken op pHPT patiënten is een minimaal invasieve benadering de behandeling van voorkeur. In MEN1 patiënten loopt het percentage van multiglandulaire afwijkingen op tot 54%. Daarom dienen MEN1 patiënten

behandeld te worden middels een CNE en een subtotale parathyreoïdectomie, waarbij 3½ van de vier bijschildklieren wordt verwijderd.

Een zeldzame vorm van recidief hypercalciëmie is geassocieerd met parathyromatosis. Parathyromatosis is het resultaat van spill van bijschildklierweefsel gedurende de primaire operatie. Hierdoor kan er in de jaren na de eerste operatie parathormoon producerend bijschildklierweefsel uitgroeien in het voormalige wondbed en zodoende resulteren in recidief hypercalciëmie. Kennis van het bestaan van parathyromatosis is cruciaal voor elke bijschildklierchirurg.

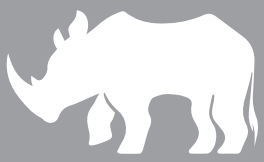
CHAPTER 11

Review Committee

Acknowledgements (dankwoord)

List of Publications

Curriculum Vitae



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Acknowledgements (dankwoord)

Het is af! Man, man, man wat ‘n boudel. Ondanks dat de weg het doel is, was de weg dit keer best lang. Hierbij wil ik iedereen bedanken die betrokken geweest is bij de tot standkoming van dit proefschrift. Zoals het een Groninger betaamt hou ik het kort en bondig, maar daarom niet minder gemeend en recht uit het hart.

In de eerste plaats, **Thijs van Dalen**, **Inne Borel Rinkes** en **Menno Vriens**, zonder jullie hulp, vriendschap en betrokkenheid was dit boekje niet mogelijk geweest. Mijn dank is zeer groot. Zowel de manier waarop jullie het vak uitoefenen, als de manier waarop jullie in het leven staan is exemplarisch.

Van alle medeauteurs wil ik met name **Anne Vollebregt** en **Bernard Houweling** bedanken voor de tomeloze inzet. Heel veel success met jullie carrières!

Leden van de leescommissie, **Prof.dr. W.W. van Solinge**, **Prof.dr. Th.J.M.V van Vroonhoven**, **Prof.dr. W.P.Th.M. Mali**, **Prof.dr. L.P.H. Leenen**, **Prof.dr. J.W.A. Smit**, hartelijk dank voor beoordelen van mijn proefschrift.

Dit promotietraject vond plaats in een periode waarin ik mezelf heb kunnen ontwikkelen als chirurg en als mens. Dank aan alle **collega’s en assistenten** van de **afdelingen Heelkunde van het Diakonessenhuis Utrecht**, **St. Antonius Nieuwegein** en het **Universitair Medisch Centrum Utrecht**. Het was een groot plezier en voorrecht om met jullie samen te werken.

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Beste **Helmer** en **Anne**, fijn dat jullie mijn paranimfen willen zijn, jullie intelligentie en ruimhartige karakters is iets om jaloers op te zijn.

Taeke, barre man, grafisch vormgever en illustrator, maar vooral levensgenieter, wat een prachtige omslag!

Lieve **ouders**, **broer**, **Marije**, **Maartje** en **Jelle**, jullie zijn zonder enige twijfel het belangrijkst in m'n leven. Dank voor jullie onvoorwaardelijke steun en liefde.

Lieve **Marije**, het leven is mooier met jou. Met jou aan mijn zijde kijk ik uit naar de toekomst.

Hora Est. 't Is mooi west. Bedankt!
Bas, Utrecht 21 juli 2013

List of Publications

1. Clinical relevance of direct postoperative serum calcium measurements in primary hyperparathyroidism. **Twigt BA**, van Dalen Th. *Submitted*.

2. Clinical Outcome of Implant Removal after Fracture Healing Results of a prospective multicentre clinical cohort study. Vos DI, Verhofstad MHJ, Vroemen JPAM, van Walsum ADP, **Twigt BA**, Mulder PGH, van der Graaf Y, van der Werken Chr. *Submitted*.

3. Hypercalcemia in patients with bipolar disorder treated with lithium: a cross-sectional study. **Twigt BA**, Houweling BM, Vriens MR, Regeer EJ, Kupka RW, Borel Rinkes IHM, Valk GD. *Accepted pending minor revisions (International Journal of Bipolar Disorders)*.

4. Een meisje met een pijnlijke hand. Houweling BM, Schmidt A, **Twigt BA**, Wittich Ph. *Accepted for Nederlands Tijdschrift voor Traumatologie*.

5. Massive transfusion in multi trauma patients. Wessem KJP, **Twigt BA**, ten Duis K, Leenen LPH. *Accepted for the International Journal of Case Reports and Images*.

6. Differences between sporadic and MEN related primary hyperparathyroidism; clinical expression, preoperative workup, operative strategy and follow-up. **Twigt BA**, Scholten A, Valk GD, Borel Rinkes IHM, Vriens MR. *Orphanet Journal of Rare Diseases* 2013; 8(1):50.

7. Recurrent hyperparathyroidism caused by benign neoplastic seeding; two cases of parathyromatosis and a review of the literature. **Twigt BA**, van Dalen Th, van Vroonhoven ThJMV, Consten ECJ, *Acta Chirurgica Belgica* 2013; 113:228-232.

8. Type C distal radial fractures treated with conventional AO plates; an easy and cost saving solution in a locking plate era. **Twigt B**, Bemelman M, Lansink K, Leenen L. *International Orthopaedics* 2013; 37(3):483-8.

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16. Colo-colonic intussusception caused by a submucosal lipoma: case report and review of the literature. **Twigt BA**, Nagesser SK, Sonneveld DJ. *Case Reports in Gastroenterology*. 2007; 1(1):168-73.

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Curriculum Vitae

Bas Twigt was born on the 5th of September 1976. He grew up in the beautiful province of Groningen (Delfzijl), where he graduated from the Fivelcollege (atheneum) in 1994. In the following year he participated in an exchange program and found himself a second home and family in Jonquière, Quebec, Canada (Vaillaincourt-Mercier family). Back in the Netherlands, due to the medical numerus fixus program, he started applied physics and astronomy and earned his propaedeuse degree in 1996. In 1996 het started Medical School at the University of Groningen. After his graduation, in the summer of 2002 he undertook a coast to coast bike ride in Canada (A mari usque ad mare, Vancouver-Halifax, 6080km). In september 2002 he started working as a surgical resident (ANIOS) in the Refaja Hospital of Stadskanaal and thereafter in the Diakonessen Hospital in Utrecht. In 2005 he started his training in General Surgery (dr. G.J. Clevers) at the Diakonessen Hospital Utrecht. During his residency he started this thesis under the supervision of dr. Th. van Dalen and prof. dr. I.H.M. Borel Rinkes. He continued his surgical training in the University Medical Center Utrecht (prof. dr. I.H.M. Borel Rinkes). The last year and a half of his residency he started specializing in traumasurgery under the supervision of prof. L.P.H. Leenen. After finishing his surgical training in 2010 he got the opportunity to be a Trauma Fellow at the St. Antonius Hospital in Nieuwegein (dr. E.R. Hammacher) and the University Medical Center Utrecht (prof. L.P.H. Leenen). After finishing his Trauma Fellowship he applied for an AO traumafellowship in Chur (Chefartzt dr. Chr. Sommer), where he spent the first months of 2013. From April 1st 2013, he is working as general and traumasurgeon in the Chirurgenmaatschap Amsterdam CMA, location BovenIJ. In addition, he is an ATLS instructor and a board member of the Ongevalstichting (accident foundation), which is committed to promote and improve trauma care in the Netherlands. The author is married with Marije Arnold and has two beautiful children, Maartje en Jelle.