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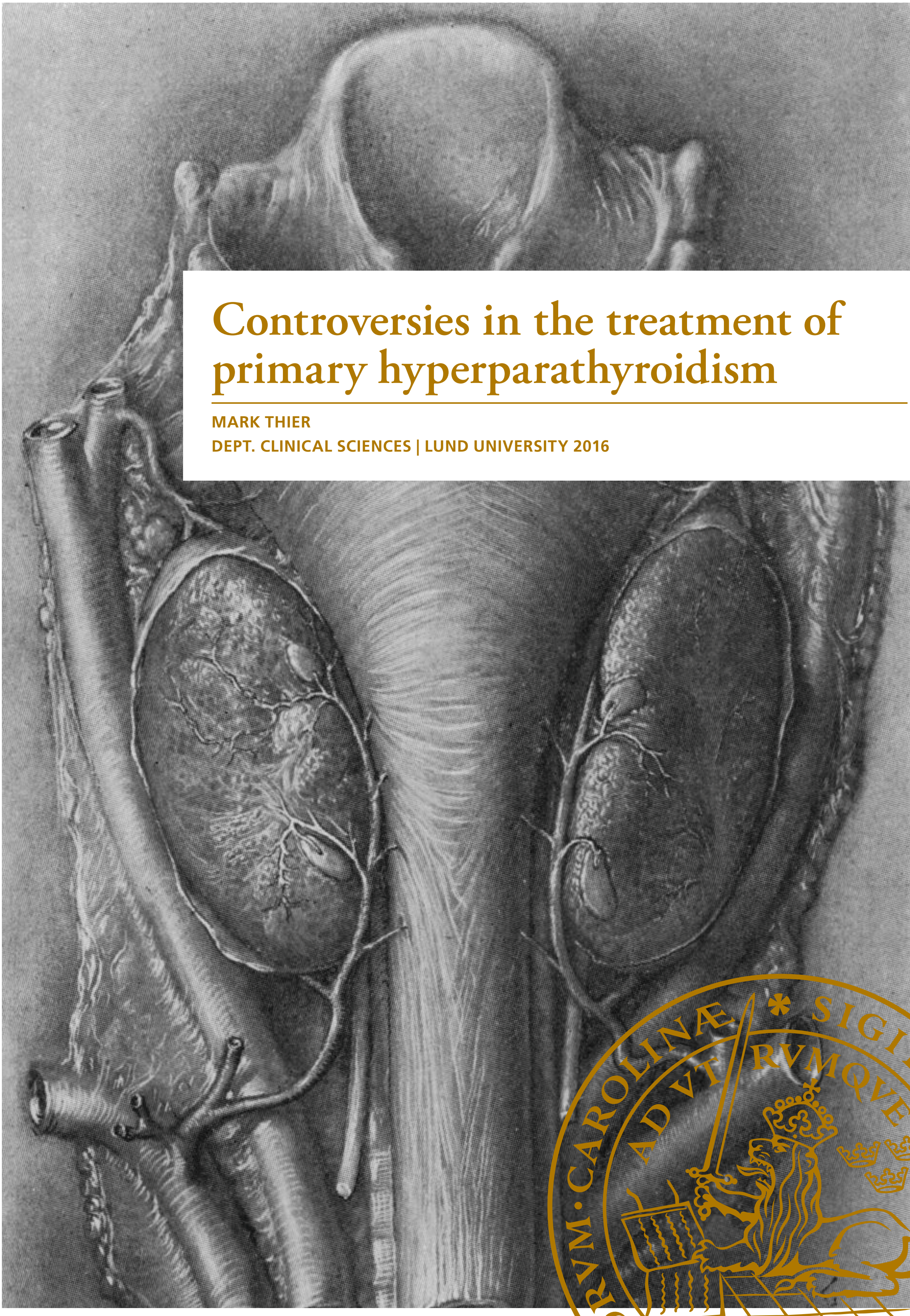

Controversies in the treatment of primary hyperparathyroidism

MARK THIER
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Abstract:

Background: The surgical treatment of primary hyperparathyroidism (pHPT) and its potential pitfalls are frequently dicussed, especially since the changing presentation of the disease to milder, often asymptomatic form is associated with a number of challenges, such as negative, preoperative localization studies, fewer organ complications and less obvious benefits of surgery.

Aims: This thesis contributes with four clinical studies to the ongoing discussion about optimal surgical treatment of patients with pHPT and negative, preoperative localization studies, practical implications of the changing presentation of pHPT, long-term results of unilateral, parathyroid surgery and the preoperative predictability of multiglandular disease.

Methods: In paper I, surgical outcome for patients with negative scintigraphy, treated with the intentention to perform unilateral neck exploration, were analyzed. In paper II, pre- and postoperative data on patients surgically treated from 1989 to 2006 were compared for three time periods. In paper III the recurrence rate during 15 years of follow-up on patients undergoing unilateral or focused parathyroid surgery between 1989 and 2010 was investigated. Paper IV was a retrospective study with uni- and multivariable analysis of possible preoperative factors for predictability of multiglandular disease (MGD) in patients surgically treated for pHPT from 1989 to 2013.

Results: In paper I, 16 out of 35 patients (46 %) with negative, preoperative sestamibi scintigraphy were operated with a unilateral approach and intraoperative PTH monitoring (iOPTH). Overall cure rate was 94 % and did not differ betweeen the groups but operation-time was longer for the bilateral group of patients. There was no patient with postoperative hypocalcemia after unilateral surgery compared to three in the bilateral group (p 0.23). The incidence of MGD in this cohort was 5.7 % (2 out of 35 patients). In paper II, preoperative ionized calcium and PTH levels as well as adenoma weight were lower in the latter time periods and there was no change in pre- and postoperative bone density, renal function and Vitamin D status during the study period. The results of paper III demonstrate high cure rate (98.9 %) after unilateral parathyroid surgery and only one patient (0.34 %) experienced recurrent disease during 15 years of follow-up. Paper IV revealed negative scintigraphy, diabetes and elevated levels of osteocalcin as independent predictors for MGD.

Conclusion: Focused or unilateral parathyroid surgery can safely be performed with iOPTH even in patients with negative scintigraphy since the majority of these patients suffer from single gland disease. Present patients with pHPT appear to have milder increase in calcium levels and smaller parathyroid glands but no specific benefit of surgical intervention at lower levels of ionized calcium was evident. Unilateral exploration with iOPTH has excellent long-term results. Negative scintigraphy, elevated levels of osteocalcin and the presence of diabetes are predictive for multiglandular disease. While scintigraphy is the only clinically usable factor, the results may suggest differences in the pathogenesis of single gland disease and multiglandular disease.

Key words: primary hyperparathyroidism, multiglandular disease, recurrence, negative localization

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To my beloved parents, family and friends

Content

List of publications

This thesis is based on the following original papers, which will be referred to as by their Roman numerals in the running text. All papers are appended at the end of the thesis

I. Surgery for patients with primary hyperparathyroidism and negative sestamibi scintigraphy--a feasibility study.
Thier M, Nordenström E, Bergenfelz A, Westerdahl J.Langenbecks Arch Surg. 2009 Sep;394(5):881-4. doi: 10.1007/s00423-009-0524-6. Epub 2009 Jun 23

II. Presentation and Outcomes after Surgery for Primary Hyperparathyroidism during an 18-Year Period.
Thier M, Nordenström E, Bergenfelz A, Almquist M.
World J Surg. 2015 Nov 17. Epub ahead of print

III. Results of a Fifteen-Year Follow-up Program in Patients Operated with Unilateral Neck Exploration for Primary Hyperparathyroidism.
Thier M, Nordenström E, Almquist M, Bergenfelz A.
World J Surg. 2015 Dec 9. Epub ahead of print

IV. Clinical and biochemical predictors of multiglandular disease in patients with primary hyperparathyroidism
Mark Thier, Sébastien Daudi, Anders Bergenfelz, Martin Almquist,
Department of Clinical Sciences, Lund University, Sweden
Submitted

Thesis at a glance

	Aim	Method	Result	Conclusion
I	Is it feasible to perform limited parathyroid exploration in patients with pHPT and preoperatively negative sestamibi scintigraphy with the guidance of iOPTH and what is the incidence of MGD in this cohort?	Prospective study on 35 patients with non-localized pHPT disease	Unilateral surgery,with shorter operation time and no postoperative hypocalcemia could be performed in 46 % of the patients.	It is safe to perform unilateral surgery in patients with negative, preoperative localization studies. The incidence of MGD in this cohort was lower than expected.
II	Is pHPT nowadays a milder disease and if so, is this change reflected in preoperative presentation and postoperative outcomes?	Pre and postoperative parameters were compared in three time periods in this longitudinal cohort study	Preoperative ionized calcium, PTH levels and adenoma weight were lower in the latter years of the study period. No change in pre- and postoperative bone density, renal function or vitamin D values were found	Patients with pHPT appear to have milder disease during the later years of the study. No extra benefit in terms of improved bone density or renal function was evident with surgery for these patients
III	To investigate the long-term recurrence rate in patients who underwent unilateral parathyroidectomy.	Prospective study on 15 years of follow-up after unilateral parathyroid surgery	The cure rate after unilateral surgery was 98.9 % with a recurrence rate of 0.34 % during 15 years of follow-up	Patients, surgically treated with unilateral surgery have a very low risk of recurrence
IV	Is it possible to predict MGD in patients with pHPT before surgery?	Retrospective study of 707 patients with uni- and multivariable analysis to identify preoperative parameters predictive for MGD	Negative scintigraphy, diabetes and elevated osteocalcin levels were found to be predictive for MGD	Negative scintigraphy is the strongest, predictor for MGD. The results questions if the aetiology for MGD is the same as for single parathyroid adenoma

Abbreviations

PTH	Parathyroid hormone
FHH	Familial hypocalciuric hypercalcemia
CV	Coefficient of variation
pHPT	Primary hyperparathyroidism
iOPTH	Intraoperative PTH monitoring
MGD	Multi-gland disease
SGD	Single-gland disease
GFR	Glomeruli filtration rate
1.25(OH2)D3	Active vitamin D
25(OH)D3	25 hydroxy-cholecalciferol

Introduction

Primary hyperparathyroidism (pHPT) has been a subject of research since the beginning of the 20th century. However, only a few randomized studies have been conducted within the field, encompassing comparatively few patients. With the changing clinical and biochemical presentation of the disease in high income countries, researchers have been focusing on morbidity and mortality of patients with "mild" pHPT and the natural history of surgically untreated patients. There is an ongoing debate if these patients benefit from surgery and how many that could be safely followed without surgical intervention. A follow-up only strategy has to be weighed against cost for outpatient care and patient compliance, especially since some patients will progress and meet criteria for surgery during observation.

An increasing variety of operation techniques and localization procedures raised additional questions about the ideal preoperative investigation and surgical treatment, as well as optimal long-term outcome and high patient safety at low costs.

This thesis contributes with four clinical studies to the ongoing discussion about surgical treatment in patients with negative preoperative localization procedures, the implications of the changing presentation of pHPT, long-term results of unilateral neck exploration and if multiglandular disease is predictable preoperatively.

Calcium homeostasis and interactions with parathyroid hormone

Calcium is an important mineral, responsible for various vital functions in humans. Approximately 99 % of the total amount of calcium is stored in the mineral matrix of the bone as calcium hydroxylapatite, reinforcing the skeleton. The remaining one % of calcium exists in three forms: in 50 % as free, ionized calcium, in 40 % as a pH-dependent, protein bound form, and in ten % as a complex with phosphate and citrate. Only the free, ionized form of calcium is physiologically active, enabling contraction of smooth and skeletal muscle, neural excitability and release of transmitter substances. Homeostasis of free, ionized calcium is maintained within a narrow range mediated by a complex interaction between parathyroid hormone (PTH) and active vitamin D (1.25(OH)2D3) through modulation of calcium reabsorption in the kidney, osteoclast activity in bone tissue and calcium uptake in the intestine.

Parathyroid hormone is a single peptide chain, with a half-life of approximately three minutes, produced by chief cells in the parathyroid gland [1]. The secretion of PTH into the blood stream is regulated by the calcium sensing receptor according to levels of free, ionized calcium. The calcium sensing receptor modulates the calcium dependent PTH secretion [2] but also influences parathyroid cell proliferation and gene transcription [3].

Parathyroid hormone increases calcium levels through several mechanisms as shown on figure 1. PTH stimulates osteoclast activity and increases the conversion from 25(OH)D3 to 1,25(OH2)D3 through hydroxylation in the kidney. The activated form of vitamin D increases tubular reabsorption of calcium in the kidney and stimulates intestinal uptake of dietary calcium. Furthermore 1,25(OH2)D3 inhibits the secretion of PTH via a negative feedback mechanism.

Calcium levels in peripheral blood can be measured either as total calcium, including protein-bound fractions, which is highly dependent on albumin levels, or free, ionized calcium. Total calcium levels are corrected in patients with hypo- and hyperproteinemia. Furthermore, total calcium analysis also has to be corrected for pH values since alkalosis increases the binding capacity of albumin and calcium. Analysis of ionized calcium is thus preferred since it reflects the biological active form of calcium. Ionized calcium appears to be more sensitive for the diagnosis of pHPT compared with total calcium, especially in patients with mild increase of calcium levels [4].

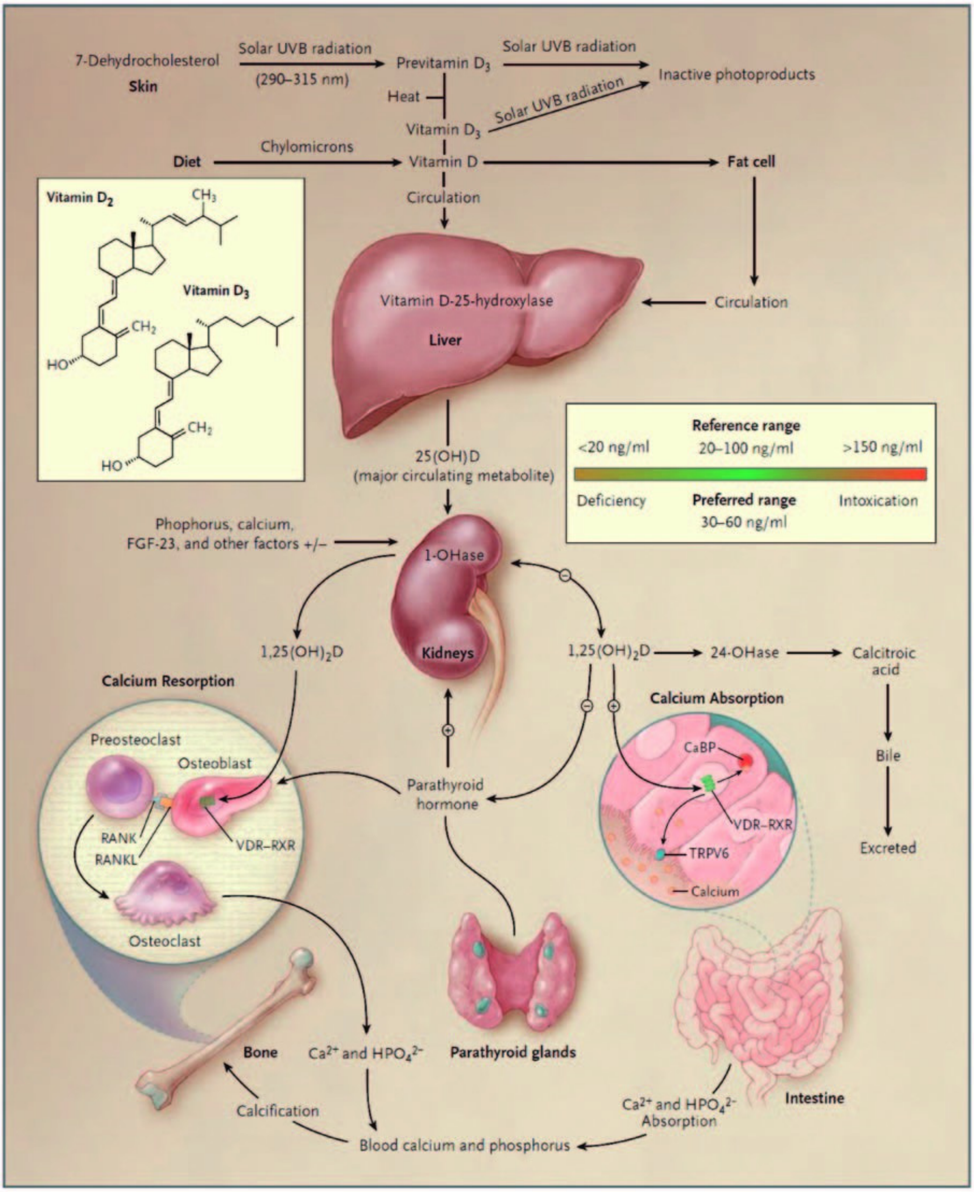

Figure 1.
Calcium hemostasis

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Historical background

Sir Richard Owen, an English paleontologist, was the first to describe small, yellow glands in close relationship to the thyroid gland in 1852 while dissecting a great Indian rhinoceros. However, he did not recognize the glands as a separate organ. Rudolf Virchow dissected the parathyroid glands in man and described them as an adjunct to the thyroid gland in 1863. In 1880, the 25 year old, Swedish medical student, Ivar Victor Sandström, was the first one to describe the parathyroid gland as an own organ in animals and humans in his publication "a new gland in man and numerous mammals". He was however unaware of the physiologic function of the glands. It was not until 1891 that Eugene Gley, a French physiologist, discovered that tetany and death after thyroidectomy in dogs only occurred if the excised specimen also contained the recently described parathyroid glands, thus being the first one to describe postoperative hypoparathyroidism. In 1891, Friedrich von Recklinghausen published a report on a patient with recurrent fractures after minor trauma, deformation of the long bones associated with brown tumors that he called osteitis fibrosa cystica, later named von Recklinghausen. Recklinghausen was still unaware of the cause of the disease.

In the meantime, research was conducted to investigate the frequent occurrence of tetany after thyroid surgery. In 1907, a young American surgeon named William Halsted, proved that reimplantation of the parathyroid glands relieves tetany after thyroidectomy in dogs [5]. In 1909, MacCallum and Voegtlin demonstrated that calcium administration could alleviate tetany caused by thyroidectomy [6]. It was not until 1915 that Friedrich Schlagenhaufer, a pathologist in Vienna, suggested that an enlarged parathyroid gland might be the cause of von Recklinghausens disease.

Felix Mandl is until today known to be among the first to cure pHPT by removing an enlarged parathyroid gland in Vienna, 1925 [7].

Anatomy and embryology of the parathyroid glands

The parathyroid glands develop between the fifth and the twelfth week after gestation in the third and fourth pharyngeal pouch and are usually four in number with a considerable variability in location and quantity. An autopsy study of 503 patients [8] showed a prevalence of four parathyroid glands in 84 % of the patients. In 13 % of patients, a supernumerary gland was found and in three %, only three glands were identified.

The position of the parathyroid glands was symmetrical with those of the other side in 80 % of the patients, which can be helpful in patients subjected to bilateral neck exploration. The parathyroid glands are typically located in the dorsal aspect of the thyroid gland. The upper parathyroid glands originate from the fourth pharyngeal pouch and can usually be found in the spatium dorsal of the recurrent laryngeal nerve in close relationship to the inferior thyroid artery. The inferior glands develop from the third pharyngeal pouch and descend with the thymus towards the inferior aspect of the thyroid gland. Compared to the upper parathyroid glands, they are usually located more ventrally and have a greater variation in location due to the longer descending path.

Epidemiology

Primary hyperparathyroidism is a common endocrine disorder with a prevalence from 0.2 to one % in the general population [9, 10] to approximately three % in female patients aged between 55-70 years [11-13]. Previously considered a rare diagnosis with advanced bone and renal disease, with the increasing availability of serum calcium measurements, the yearly incidence is nowadays approaching 25/100 000 [14]. Primary hyperparathyroidism is either caused by parathyroid adenoma, SGD or MGD with the first entity being the most common. According to the Scandinavian quality register (SQRTPA), 85 % of the patients with pHPT were diagnosed with parathyroid adenoma in 2014 and 83 % had symptoms of pHPT [15].

Primary hyperparathyroidism and organ complications

Overt pHPT is associated with osteoporosis, increased risk for bone fractures, kidney stones, nephrocalcinosis, reduced renal function, hypercalcemic crisis and psychic symptoms but also a reduced quality of life [16-20]. Several studies have demonstrated an increased prevalence of malignancies and cardiovascular and metabolic disturbances, resulting in an increased mortality compared to the general population [21-28].

A large, controlled, Swedish series of 10995 patients with pHPT showed an increased mortality rate compared to healthy controls. The main causes of premature death were cardiovascular, urogenital, metabolic disease and cancer [29, 30]. There is a similar risk for premature death in patients with multiglandular disease [30] and also an increased prevalence of various malignancies in these patients [21]. The results have been confirmed by other, population-based studies even in patients with mild disease [20, 31, 32]. It should be noted, however, that the risk profile in the United

States may be different from that in Europe, since there is little data available, that support increased mortality rates in American studies [33].

Mild and asymptomatic pHPT

The classic presentation of primary hyperparathyroidism with advanced osteoporosis, kidney stone, renal failure and gastric ulcer disease is rarely found in high income countries nowadays. On the contrary, patients with pHPT are more frequently diagnosed as "asymptomatic" and with a mild increase in calcium and PTH levels [14, 15, 34]. Other interesting subgroups of pHPT are patients with normocalcemic pHPT and patients with hypercalcemia and non-suppressed, normal PTH levels. [35-37].

It is important to note however, that reduced bone mineral density, increased fracture admission rates, neuropsychiatric symptoms, nephrolithiasis and reduced quality of life can be found even in the subgroup of patients of mild increase in serum calcium levels [20, 38-42]

Two recent studies revealed that both kidney stones and vertebral fractures can be found in a considerable number of patients with mild or apparently asymptomatic pHPT if thoroughly investigated [43, 44]. The results of those studies were applied to the latest guidelines for management of mild and asymptomatic, pHPT [45]

In a large unselected series of patients with mild pHPT from Scotland (PEARS study), an increased mortality rate was found compared to matched controls [46].

Further, several studies have shown that mild hypercalcemia may develop into overt disease, which meets criteria for surgical treatment in up to 41 % of patients with pHPT over time. In these studies it has not been possible to predict which patients will progress or not [18, 40, 46-48]. Results from the PEARS study in Scotland showed however, a relatively low risk for progression; two % of the total cohort progressed over 10 years of observation. Therefore, some authors advocate for a more conservative approach in patients with mild pHPT and age over 50 [46, 49, 50].

Benefits of surgery

Surgery is the only curative treatment in pHPT with generally excellent cure rates, exceeding well over 90 %, fast recovery after surgery and few complications [51]. Surgery is cost-effective compared to observation in patients with a life expectancy of at least 5 years [52].

Bone mineral density and fracture risk

The improvement of bone mineral density (BMD) after parathyroid surgery for overt disease is well described by numerous, randomized controlled studies [53-55] and the benefit is increasing with the severity of osteoporosis [54, 56]. An improvement of up to 10 % in BMD markers during the first 12 months after surgery may be expected [18]. An increase in postoperative BMD has also been shown in patients with mild disease in three randomized, controlled studies [39, 57, 58] while other investigations could not verify a benefit of surgical treatment [38, 54]. To which extent an improvement in postoperative BMD can prevent future fractures is not clear. Some authors found a decreased fracture risk after parathyroid surgery in retrospective studies [56, 59, 60], while others did not [46].

Randomized, controlled trials comparing surgery and follow-up with more patients and longer observation time to clarify the benefit of surgery concerning fracture risk, especially in patients with mild disease are therefore highly warranted

Kidney stones and renal function

The prevalence of kidney stones in a large cohort with primary hyperparathyroidism was considerably higher compared to a healthy control group [20]. Despite the fact that the presence of symptomatic renal stones in itself is an indication for parathyroid surgery, the effect of surgery on nephrolithiasis remains controversial. Normalization of calcium levels leads to decreased renal calcium excretion [58] and some authors also have presented a reduced risk for developing new stones [46, 61] while others could not confirm any difference in postoperative stone formation [62]. Only few studies have demonstrated an improvement in glomeruli filtration rate postoperatively [63, 64], while multiple studies could not prove a beneficial effect of parathyroidectomy on renal function [65, 66]. Additionally, renal function in several randomized, controlled studies has remained stable without surgical intervention [57, 58]

Cardiovascular disease and mortality

While numerous studies have shown benefits of early surgical intervention concerning short and long-term cardiac dysfunction [67-72], there is limited evidence proving cardiac dysfunction to be reversible after parathyroid surgery [72]. The results of two, randomized controlled studies showed however no postoperative improvement in cardiovascular risk factors and only minor improvement in postoperative left ventricular mass compared to observation.

Data on postoperative mortality is limited. A large, population-based series of Swedish patients comprising 10995 patients, operated between 1958 and 1997 showed lower postoperative cardiovascular mortality, while overall mortality remained high up to 15 years after surgery. Patients treated during the latter time period had a mortality rate comparable to that of the control population. Thus, it was concluded that treating patients with mild disease may lead to normalized postoperative mortality rates [29, 30]. Until now, there are no randomized, controlled trials investigating the long-term mortality of patients undergoing surgery vs. observation. It has to be taken in account, that several confounding factors, such as 25 (OH)D3 deficiency and obesity are frequently present in the general population and are frequently associated with hypertension and the so called metabolic syndrome [73, 74]

Quality of life

Quality of life in patients with overt pHPT and in patients with mild disease has been shown to improve after surgery by several randomized controlled studies [22, 54, 58]. Even in surgical series reporting on patients with asymptomatic primary hyperparathyroidism, an improved quality of life has been reported in up to 80 % [47], thus questioning the absence of symptoms in these patients

Recent treatment guidelines [45, 75] in Europe and the USA suggest operative treatment should be considered for all pHPT patients with moderate to pronounced hypercalcemia, signs of decreased renal function, decreased bone mineral density, age below 50 and kidney stones, as shown in Table.1. American treatment guidelines are somewhat more conservative than European ones, especially in patients with asymptomatic disease.

Table 1
Guidelines for surgical treatment in asymptomatic HPT [45]

	1990	2002	2008	2013
Measurement				
S-calcium (above upper limit of normal)	>0.25-0.4 mmol/L	>0.25 mmol/L	>0.25 mmol/L	>0.25 mmol/L
24 hour urinary ca	>10mmol/d	>10mmol/d	Not recommended	>10mmol/d
GFR	Reduced 30%	Reduced 30%	<60 mL/min	<60 mL/min
Screening for kidney stones	Not recommended	Not recommended	Not recommended	Recommended by x-ray, CT or ultrasound
BMD	Z score < -2.0 at forearm	T score ≤ -2.5 at any site	T score ≤ -2.5 at any site[a] and/or previous fracture	T score ≤ -2.5 at any site[a] and/or previous vertebral fracture on imaging
Age	<50	<50	<50	<50

GFR: gomeruli filtration rate [a] Use Z score in individuals < 50 years of age

Surgery

Successful surgery in primary hyperparathyroidism requires the removal of all hyperfunctioning parathyroid tissue to obtain normocalcemia. There are several surgical approaches and perioperative adjuncts to choose from. Bilateral neck exploration with the intention to identify all parathyroid glands has been the standard approach in parathyroid surgery and is still commonly used with excellent results [76, 77].

In the light of the frequent presence of SGD and with advances in preoperative, radiological localization modalities, surgery has evolved into a more focused approach. Limited neck exploration can be performed with open or minimally invasive technique as unilateral neck exploration where only one side of the neck is to be explored or focused operation with identification and excision of a preoperatively localized parathyroid adenoma.

Sten Tibblin, shown in the picture to the left, consultant surgeon and head of the endocrine and breast surgery unit at Lund University Hospital until 1999 was one of the early advocators of limited parathyroid exploration [78].

The advantage of focused and unilateral neck surgery lies in shorter operation time, lower risk of postoperative hypocalcemia and less adhesions in the event of future neck surgery [76, 77]. Even in patients with negative preoperative localization studies, a considerable proportion of patients suffer from single-gland disease [79]. These patients should accordingly be able to benefit from a less extensive, surgical approach.

The use of intraoperative PTH monitoring to verify biochemical cure is widely used but not mandatory, since PTH monitoring only increases cure rates marginally in patients with preoperatively well localized parathyroid disease [80, 81]. Several studies, have confirmed a high cure rate after limited neck exploration. [77, 82, 83], however, data on long-term cure rates after unilateral or focused parathyroidectomy is limited. Advocators for bilateral neck exploration argue that pathological parathyroid tissue may be missed in patients undergoing limited parathyroid exploration [84-87], with potentially persisting hypercalcemia and eventually a higher risk for recurrent disease. Overall, surgery for pHPT, independent of operative technique, results in excellent cure rates approaching up to 98 % in experienced hands [76, 77]. Complications after parathyroid surgery are generally rare but include postoperative hemorrhage, recurrent laryngeal nerve palsy and postoperative hypoparathyroidism and the risk increases with the extent of surgical exploration [76, 88].

Preoperative localization procedures

Reliable and reproducible, preoperative localization of hyperfunctioning parathyroid glands allows for selective parathyroid surgery. A variety of radiological techniques are now available, e.g. ultrasound, sestamibi scintigraphy, SPECT, 4D-CT and MRI, with the first two being the most commonly used. The results of ultrasound are known to be highly dependent on the expertise of the investigator, and the sensitivity reported in different studies have been ranging from 57 % to 96 % [89, 90].

Sestamibi scintigraphy is reproducible and the results less investigator dependent. The sensitivity of sestamibi scintigraphy may, in ideal conditions, reach approximately 89 %. The sensitivity decreases with concordant thyroid disease, smaller parathyroid glands, lower chief cell count and parathyroid hyperplasia and the cost-effectiveness of scintigraphy guided parathyroidectomy has been questioned by some authors[90-92]. Preoperative investigation with 4D-CT scan has showed promising results in recent studies including patients with previously negative scintigraphy [93, 94]. Single photon emission computed tomography (SPECT), especially in combination with sestamibi scintigraphy, has demonstrated a detection rate of 88 % [95] but is not widely available. In the event of negative preoperative localization procedures, bilateral parathyroid exploration is still regarded as the standard procedure due to a higher incidence of multiglandular disease in this patient cohort [79]. However, despite a somewhat higher incidence of multiglandular disease, a single parathyroid adenoma is still the predominant cause of hypercalcemia in the majority of the patients [92]. These patients could therefore potentially benefit from less extensive surgery than classical bilateral neck exploration.

Medical treatment

Calcimimetic drugs such as Cinacalcet increase the sensitivity of the calcium sensing receptor to extracellular calcium, thus potentially normalizing both PTH and calcium levels. There is, however, no data supporting that bone mineral density improves by medical treatment with calcimimetics alone [96]. Cinacalcet is more commonly used for treatment of patients with renal hyperparathyroidism and in carefully selected patients with pHPT where surgery is contraindicated.

Bisphosphonates, such as Alendronate are known to increase bone mineral density in patients with pHPT and osteoporosis but there is no effect on calcium or PTH levels over time [97].

Non-surgical management or follow-up only of patients with pHPT, include frequent monitoring of biochemical markers and bone mineral density over a long time due to the apparent risk of disease progression [18, 40, 46-48]. Hence, surgical treatment is regarded as more cost-efficient than medical treatment [52, 98]

Aims of the thesis

This thesis contributes with four clinical studies to the ongoing discussion about optimal surgical treatment of patients with primary hyperparathyroidism and negative, preoperative localizations studies, the changing presentation of pHPT and its practical implications, long-term results of unilateral surgery and the predictability of multiglandular disease.

Study I	To investigate the feasibility of unilateral parathyroid exploration in patients with negative preoperative scintigraphy. To evaluate the incidence of multiglandular disease in this patient cohort.
Study II	To investigate whether or not the preoperative presentation of patients with primary hyperparathyroidism has changed over time and if it does reflect in a change in postoperative outcome.
Study III	To investigate the long term recurrence rate of patients with primary hyperparathyroidism, operated with focused or unilateral parathyroid exploration
Study IV	To investigate if it is possible to identify preoperative factors predictive for multiglandular hyperparathyroidism

Material and methods

Database

Since 1989, data on all patients undergoing surgery for pHPT at Lund University Hospital have been prospectively registered in a local database for quality control. The database contains information about preoperative parameters such as age, gender, preoperative localization procedures, bone density measurements and biochemistry as well as details on operation technique, histopathology and follow-up for up to 15 years after surgery. The database is stored behind the firewall, on a local server of Skåne University Hospital in Lund.

Ethical aspects

The studies of this thesis were approved by the local ethical committee at Lund University (H4890/2004). The participants of the studies gave informed consent after written and oral information.

Diagnosis of pHPT

The diagnosis of pHPT was based on ionized calcium levels and/or serum calcium above the upper limit for normocalcemia in combination with PTH in the upper reference range or above.

Exclusion criteria

Patients with secondary hyperparathyroidism, a family history of pHPT (MEN1, MEN2 or hereditary pHPT), familial hypocalciuric hypercalcemia (FHH) and patients who underwent reoperation for persistent or recurrent pHPT were excluded from the studies as well as patients who were scheduled for concomitant thyroid surgery and who did not complete at least 12 months of follow-up.

Definition of cure

Calcium levels below the upper limit for normocalcaemia after surgery, regardless of PTH levels are regarded as biochemical cure. Postoperative hypercalcemia within six to twelve months from primary surgery is considered to be persistent hyperparathyroidism. Hypercalcemia after six to twelve months from surgery is defined as recurrent pHPT.

Table 2.
Follow-up program after parathyroid surgery at Lund University Hospital

Pre-operative	Peri-operative	6 weeks	6-12 months	5 year	10 year	15 year
Bio-chemistry	Op technique	Biochemistry	Biochemistry	Biochemistry	Biochemistry	Biochemistry
Bone density	Imaging		Bone density			
	Pathology report		Renal function			

Biochemical variables

Serum ionized calcium concentrations (reference range 1.15-1.35 mmol/L) were analyzed from blood samples normalized to pH 7.4 with the ion-selective electrode ABL 505 (Radiometer, Copenhagen Denmark). The method has a coefficient of variation, CV, of <1 % at 1.27 mmol/L. Levels of total serum calcium (reference range until 2009: 2.20-2.60 mmol/l and from 2010: 2.15-2.50 mmol/L) and creatinine were measured by a routine laboratory analyzer on a Hitachi 917 with a coefficient of variation (CV) of 2.0 % at 2.40 mmol/L.

Urinary calcium was measured after formation of calcium complexes in two steps, with 5-nitro-5'-metyl-BAPTA followed by EDTA. The sum of ionized calcium and calcium complexes is measured bichromatically at 376 and 340 nm. The method has a CV of 1.2 % at 1.8 mmol/L and 1.0 % at 2.6 mmol/L. The reference range for U-Ca is 2.5-7.5 mmol/24 h.

Plasma PTH, was analyzed by N-tact PTH assay (Incstar, Stillwater, Minn) with a sensitivity of 0.1 pmol/L. On 20th March 2000, the method was changed to an assay for intact PTH (Hitachi Modular –E), reference range 1.6-6.9 pmol/L. The analysis has a total CV of 5.9 % at 100 pmol/L. Due to this change of methods, a correction algorithm was used between old and new values: new value=1.4x old value-0.2, as defined by the Department of Clinical Chemistry at Lund University Hospital.

High performance liquid chromatography was used for assessment of the level of serum 25-hydroxyvitamin D3, 25(OH)D3. During the study period, the equipment for high performance liquid chromatography changed to Nichols Advantage (Nichols Institute Diagnostics), reference range 25–125 nmol/l. The CV for 25(OH)D3 is 15 % at 50 nmol/l.

Since the results for Nichols Advantage method is presented as nmol rather than µg/l, old values were corrected to the new method by using the algorithm: µg/l×2.5= nmol/l according to the department of clinical chemistry.

Glomerular filtration rate (GFR), was determined by a technique that measures renal clearance of the contrast agent iohexol. The average value for young healthy subjects is 127 ml/min with a reduction in subjects older than 55 years of age. In 65-year-old subjects, the expected GFR would be about 80 ml/min.

Osteocalcin was measured through one-step immunometric sandwich assay using ElectroChemiLuminiscenceImmunoassay based on a derivate of Reuthenium. Reference range is 10-43 g/L (adults). The CV for this method is 3 % at 19 g/L.

Alkaline phosphatase (ALP) was measured bichromatically at 450 and 480 nm at an alkaline pH, reference range 0.60-1.8 mmol/L. The CV for this method is 6.9 % at 0.57 mmol/L.

Phosphate is measured bichromatically at 340 and 700 nm. The concentration was determined by the difference in absorbance. Reference range is 0.8-1.5 mmol/L (for women >18 years). The method has a CV of 5.8 % at 0.7 mmol/L.

Bone mineral density

Since 1994, BMD of the lumbar spine (L2-L4) and in the femoral neck and shaft were investigated by dual-energy X-ray absorptiometry (DEXA). Measurements were made with the Lunar Expert XL equipment, software version 1.72 (Lunar Corp, Madison, Wis). The method has a CV of one %. BMD is expressed in gram per square centimeter (g/cm2) and as age and gender specific standard deviations (Z-scores). Individual change after surgery in BMD (delta values) was calculated according to the following formula: (BMD 1 year after surgery – preoperative BMD / preoperative BMD) * 100, and are presented in %.

Preoperative localization procedures

Sestamibi subtraction scintigraphy has been performed routinely at Lund University hospital since 1994 according to following scheme: thirty megabecquerels QgmT was injected intravenously. Data recording started 10 minutes later and continued for 10 minutes. Twenty minutes after the first injection 500 MBq gQmTc sestamibi was administered intravenously. Six minutes later data acquisition started and continued for 20 minutes. Patients were immobilized to provide identical locations during both sequential scintigraphic investigations. A standardized computer subtraction of the gQmTc thyroid image was performed to receive an image of the abnormal parathyroid gland(s) for both the scintigraphic methods. The result was classified according to five levels: (1) no adenoma visualized, (2) probably negative can, (3) weak adenoma indication, (4) probable adenoma, and (5) strongly indicative for parathyroid adenoma. In the analysis, levels 3, 4, and 5 were considered as positive scans, whereas levels 1 and 2 were considered as negative scans.

Ultrasound:

Neck ultrasound for identification of enlarged parathyroid glands was predominantly performed at the department of radiology at Lund University Hospital.

Intraoperative PTH measurement

For intraoperative analysis of PTH, a quick PTH assay was used as described earlier with an intra-assay variation between 0.8 and 10 pmol/L of less than 8 % for the rapid method. The correlation between the two methods is 0.99.

For the first study (paper I), a decrease of iOPTH of > 50 %, five minutes and/or > 60 %, 15 minutes after gland removal was used to verify successful removal of pathological parathyroid tissue. For the other studies, the Miami Criterion [99], e.g., a decrease of iOPTH of >50 % from baseline value ten minutes after removal of pathological parathyroid gland tissue was used to verify biochemical cure. Intraoperative PTH values were measured and recorded in all patients at baseline, five, ten and fifteen minutes after removal of pathological gland tissue.

Paper I

Patients:

Consecutive patients with pHPT and negative preoperative sestamibi scintigraphy subjected to first time surgery at Lund University Hospital between 2003 and 2006 were included in the study.

Surgery:

The patients were operated with a minimal transverse 15-20 mm long incision. Surgery commenced with exploration of the patients´ left side. If no adenoma was found or iOPTH monitoring indicated additional pathologic parathyroid glands, the right side of the patients´ neck was explored through a second incision with the option of combining the two incisions to standard open technique if needed.

Statistics:

If not stated otherwise, results for continuous variables are expressed as median and range. For categorical data, absolute numbers in addition to percentage are shown. Differences in numeric data between groups were analyzed with the Mann-Whitney test due to skewed distribution of numbers. For categorical data, statistical significance was calculated by using the Chi-squared test and the Fishers exact test when frequencies were less than five. A probability level of $p<0.05$ was considered to be significant. Statistical analysis was carried out with Statview 5.01 (Abacus Corporation, USA).

Paper II

Patients:

Patients, subjected to first time surgery for sporadic pHPT at Lund University Hospital between 1989 and 2006 were included in this longitudinal cohort study. Pre- and postoperative data on the patients in the whole cohort was stratified by gender and histology, and analyzed and compared for three time periods: 1989-1994, 1995-2000 and 2001-2006.

Surgery:

During the study period, either bilateral neck exploration or unilateral or focused exploration (through a lateral incision or a central Kocher incision) was performed, depending on preoperative localization and results of iOPTH. To verify successful removal of all pathological parathyroid tissue, iOPTH measurement was used in all patients. Frozen section was used selectively.

Statistics:

Due to skewed distributions of numbers, medians with interquartile range for pre- and postoperative values were calculated for the three time periods, and compared using the Kruskal-Wallis test. Patients with persistent disease were excluded from postoperative analysis. Change over time in preoperative calcium levels, PTH, GFR and postoperative change in BMD were analyzed by using Spearman's linear regression model.

A p-value <0.05 was considered significant. All tests were two-sided. Statistical analysis was carried out with STATA 11 (StataCorp LP, Texas)

Paper III

Patients:

Patients operated with unilateral or focused parathyroid exploration for pHPT at Lund University Hospital from 1989-2010 were included in the study. Patients who underwent bilateral neck exploration, whether preoperatively planned or peroperatively required for cure, were excluded from the study. The study group consisted of patients with preoperatively localized parathyroid adenoma as well as patients with non-localized pHPT.

Surgery:

All patients underwent surgery performed under general anesthesia, either with an anterior Kocher incision or a lateral mini-incision over the sternocleidomastoid muscle in patients operated with a focused approach.

In patients with negative preoperative localization studies, operation was performed with exploration of the left side first as previously described by the authors [78].

To verify successful removal of all pathological parathyroid tissue, intraoperative PTH monitoring was used.

To verify successful removal of all pathological parathyroid tissue, iOPTH monitoring (iOPTH) was used.

Statistics:

The association between variables over time was tested with the Spearman rank correlation test. Nominal data is shown as numbers and percentage. Medians with interquartile range (IQR) were calculated for continuous data. All tests were two-sided. Overall survival data was calculated by Kaplan Meier survival curves. A p-value <0.05 was considered statistically significant. Statistical analysis was carried out with STATA 11 (StataCorp LP, Texas)

Paper IV

Patients:

Consecutive patients who underwent surgery for sporadic pHPT at Lund University Hospital from 1989-2013 were included and classified into either SGD or MGD. Multiple gland disease was defined as excision of more than one pathologic gland during surgery regardless of cure, or in patients with persistent pHPT after excision of a single pathological parathyroid gland.

Single gland disease was defined as the patient being cured after the excision of one pathological gland.

Statistics:

The cohort was analyzed and stratified as SGD or MGD. All variables were analyzed for normal distribution by using histograms and box plots. Medians with interquartile range (IQR) were calculated for continuous data in the SGD and MGD subgroups. Continuous data was compared using two-sample student's t-test and Mann-Whitney U test for normal and skewed distributions where appropriate. Pearson's chi-squared test was used to compare categorical data between groups. Uni- and multivariable logistic regression models were developed to identify preoperative factors independently associated with MGD. The following independent variables were included in the analysis: gender, positive preoperative scintigraphy (yes or no), diabetes (yes or no), age, ionized calcium, phosphate, alkaline phosphatase PTH, U-Ca, osteocalcin, iohexol clearance, 25(OH)D3, and BMD z-score for the radius. Continuous variables with less than ten % missing values had missing values replaced with the median. This was done for phosphate, ALP and PTH. For missing values of ionized calcium, a conversion factor (ionized calcium to total calcium) was used to calculate total calcium, which had no missing data. Levels of osteocalcin, U-Ca, 25(OH)D3, iohexol clearance, and BMD Z-score had more than ten % missing values each. These variables were converted into tertiles, with missing as a separate category. Neck ultrasonography was performed in less than half of the patients and was therefore not included as a study variable. Odds ratios (OR), p-values, and 95 % confidence intervals (C.I.) were calculated. A p-value <0.05 was considered statistically significant. All tests were two-tailed. STATA version 11 (StataCorp LP, Texas) was used in the study.

Results

Paper I

There were 35 patients with negative scintigraphy included in the study, 16 underwent unilateral surgery and 19 patients required bilateral exploration. The overall cure rate was 94 % (33 of 35 patients). Among the 35 patients with pHPT, 33 patients had a single parathyroid adenoma according to histopathology report.

The postoperative results are displayed in Table 3. There was no difference in the median adenoma weight in the unilateral group of patients, median 0.48 gram (range 0.15 to 2.5 gram), compared to the bilateral group median 0.40 gram (range 0.12 to 1.60 gram), p 0.45. Median operation time in the unilateral group was shorter than in the bilateral group (40 minutes vs. 95 minutes; $p<0.001$).

There was no difference in the complication rate for recurrent laryngeal nerve palsy, postoperative bleeding or hematoma between the two groups of patients.

Unilateral group

Unilateral parathyroid surgery was successfully performed in 15 out of 35 (43 %) patients. One out of 16 patients operated with unilateral exploration had persistent hypercalcemia. Intraoperative PTH in the patient with persistent disease declined 48 % at five minutes after removal of a macroscopically enlarged left lower parathyroid gland and 54 % after 15 minutes and did not meet the criteria for sufficient decline of PTH for cure. The surgeon decided to terminate operation without bilateral exploration due to an additional decline in PTH at 20 minutes after gland excision. No patient suffered from postoperative hypocalcemia.

Bilateral group

Out of 19 patients in this group, 17 patients had single gland disease as assessed intraoperatively and a parathyroid adenoma according to histopathology. Three patients suffered from postoperative hypocalcemia. 18 out of 19 patients were cured which was correctly predicted by iOPTH.

In one patient multiglandular disease was suspected intraoperatively, and two glands on the left side were removed without a decrease in iOPTH. Exploration of the contralateral side was negative. Intraoperative PTH declined to normal levels after exploration and the operation was terminated. Histopathology report showed parathyroid hyperplasia.

One patient had recurrent pHPT. In this patient, four enlarged glands were identified during surgery. An insufficient decline in PTH, 13% after removal of three, slightly enlarged parathyroid glands, indicated multiglandular disease. Histopathological report showed however normal parathyroid glands. Familial hypocalciuric hypercalcemia or a fifth not identified enlarged parathyroid gland, was discussed as a possible cause for the disease. At six months follow-up, the patient was normocalcemic but hypercalcemia recurred after additional six months.

Intraoperative PTH

Intraoperative PTH predicted operative success in 29 of 33 patients with a sensitivity of 88 %. Surgical failure was detected with a specificity of 100 %.

Table 3.
Clinical data on the patients with primary hyperparathyroidism and negative scintigraphy who underwent unilateral and bilateral operation.

	Unilateral operation n=16	Bilateral operation n=19	p-value
Sex m/f	4/12	4/15	
Age (year)	72	67	0.82
Preop calcium (mmol/L)	2.78	2.80	0.58
Preop PTH (pmol/L) median	9.7	9.8	0.87
Operationtime (min) median	39.5	95.0	<0.001
Adenomawheight (g) median	0.48	0.40	0.45
Postop. hypocalcemia number(%)	0(0)	3(16.7)	0.23
Hospital stay (days) median	2	2.3	0.20

Paper II

Preoperative biochemistry and bone density

Preoperative characteristics in the whole cohort stratified by gender and study period are displayed in table 4.

Sex and age at the time for surgery did not differ between the time periods. In the whole cohort, a lower median level of preoperative ionized calcium was found in the time period 2001-2006 compared to 1989-1994, 1.45 mmol/L vs. 1.50mmol/L; p<0.001. Univariate Spearman linear regression with operation year as independent variable confirmed this trend (rho= -0.16, p<0.001). Preoperative PTH levels in the cohort of patients operated due to solitary parathyroid adenoma were lower in 2001-2006 than in 1989-1994, 10.0 pmol/L vs. 11.6 pmol/L; p 0.04. Median adenoma weight was also lower in 2001-2006 compared with 1989-1994, 0.5 gram and 0.7 gram, respectively, p 0.04.

Median preoperative BMD of the lumbar spine in male patients diagnosed with a solitary parathyroid adenoma was lower in 2001-2006 than in 1995-2000, 1.065 g/cm2 vs. 1.192 g/cm2; p 0.04. In agreement, median preoperative Z-score of BMD in the lumbar spine in male patients with parathyroid adenoma was lower in 2001-2006 than in 1995-2000, -1.10 s.d. vs. 0.20 s.d.; p 0.02.

There were no further differences in preoperative BMD, median urinary calcium, GFR, or 25(OH)D3 (Table 4).

Table 4. Preoperative characteristics in the whole cohort of patients with primary hyperparathyroidism. Medians, and interquartile range are shown

	All				Women				Men			
Time period	**1989-1994**	**1995-2000**	**2001-2006**	**p**	**1989-1994**	**1995-2000**	**2001-2006**	**p**	**1989-1994**	**1995-2000**	**2001-2006**	**p**
Patients (n)	114	130	160		88	98	128		26	32	32	
Age (years)	65 *55-75*	70 *55-77*	67 *59-76*	*0.42*	68 *57-78*	73 *58-78*	68 *59-76*	*0.32*	62 *49-71*	64 *49-73*	62 *51-76*	*0.73*
P-Calcium (mmol/L)	2.74 *2.65-2.90*	2.77 *2.67-2.88*	2.76 *2.66-2.88*	*0.8*	2.80 *2.70-2.90*	2.77 *2.70-2.90*	2.76 *2.70-2.90*	*0.82*	2.7 *2.58-2.81*	2.78 *2.67-2.92*	2.8 *2.70-2.95*	*0.04*
S-ionized calcium (mmol/L)	1.50 *1.44-1.57*	1.46 *1.41-1.53*	1.45 *1.40-1.52*	*<0.001*	1.51 *1.44-1.57*	1.46 *1.41-1.51*	1.44 *1.40-1.50*	*<0.001*	1.45 *1.42-1.50*	1.48 *1.40-1.59*	1.48 *1.41-1.55*	*0.81*
P-PTH (pmol/L)	11.5 *8.6-18*	12 *8.6-16.6*	11 *8.2-14*	*0.15*	11.7 *8.6-10.4*	12.1 *9-16.6*	11 *8.3-14*	*0.09*	11.1 *9.2-16.6*	11.3 *7.4-16.6*	11 *7.7-17*	*0.99*
Urinary calcium (mmol/L)	5.0 *3.2-6.9*	4.7 *2.8-6.6*	4.2 *3-6*	*0.21*	4.6 *3-6.4*	4.4 *2.5-6.5*	4 2 *0.6-5.6*	*0.35*	6.5 *4.40-8.20*	5.2 *4.10-7*	5.4 *4-6.7*	*0.43*
GFR (ml/min)	74 *56-92*	74 *61-89*	77 *64-9*	*0.43*	71 *56-92*	73 *61-89*	76 *64-91*	*0.5*	89 *83-96*	83 *61-95*	88 *76-105*	*0.24*
S-25OHD (nmol/L)	53 *38-61*	51 *42-68*	52 *31-66*	*0.31*	52 *39-61*	50 *41-66*	52 *31-65*	*0.75*	56 *34-60*	61 *48-72*	53 *30-73*	*0.17*
BMD lumbar spine L2-4 (g/cm^2)	*	1.036 *0.883-1.209*	1.009 *0.883-1.12*	*0.24*	*	0.988 *0.840-1.157*	0.991 0.837-1.111	*0.98*	*	1.189 *1.024-1.321*	1.065 *0.972-1.210*	*0.23*
Z-score of BMD lumbar spine, L2-4	*	-0.40 *-1.40-0.70*	-0.50 *-1.70-.40*	*0.30*	*	-0.50 *-1.40-.70*	-0.40 *-1.60-.50*	*0.97*	*	-0.05 *-1.23-.95*	-1.10 *-1.90-0*	*0.25*
BMD femoral neck (g/cm^2)	*	0.796 *0.684-0.908*	0.779 0.694-0.855	*0.40*	*	0.758 *0.655-0.864*	0.767 *0.692-0.841*	*0.63*	*	0.888 *0.778-0.980*	0.829 *0.724-0.928*	*0.21*
Z-score of BMD femoral neck	*	-0.60 *-1.0-0*	-0.60 *1.20-0*	*0.68*	*	-0.60 *-1.0-0*	-0.50 *-1.10-0.20*	*0.81*	*	-0.70 *-1.2-0*	-1.20 *-1.60- -0.70*	*0.08*
Adenoma weight (g)	0.70 *0.36-1.32*	0.75 *0.41-1.46*	0.5 *0.31-1*	*0.04*	0.67 0.38-1.3	0.7 0.4-1.4)	0.51 0.32-1.0	*0.08*	0.73 *0.27-1.3*	0.83 *0.34-2.1*	0.5 *0.28-1.2*	*0.28*

* Not measured routinely before 1994; BMD; bone mineral density; Z-score; standard deviations adjusted for sex and age; GFR; Glomeruli filtration rate

Postoperative biochemistry and bone density

Postoperative characteristics in the whole cohort, stratified by gender and study period are displayed in Table 5.

Median ionized calcium levels in the whole cohort of patients and in patients with solitary parathyroid adenoma at one year after surgery were higher between 2001-2006 compared to 1989-1994, 1.24 mmol/L vs. 1.22 mmol/L; $p<0.001$. Median levels of PTH at one year after surgery, in the whole cohort, and in patients with parathyroid adenoma, were higher 2001-2006 than in 1989-1994, 4.5 pmol/L vs. 3.6 pmol/L; $p<0.001$ and 4.6 pmol/L vs 3.6 pmol/L; $p<0.001$, respectively.

Postoperative renal function measured as levels of GFR at one year after surgery, were similar in all periods that were studied.

Postoperative BMD did not change in median absolute values, Z-score or delta BMD in the lumbar spine or femoral neck between time periods (1995-2000) and (2001-2006) independently of gender and histology (Table 5).

Change over time in delta values of BMD in the whole cohort, were calculated with univariate Spearman`s linear regression model with operation year as independent variable. There was no correlation in the lumbar spine (rho -0.07; p 0.30), nor in the femoral neck (rho -0.09; p 0.17) between year of surgery and delta values of BMD.

Table 5. Postoperative characteristics 1 year after surgery in the whole cohort of patients operated for primary hyperparathyroidism. Medians and interquartile range are shown. Patients with operative failure were excluded.

	All				**Women**				**Men**			
Time period	**1989-1994**	**1995-2000**	**2001-2006**	**p**	**1989-1994**	**1995-2000**	**2001-2006**	**P**	**1989-1994**	**1995-2000**	**2001-2006**	**p**
Patients (n)	114	130	160		88	98	128		26	32	32	
Operation time (min)	115 *90-155*	81 *57-117*	71 *40-110*	*<0.001*	112 *90-147*	77.5 *52-15*	63.5 *39-105*	*<0.001*	138 *77-175*	100 *78-128*	97 *59-119*	*0.13*
P-PTH 1 year (pmol/L)	3.6 *2.6-4.7*	4.1 *3.2-5.6*	4.5 3.4-5.9	*<0.001*	3.6 *2.6-4.8*	4.1 *3.15-5.8*	4.6 *3.4-6*	*<0.001*	3.7 *1.7-4.3*	3.6 *3-5.4*	4.0 *3.2-5.1*	*0.17*
S-ionized Calcium 1 year (mmol/L)	1.22 *1.20-1.25*	1.20 *1.18-1.24*	1.23 *1.20-1.27*	*<0.001*	1.23 *1.2-1.26*	1.2 *1.18-1.24*	1.24 *1.21-1.27*	*<0.001*	1.22 *1.21-1.24*	1.21 *1.17-1.26*	1.23 *1.20-1.27*	*0.40*
GFR 1 year (ml/min)	**	70 *55-86*	77 *62-88*	*0.34*	**	70 *55-85*	77 *62-86*	*0.35*	**	70 *58-88*	86 *65-98*	*0.32*
BMD lumbar spine (g/cm^2) L2-4 1 year	*	1.024 0.871- *1.221*	0.994 *0.882-* *1.103*	*0.43*	*	1.021 *0.849-* *1.221*	0.993 *0.875-* *1.102*	*0.69*	*	1.226 *1.070-* *1.326*	1.126 *1.008-* *1.245*	*0.20*
Delta BMD L2-4 (%) 1 year	*	3.48 -0.64-9.33	1.58 -0,97-7.32	*0.09*	*	3.48 -0.55-9.38	1.35 -0.93-6.72	*0.08*	*	4.48 -0.78-9.33	2.77 -1.0-9.16	*0.46*
Z-score of BMD L2-4 1 year	*	-0.25 *-1.0-1.10*	-0.20 *-1.30-0.60*	*0.56*	*	-0.30 *-1.30-0.90*	-0.20 *-1.40-0.60*	*0.71*	*	0.25 *-1.20-1.40*	-0.20 *-1.15-0.60*	*0.25*
BMD femoral neck (g/cm^2) 1 year	*	0.770 *0.688-* *0.912*	0.793 *0.70-0.876*	0.64	*	0.769 *0.673-* *0.907*	0.789 *0.694-* *0.875*	0.95	*	0.895 0.812- *1.004*	0.848 *0.741-* *0.923*	0.20
Delta BMD (%) femoral neck 1 year	*	2.80 0-5.54	2.08 -1.18-5.63	0.16	*	3.08 0-5.54	1.95 -1.14-5.14	0.13	*	2.59 0-5.04	2.70 -1.18-5.87	0.73
Z-score BMD femoral neck 1 year	*	-0.40 *-1.0-0.30*	-0.50 -0.90-0.40	0.57	*	-0.45 -1.0-0.3	-0.50 -0.90-0.40	0.98	*	-0.30 *-0.80-0.40*	-0.85 *-1.40-0.05*	0.08
Cured 1 year, n (%)	113 (99)	125 (95.9)	152 (94.7)	0.48	87 (98.7)	94 (95.6)	120(93.4)	0.55	26 (100)	31 (96.7)	31 (96.5)	0.85

* Not measured routinely before 1994; ** Few observations; BMD; bone mineral density, Z-score; standard deviations adjusted for sex and age

GFR;Glomeruli filtration rate

Paper III

Some 292 patients underwent first time surgery with a unilateral approach. The study population consisted of patients with positive and negative preoperative localization procedures, as presented in table 6. Preoperative status and postoperative follow-up data are displayed in Table 7.

Table 6.
Results of preoperative localization procedures

	N	Pos.	Neg.	Not performed	Conc. pos.[a]	Conc. neg.[b]	Not performed	Correct prediction of side	Sensitivity%
Scinti-graphy	253	219	34	39	36	1	27	191	87.2
Ultrasound	71	61	10	221				47	77.0

[a] Concordant positive localisation studies
[b] Concordant negative localisation studies

In 131 of 292 patients (45.3 %), two parathyroid glands were identified intraoperatively. Normocalcemia was achieved in 289 (98.9 %) patients postoperatively with no patient suffering from hypocalcemia. None of the 34 patients with negative preoperative localization procedures recurred after excision of a single parathyroid gland

In three (1.1 %) patients, surgery was unsuccessful with signs of persistent disease. In one of these patients, only one gland was identified and excised with iOPTH decreasing > 50 %. Histopathology showed, however, normal parathyroid tissue. This patient had preoperatively elevated serum creatinine and developed renal insufficiency at five years of follow-up. In the two remaining patients, both glands on one side were identified. After removal of one enlarged gland, both patients remained hypercalcemic despite histopathology diagnosing a parathyroid adenoma. Intraoperative PTH was false positive in these two patients as well.

Histopathology:

In 286 patients, histopathology showed a parathyroid adenoma with a median gland weight of 730 mg (range 100 to 9800 mg; i.q.r. 380-1550 mg). Four patients had a histopathological diagnosis of parathyroid hyperplasia although only one gland was excised and no signs of persistent or recurrent disease were observed during the follow-up program.

Follow-up:

The median follow-up time was five years (range 4 weeks to 15 years). During follow-up, 69 patients died. Some 275 patients (94.2 %/275 person-years/5 patients deceased) were followed for 1 year, 164 patients for 5 years (56.2 %/820 person-years/31 patients deceased), 70 patients for 10 years (24.0 %/700 patient-years/57 patients deceased) and 51 patients for 15 years after surgery (17.5 %/765 patient-years/69 patients deceased).

Recurrent disease:

During 15 years of follow up, one patient was diagnosed with recurrent disease at five years after surgery. This patient had a positive preoperative sestamibi scintigraphy before primary surgery which indicated a parathyroid adenoma corresponding to the upper left parathyroid gland. Preoperative ultrasound investigation showed an enlarged thyroid gland but no parathyroid adenoma. After removal of the upper left gland and identification of the lower right gland, which was assessed as macroscopically normal, iOPTH decreased by 61 %, and the operation was terminated. In this patient PTH was in the normal range at ten minutes after gland excision, although this was not used for decision-making at the time of the operation. Histopathology showed a parathyroid adenoma with a rim of suppressed normal parathyroid tissue. Postoperatively, ionized calcium levels were in the upper normal range (1.30 mmol/L) with elevated PTH (13 pmol/L) and 25(OH)D3 was measured to 25 nmol/L at one year after surgery. Supplementation with Vitamin D was initiated, but had to be terminated due to increasing calcium levels. At follow-up after five years, the patient had clear biochemical signs of recurrent disease (ionized calcium 1.41 mmol/L, total calcium 2.68 mmol/L and PTH 14 pmol/L). Sestamibi scintigraphy and ultrasound were negative and the patient was referred to the department of endocrinology for further follow-up. The patients´ calcium levels have been stable until April 14th 2013 without further treatment.

Table 7, Pre -and postoperative follow-up data in patients operated with unilateral neck procedures for primary hyperparathyroidism

	Preoperatively	Follow-up 4 weeks	Follow-up 1 year	Follow-up 5 years	Follow-up 10 years	Follow-up 15 years
Patients at risk (n)	292	292	287	215	90	61
Patients followed-up (n)	292	279	275	164	70	51
Deceased (n)	-	0	5	31	57	69
Missing (n) **(% of pat. at risk)**	-	13 (4.5)	12 (4.2)	51 (23.7)	20 (22.	10 (16.4)
Cured n (% of pat. at risk)	-	277 (99.3)	271 (98.5)	163 (99.4)	70 (100)	51 (100)
Persistent disease (n)	-	3	3	-	-	-
Recurrence (n)	-	-	-	1	0	0
P-Calcium (mmol/L) **(median and interquartile range)**	2.74 2.63-2.85	2.34 2.27-2.41	2.31 2.25-2.39	2.33 2.28-2.39	2.36 2.28-2.42	2.35 2.27-2.44
S-ionized Calcium (mmol/L) **(median and interquartile range)**	1.46 1.41-1.52	1.24 1.21-1.27	1.22 1.2-1.26	1.22 1.20-1.25	1.22 1.2-1.25	1.23 1.20-1.25
P-PTH (pmol/L) **(median and interquartile range)**	10 7.4-14	5.2 3.85-7.3	4.65 3.5-6.35	4.55 3.55-6.05	4.25 3.2-6.2	4.7 3.6-5.4
Creatinine **(median and interquartile range)**	71 60-85	-	72 61-83	74 66-91	70 62-82	73 64-87
S-25OHD (nmol/L) **(median and interquartile range)**	50 37-64	45 38-62	56 36-69	64 45-80	*	*

*** Not measured routinely 10 and 15 years after surgery**

Paper IV

There were 707 patients with pHPT included in the present study, 546 women (77.2 %) and 161 men (23.8 %). Characteristics for patients with SGD and MGD respectively are shown in table 8. Some 628 patients had a solitary parathyroid adenoma (88.8 %) and 79 patients had MGD (11.2 %).

Gender, age, BMD z-score, or biochemical presentation did not differ between patients with a histopathological diagnosis of MGD or SGD.

Multiglandular disease was more common in patients with negative preoperative scintigraphy (15 out of 85 patients; 18 %) than in patients with positive scintigraphy (34 out of 366 patients; 9 %), p 0.03. Patients with MGD were more likely to suffer from diabetes (12 out of 79 patients; 15 %) than patients with SGD (45 out of 628 patients; 8 %) $p<0.01$ and had lower levels of urinary calcium, median 3.80 mml/L vs. 4.44 mmol/L for patients with MGD and SGD respectively, p 0.04.

Scintigraphy was highly indicative for SGD with 332 patients diagnosed with SGD postoperatively out of the 366 (90.7 %) patients with positive scintigraphy. Some 311 (93.5 %) of patients with positive scintigraphy did not suffer from diabetes.

Logistic regression analysis

Table 9 shows the results of the univariable and multivariable logistic regression analyses.

In the univariable logistic regression analysis, a negative sestamibi scintigraphy was associated with MGD, OR 2.09 (95 % confidence interval (CI) 1.08 to 4.05) as well as osteocalcin, 2nd tertile, OR 3.12 (1.51 to 6.45). The multivariable logistic regression analysis was performed using the same variables as those used in the univariable model. Diabetes was associated with the outcome MGD with OR 2.75 (1.31 to 5.80) as well as osteocalcin (2nd and 3rd tertiles), OR 3.79 (1.75 to 8.21) and OR 2.36 (1.02 to 5.48), respectively.

Table 8. Descriptive statistics for the entire cohort stratified into single gland and multiple gland disease. Medians and interquartile range are displayed for continuous variables.

	Single gland disease N=628	Multiple gland disease N=79	
Characteristics	**n (%)**	**n (%)**	**p**
Gender			
Female	490 (89.7)	56 (10.3)	0.15
Male	138 (85.7)	23 (14.3)	
Sestamibi scintigraphy[a]			
Positive	332 (90.7)	34 (9.3)	0.03
Negative	70 (82.4)	15 (17.6)	
Not performed	226 (88.3)	30 (11.7)	
Diabetes			
Yes	45 (78.9)	12 (21.1)	<0.01
No	581 (90.4)	62 (9.6)	
Age, years, media (i.q.r)	*65 (56-74)*	*68 (56-76)*	0.21
Ionized calcium, mmol/L, median (i.q.r.)	*1.45 (1.40-1.52)*	*1.46 (1.38-1.52)*	0.83
Phosphate, mmol/L, median (i.q.r.)	*0.79 (0.70-0.90)*	*0.79 (0.66-0.88)*	0.48
Alkaline phosphatase, µkat/L median (i.q.r)	*1.80 (1.30-3.0)*	*1.70 (1.20-2.40)*	0.17
PTH, pmol/L, median (iq.r.)	*9.90 (7.30-13.0)*	*10.0 (8.50-15.0*	0.09
U-Ca, mmol/L (26%)* median (iq..r)	*4.44 (2.80-6.60)*	*3.80 (2.80-5.10)*	0.04
Osteocalcin, µg/L (18%)*, median (i.q.r.)	*30.0 (18.0-46.0)*	*33.0 (26.0-49.0)*	0.06
Iohexol clearance, ml/min (26%)* median (i.q.r.)	*78.0 (65.0-90.5)*	*72.50 (60.0-93.0)*	0.31
25(OH)D_3, nmol/L (17%)* median (i.q.r.)	*50.0 (37.0-65.0)*	*46.0 (35.0-57.0)*	0.23
BMD Z radius, g/cm^2 (36%)*, median, (i.q.r.)	*-0.60 (1.60-0.30)*	*-0.40 (-1.50-0.70)*	0.39

* missing% if > 1% ; PTH; parathyroid hormone, U-Ca; urinary calcium, 25 (OH)D3; 25 hydroxy vitamin D3, BMD; bone mineral density, i.q.r.; interquartile range; Z-score; standard deviation adjusted for age and sex

Table 9. Results of univariable and multivariable logistic regression analysis. Odds ratios (OR) are calculated for the outcome multiple gland disease and 95% confidence interval are presented. For categorical variables, the reference category has an odds ratio of 1,00.

	Univariate logistic regression		Multivariate logistic regression	
Characteristics	OR	95% CI	OR	95% CI
Gender				
female	1.00		1.00	
male	1.46	0.87-2.46	1.42	0.70-2.85
Sestamibi Scintigraphy				
positive	1.00		1.00	-
negative	2.09	1.08-4.05	2.32	1.13-4.78
Diabetes				
Yes	2.50	1.26-4.97	2.97	1.40-6.30
No	1.00		1.00	
Age	1.01	0.99-1.03	1.00	0.98-1.02
Ionized calcium	0.78	0.08-7.15	0.32	0.28-3.65
Phosphate	0.58	013-2.59	0.71	0.12-4.24
alkaline phosphatase	0.88	0.73-1.04	0.76	0.43-1.35
PTH	1.01	0.99-1.02	1.39	0.82-2.38
U-Calcium				
1st tertile	1.00			
2nd tertile	1.30	0.69-2.44	1.26	0.63-2.49
3rd tertile	0.57	0.27-1.21	0.34	0.10-1.14
Osteocalcin				
1st tertile	1.00			
2nd tertile	3.12	1.51-6.45	3.39	1.75-8.21
3rd tertile	1.95	0.90-4.22	2.11	1.02-5.48
Iohexol clearance				
1st tertile	1.00			
2nd tertile	0.67	0.35-1.27	0.65	0.32-1.35
3rd tertile	0.68	0.36-1.29	0.57	0.21-1.02
25(OH)D_3				
1st tertile	1.00			
2nd tertile	0.93	0.51-1.68	0.86	0.45-1.65
3rd tertile	0.58	0.29-1.14	0.49	0.22-1.04
BMD Z radius				
1st tertile	1.00			
2nd tertile	1.13	0.55-2.32	1.04	0.48-2.24
3rd tertile	1.34	0.66-2.6	1.21	0.56-2.59

Discussion

The aim of this thesis was to enhance the knowledge of several clinical aspects of pHPT, concerning clinical presentation, surgical treatment and outcome.

Primary hyperparathyroidism can at present only be cured by surgical removal of all hyperfunctioning parathyroid tissue with several operation techniques available. Surgical treatment should result in high cure rates and a low risk for complications and recurrent disease.

Histopathology

Parathyroid adenoma can histologically only be distinguished from parathyroid hyperplasia by the presence of a suppressed rim of normal parathyroid tissue. However, sometimes it can be difficult to differentiate between the two entities by histopathology alone [100]. Therefore, clinical outcomes, such as normocalcemia after removal of one pathologic gland have to be applied to reliably diagnose single gland disease [79]. Multiglandular disease is defined accordingly, as postoperative hypercalcemia after removal of one pathologic gland or normocalcemia after removal of several, pathologic parathyroid glands.

Operation technique

The aim of bilateral neck exploration is to identify at least four parathyroid glands in order to remove all pathologic parathyroid gland tissue to ensure postoperative normocalcemia. This approach puts two laryngeal recurrent nerves at risk instead of one as is the case of unilateral or focused parathyroid surgery. Additionally, there is an apparent risk for postoperative hypocalcemia due to bilateral surgery. The benefit of bilateral neck exploration is that asymmetrical parathyroid hyperplasia can be distinguished from parathyroid adenoma, especially in patients with mild disease. Accordingly, some authors advocate bilateral neck exploration in all patients [84]. However, according to numerous trials, a more selective surgical approach offers comparable cure rates, shorter operation time and lower risk for postoperative hypocalcaemia as well as no risk for bilateral recurrent laryngeal nerve palsy, compared to classical bilateral exploration [76, 77, 82].

Focused parathyroid surgery is mainly used in patients with preoperatively well localized parathyroid adenoma. According to some authors, patients with negative preoperative localization procedures seem to have a higher incidence of multiglandular parathyroid disease, smaller adenomas with higher count of chief cells, atypical adenoma localization or concomitant thyroid disease. These findings implicate more extensive surgery such as bilateral neck exploration [91, 101]. However, given the fact that pHPT is mainly caused by single gland disease, and even frequently found in patients with negative localization studies, [91, 102, 103], the majority of these patients could benefit from less extensive surgery to obtain biochemical cure.

Cure

In this thesis, cure of pHPT was defined as postoperative ionized calcium < 1.35 mmol/L or total calcium levels < 2.50 mmol/L regardless of postoperative PTH levels. Some authors consider patients with calcium levels within the normal range but with an increase in PTH to suffer from persistent sub-clinical pHPT [84] It is known however, that postoperatively elevated PTH levels after pHPT surgery despite normocalcaemia occur in up to 30 % of all patients that have undergone pHPT surgery due to vitamin D insufficiency, impaired renal function and decreased peripheral sensitivity for PTH [104-110].

Follow-up

Since 1989, all patients undergoing surgery for pHPT are subjected to a standardized follow-up program at four weeks and six to twelve months after surgery to determine whether or not the patient is cured or suffering from persisting disease, including evaluation of renal function and bone density at the one year follow-up. Further follow-up is performed with calcium and PTH levels as well as markers for renal function every fifth year up to 15 years after surgery. Persistent disease is defined as hypercalcemia within six to twelve months after surgery.

Paper I

In a cohort of patients with negative scintigraphy, the incidence of multiglandular disease and the feasibility to perform limited parathyroid surgery was investigated. Some 94.3 % of the patients were diagnosed with a solitary parathyroid adenoma despite earlier research indicating a higher incidence of MGD in patients with preoperatively non-localized pHPT [111, 112]. All patients underwent surgery with the intention to perform limited parathyroid exploration (focused or unilateral approach), guided by iOPTH. The results showed that 43 % of the patients were cured by unilateral operation with iOPTH. The overall cure rate for the whole group of patients was 94.3 %, at one year after surgery. The study confirms longer operation time in patients who underwent bilateral parathyroid exploration, compared to patients treated with limited parathyroid exploration. None of the patients in the unilateral group suffered from postoperative hypocalcemia compared to three patients in the bilateral group (p 0.23). In this cohort with relatively few patients, a higher proportion of MGD in patients with negative sestamibi scintigraphy could not be confirmed. However, even with an increased incidence of MGD, the results suggest that a considerable portion of the patients could be offered unilateral or focused parathyroid surgery with the aid of iOPTH with good outcomes.

Paper II

The biochemical and clinical presentation of pHPT has changed over time [113-115] and is now predominantly characterized by a mild elevation of calcium and PTH levels, lower parathyroid gland weight and few or no symptoms [116]. Several studies [37, 117] showed an increase in the rate of MGD in patients with mild pHPT, especially if the weight of the first removed gland is below 200 mg [118, 119]. This could potentially have a negative impact on the sensitivity of localization procedures, cure rates and outcomes. The main purpose of this study was to investigate whether preoperative parameters such as levels of calcium, PTH, 25(OH)D3, renal function and BMD have changed during the study period of 18 years.

The results showed lower levels of preoperative, ionized calcium, lower gland weight and lower PTH in patients with pHPT over time also confirmed by previous studies [17, 113, 114, 118, 120-122]. The cure rate did not change over time and there was no increased incidence of MGD over the studied time periods. With a median adenoma weight of 500 to 700mg, the gland weight in the present cohort is still well above the previously described cut-off value of 200mg, indicating an increased risk for multiglandular disease [118, 119].

It was hypothesized that a lower grade of hypercalcemia over time would lead to lesser impairment of GFR. However, median preoperative GFR was similar in all three time periods that were studied. Tassone et. al.[63] described the relationship between PTH and kidney function in patients with pHPT and found that only severely impaired GFR (below 60 ml/min) cause an additional increase in levels of PTH. The patients in the present cohort had values above this threshold with median GFR ranging from 70.5 ml/min to 89 ml/min.

Preoperative levels of 25(OH)D3 did not differ between the time periods, despite a milder elevation of preoperative calcium and PTH. Earlier studies identified multiple factors, such as exposition to UV-B radiation, nutrition, kidney function, and PTH to cause alterations in Vitamin D metabolism [123-126]. It is not completely understood to which extent the levels of Vitamin D are contributing to the development of pHPT.

It was expected that preoperative BMD to be better preserved in patients with a milder increase in calcium, e.g., during the latter time periods that were studied. However, in contrast, BMD in male patients operated from 2001 to 2006 had lower absolute values of BMD and lower Z-values in the lumbar spine. Previous studies have shown that patients with mild pHPT rarely deteriorate in bone mineral density over time but that surgical intervention leads to a significant improvement in BMD compared to patients who were observed only [46, 48, 127]. The impact of increased osteoclast activity in patients with pHPT is predominantly affecting cortical bone tissue [128]. Since only 90 (22%) patients in the present cohort were male and the differences in preoperative BMD were mainly seen in cancellous bone tissue, it could be hypothesized that the pathophysiology of bone metabolism in male patients with pHPT differs from that in females alternatively that there were other underlying causes for the decreased BMD in the lumbar spine in this cohort. Recent guidelines for the management of asymptomatic, primary hyperparathyroidism from 2012 recommend screening for vertebral fractures since recent research reveiled vertebral fractures in up to 34 % of patients with mild or asymptomatic pHPT [43]. It is therefore possible that the effect of hypercalcemia in patients with pHPT on cancellous bone has been underestimated.

With unchanged preoperative levels 25(OH)D3 and renal function, there were no differences in outcomes concerning GFR and levels of 25(OH)D3 to be expected, as indeed was found in the present study. Also the postoperative change of BMD, did not differ between the study periods.

The study could therefore not confirm any benefit of surgical intervention at lower values of calcium and PTH, with regards to BMD and renal function.

Paper III

The aim of this study was to investigate the risk for long term recurrence in patients with pHPT operated with focused or unilateral exploration, guided by iOPTH.

Early concerns about an increased recurrence rate after the introduction of limited parathyroid exploration have been raised. A previous study confirmed additional abnormal parathyroid gland tissue in patients with preoperatively localized parathyroid adenoma in up to 22 % [87]. The results of this prospective study showed that the risk for recurrence during a 15-year follow-up was extremely low (one out of 292 patients; 0.34 %). The results are concordant with previous retrospective studies, some of them reporting on surgical outcome without the use of iOPTH [77, 85].

In three patients with persistent disease, two were initially diagnosed with solitary parathyroid adenoma, as was the patient with recurrent disease. The results of iOPTH in these patients were false positive, confirming that in the subgroup of patients with multi glandular disease, double adenomas are poorly predicted [129, 130].

In four patients, histopathology report suggested parathyroid hyperplasia due to absence of suppressed, normal parathyroid tissue. All four patients were biochemically cured after removal of one parathyroid gland, without signs of long-term recurrence. Thus, histopathology in itself is a poor predictor of outcome.

None of the 34 patients in this study with negative preoperative localization procedures recurred after excision of a single parathyroid gland. Combined with the results of paper I, the results confirm that even in the subgroup of patients with pHPT and negative scintigraphy, parathyroid adenoma is the predominant cause of the disease.

Paper IV

The main subject of this study was to identify preoperative variables that could predict MGD in patients with pHPT.

In this study, MGD was present in 18 % of patients with negative sestamibi scintigraphy compared to nine % in patients with positive localization studies (p 0.03), confirming negative localization studies as a clinically valuable indicator for multiglandular disease. These results are concordant with previous studies [111, 131, 132] but are in contrary to the histopathological results of paper I that showed parathyroid adenoma in 33 out of 35 patients (94.3 %) with negative scintigraphy. The higher number of patients with negative scintigraphy in paper III most probably provides a more reliable estimate of the incidence of MGD in patients with negative sestamibi scintigraphy. Multiglandular hyperparathyroidism is one possible reason for negative preoperative localization procedures among several others such as concordant thyroid disease, small parathyroid glands, abnormally localized glands and a lower count of chief cells.

Despite several groups reporting differences in patients with single gland disease compared to patients with multiglandular disease with higher serum calcium and intact PTH levels [37, 133], no differences between patients with SGD and MGD could be identified regarding ionized calcium and intact PTH levels. This result is in line with previous research in the field [134].

Preoperative urinary calcium was significantly lower in the MGD group of patients. However, logistic regression did not confirm urinary calcium as being an independent predictive factor for MGD.

Schneider et al. reported a significantly higher incidence of MGD in patients with mild pHPT and lower urinary calcium then in patients with overt disease [37]. Mild disease in this study was however defined as asymptomatic hyperparathyroidism with either calcium levels or PTH within the normal range, whereas the present cohort mainly consisted of patients with symptomatic pHPT with significantly elevated levels of calcium and PTH.

Logistic regression analysis identified diabetes and osteocalcin as a predictor of MGD. Patients with positive scintigraphy without diabetes were unlikely to suffer from MGD. Due to overlap of data, it was, however, not possible to develop a reliable scoring system for predicting MGD in patients with pHPT.

It is well known that pHPT is associated with diabetes type 2 [135-137]. Parathyroid hormone, insulin and osteocalcin interact by modulating insulin secretion, sensitivity and peripheral lipolysis [138-140]. It is still unclear, whether or not MGD develops as part of metabolic dysregulation or eventually causing it. There was no difference in osteocalcin levels in patients with or without diabetes, nor a correlation between osteocalcin levels and diabetes. Further, glucose levels did not differ between the groups.

Recent research [141-143] suggests that growth factors, e.g. insulin-like growth factor-1 (IGF-1), FGF23 and vascular endothelial growth factor (VEGF) not only modulate insulin sensitivity but are of importance in the development of parathyroid adenomas and hyperplasia. It has been shown that IGF-1 is decreased in both parathyroid adenoma and hyperplasia but no difference could be found between the immunoreactivity of the two entities [143].

For improved surgical outcome in patients with MGD, it would be of great value to investigate the interaction between PTH, bone markers, growth factors and metabolic disease in pHPT.

Strengths and limitations

Paper	Strengths	Limitations
I	Prospective study. Patients were all diagnosed, treated and followed by the authors. Homogenous patient cohort	Small number of patients.
II	Multiple variables, compared both pre- and postoperatively	Retrospective study. Multiple testing. The study would benefit from longer observation time
III	Prospective study. Well controlled cohort with long follow-up time. Localized and non-localized patients were included in the study	Loss of follow-up due to mortality and morbidity. Peroperative exclusion of patients with insufficient ioPTH decline
IV	Multiple preoperative variables in the analysis. Well controlled cohort	No ultrasound, missing values

Conclusions

- Patients with negative preoperative scintigraphy can be operated with a unilateral approach guided by iOPTH with excellent cure rates and low risk for postoperative complications. In this patient cohort there was no evidence of a higher incidence of multiglandular disease.
- In patients undergoing surgery for pHPT during an 18 year period, a significant change towards lower preoperative ionized calcium levels, lower adenoma weight and lower PTH in patients with parathyroid adenoma was observed. Despite treating patients at lower levels of calcium, there was no change in preoperative renal function, bone mineral density or a change of cure rate, postoperative renal function or bone density.
- Unilateral parathyroid exploration with iOPTH results in high cure rates and very low risk for long-term recurrence. Long term follow-up after six to twelve months seems not to add any substantial benefits
- Negative sestamibi scintigraphy, diabetes and elevated osteocalcin levels were independent predictors of MGD. Sestamibi scintigraphy appears to be the most clinical usable predictor.

Future perspectives

Primary hyperparathyroidism is a common disease with a prevalence of one % in the western world. Being the third most common endocrine disease after diabetes and thyroid diseases [14], large numbers of pHPT patients have to be under surveillance or subjected to surgery with significant socioeconomic consequences. Evidence-based guidelines for treatment are therefore necessary for safe and cost-effective management. Current treatment guidelines in the USA and Europe recommend surgery in patients with symptomatic pHPT. Surgery is also recommended for patients with asymptomatic or mild disease if the patient is below 50 years of age, suffering from osteoporosis or impaired renal function or with s total calcium value >0.25 mmol/L above the reference range . Surgery is also recommended in case of asymptomatic vertebral fractures and kidney stones. Operative treatment of pHPT is safe with high cure rates and a low risk for postoperative complications and morbidity in experienced hands.

The benefits of surgery in patients with overt disease, proven by numerous studies, are improvement in bone mineral density, quality of life and neuropsychiatric symptoms [22, 39, 54, 57, 58, 144]. It is, however not as clear whether or not the fracture risk also decreases after surgery. While there are several large European studies demonstrating an increased mortality in patients with pHPT and few studies even indicating lower mortality after parathyroid surgery [25, 29, 30], there are no randomized controlled trials to confirm these data.

Since the introduction of surgical treatment in patients with primary hyperparathyroidism in 1925 [7], the clinical and biochemical presentation of the disease has changed. Present patients are frequently diagnosed during routine health check-up or screening for osteoporosis with densitometry.

Since the majority of these patients are asymptomatic or diagnosed with mild hypercalcemia, current research has focused on prognosis, morbidity, mortality and the benefits of available treatment options in this group of patients.

Ongoing research at Lund University in pHPT patients has focused on pHPT patients over 65 years of age with mild to moderate hypercalcemia (< 1.50 mmol/L), preserved renal function and a bone density with Z score at any site not lower than-2.5 s.d.. These patients are randomized to observation or surgery with an extensive follow-up program over 2 years including biochemistry, bone density, renal function, cognitive tests, and risk factors for cardiovascular disease, cardiac function and arteriosclerosis. Data from this study will hopefully show if surgery is worthwhile in this important subgroup of patients.

The available evidence shows that a considerable number of asymptomatic patients and patients with mild hypercalcemia patients will develop symptomatic pHPT or progress biochemically, and thus meeting the criteria for surgery during follow-up. The cost for surveillance increases over time, eventually exceeding costs for surgery. It would therefore be of value to predict which patients will progress over time.

Data from long term follow-up (paper III) showed that patients undergoing successful unilateral neck exploration have very low risk for recurrent disease. Subsequently this patient group do not need long term follow-up. Future studies should focus on the long term results in patients with more difficult to treat disease, e.g., patients with negative localization studies and patients with multiglandular disease. Further research in the natural history of pHPT, stratification by risk for progression, and its effect on morbidity, could then lead to an improvement of current treatment guidelines.

Despite the development of new localization techniques, the ideal modality that combines cost-effectiveness and a high predictive value is yet to be identified. Sensitivity of the most commonly employed localization procedures, e.g., ultrasound and sestamibi scintigraphy, decreases with the size of the pathological parathyroid glands [90]. Generally speaking, the sensitivity is poor in patients with multiglandular disease [87]. Data from the Scandinavian Quality Register (SQRTPAS) shows that in 2014, 60 % of patients currently undergo surgery with unilateral neck exploration or focused parathyroidectomy with the help of localization procedures, which are employed in 90 % of patients. The sensitivity for ultrasound to predict single gland disease across departments in Sweden is 60 % and for sestamibi scintigraphy 65 % according to data from SQRTPAS. This entails a considerable cost in spite of moderate difference in surgical strategy compared to random, which theoretically should enable a unilateral approach in > 45 % patients. It could therefore be argued, that patients could be operated with a unilateral or minimal invasive approach with the use of iOPTH without any preoperative localization procedure to a lower cost and with no difference in cure rate and complications.

Populärvetenskaplig sammanfattning (in Swedish)

Bisköldkörtlarna är fyra risgrynstora körtlar, anatomiskt belägna bakom sköldkörteln, två på var sida. På grund av körtlarnas utveckling under fosterlivet är andra lägen inte ovanligt och fler än fyra körtlar förekommer i drygt tio % av fallen. Med hjälp av kalciumreceptorn känner körtlarna av och reglerar kalcium i blodet genom produktion av parathormon (PTH) som höjer kalciumvärdet genom bland annat nedbrytning av ben och minskad utsöndring av kalcium i njurarna. Parathormon ökar även produktion av vitamin D som i sin tur bidrar till att ytterligare höja kalciumvärdet i blodet genom ökat upptag av kalcium i tarmen. Primär hyperparathyroidism, överfunktion av en eller flera bisköldkörtlar är en vanlig sjukdom som drabbar cirka en procent av befolkningen i i-länderna. Sjukdomen finns i två former; enkörtelsjukdom (cirka 85 procent av samtliga patienter), och flerkörtelssjukdom. Sjukdomen är vanligast förekommande hos kvinnor efter menopausen, där uppskattningsvis tre % lider av primär hyperparathyroidism. Överfunktion i bisköldkörtlarna med ökad insöndring av PTH till blodet kan leda till urkalkning av skelettet (osteoporos), med ökad risk för benbrott. Patienterna har även en ökad risk för njursten och njurfunktionsnedsättning. Patienter med primär hyperparathyroidism anses också ha ökad risk för dödlighet av sjukdomar i hjärta och kärl, cancer samt en ökad risk att drabbas av diabetes.

Behandling

Operation är för närvarande den enda behandling som kan bota sjukdomen. Vid ingreppet avlägsnas den eller de förstorade bisköldkörtlarna som på grund av ökad hormoninsöndring är orsak till sjukdomen. Det finns ett flertal operationsmetoder. Den klassiska operationen innebär att kirurgen lägger ett horisontellt snitt på halsen och frilägger sköldkörtel och samtliga bisköldkörtlar. Förstorade bisköldkörtlar avlägsnas och patologen genomför därefter en snabbundersökning av borttagen vävnad medan patienten är sövd för att bekräfta att den avlägsnade bisköldkörteln är förstorad och sjukligt omvandlad.

Eftersom ungefär 85 procent av alla sjukdomsfall av primär hyperparathyroidism är orsakade av en förstorad bisköldkörtel i form av en godartad tumör, så kallat adenom, försöker man numera identifiera förstorade bisköldkörtlar med röntgenundersökningar, framförallt ultraljud och isotopundersökning (skintigrafi) före ingreppet. Om undersökningen visar vilken körtel som är drabbad, opereras patienten enbart på denna sida (ensidig halsoperation) vilket har flera fördelar: kortare operationstid och mindre risk för komplikationer som till exempel skador på stämbandsnerven och lågt calciumvärde efter operationen på grund av skada på normala bisköldkörtlar under ingreppet. För att säkerställa att det inte finns ytterligare sjuka bisköldkörtlar, kan PTH nivåerna i blodet bestämmas under operation. Detta är viktigt då ett antal studier visat på ökad förekomst (upp till 30 procent) av flerkörtelsjukdom hos patienter med mild sjukdom. Om de gjorda undersökningarna inte kan identifiera någon förstorad bisköldkörtel, rekommenderas vanlig operation med klassisk metodik med identifiering av samtliga körtlar under operation.

Den mer begränsade operationstekniken, där man vid misstänkt enkörtelsjukdom enbart opererar på en sida, var mycket kontroversiell när den introducerades under tidig 1980-tal. Motståndarna till denna nya metod, som gick under benämningen ensidig halsexploration, befarade ökad återfallsrisk på grund av förbisedd flerkörtelsjukdom, medan förespråkarna framförde kortare operationstid samt minskad komplikationsrisk som argument för att anamma den nya tekniken.

Fördelar med operation

Det är bekräftat av flera väl genomförda studier, att bentätheten ökar efter operation för primär hyperparathyroidism. Vissa undersökningar har även visat på minskad risk för benbrott efter framgångsrik kirurgi. Förekomst av njursten, åtminstone symptomatisk sådan, anses minska och besvär som trötthet och minnesstörningar kan förbättras. Vissa studier har även antytt att risken att dö återgår till samma risknivå som för befolkningen i övrigt efter operation.

Antalet nyupptäckta fall av primär hyperparathyroidism har ökat på grund av rutinmässig kalciumanalys i blodet vid hälsokontroll samt screening för benskörhet. Eftersom en stor andel av dessa patienter enbart har lätt förhöjda kalciumvärden i blodet och få eller inga typiska besvär, har forskningen koncentrerats på att undersöka översjuklighet och dödlighet vid sjukdomen i denna patientgrupp.

Delarbete I

I detta delarbete undersöktes 35 patienter där istopundersökning (skintigrafi) inte kunde påvisa en förstorad bisköldkörtel. Alla operationer påbörjades på vänster sida och 16 patienter (46 %) kunde opereras med ensidig halsoperation. Parathormon mättes hos alla patienter under operationen och bekräftade bot hos 33 av 35 patienter (88 %). Samtliga patienter där PTH nivåerna inte sjönk tillräckligt under operationen hade flera sjuka körtlar som var nödvändiga att avlägsna. Nästan hälften av patienterna (15 patienter, 43 %) botades med ett mindre ingrepp på ena sidan och den överväldigande majoriteten (33 av 35 patienter, 94 %) bedömdes lida av enkörtelsjukdom (adenom). Det senare fyndet var oväntat då tidigare forskningsrapporter funnit att proportionellt fler patienter med negativ skintigrafi lider av flerkörtelssjudom. Resultaten visar att nästan hälften av alla patienter med negativ isoptopundersökning kan botas med ensidig halsoperation. Förutsättningen är dock samtidig bestämning av PTH utförs för att bekräfta att rätt körtel borttagits, och att inga ytterligare sjuka bisköldkörtlar lämnas kvar. Resultaten var lika bra som med den gamla operationstekniken där alla fyra körtlar identifierats men med minimal risk för lågt kalkvärde och kortare operationstid.

Delarbete II

I detta delarbete undersöktes huruvida 404 patienter som opererades i Lund mellan 1989 och 2006, uppvisade en mildare sjukdom över tid analyserat med kalcium och PTH i blodet, bentäthet och njurfunktion. Ett annat syfte var att studera om nyttan av operation i form av förbättrad njurfunktion, bentäthet och övriga blodprover påverkades över tid. Patienterna delades in i tre tidsperioder och sedan jämfördes kalcium, PTH, körtelvikt, bentäthet, njurfunktionsprover och D-vitaminvärden mellan de tre tidsepokerna före- och efter operationen.

Patienter som opererades under de senare tidsperioderna hade lägre körtelvikt, samt lägre nivåer av kalcium samt PTH. Däremot skiljde sig inte bentäthet, njurfunktion och vitamin D före operation för de tre tidsperioderna.

Då patienter som opererades i den senare tidsperioden hade lägre värden av PTH och kalcium, kan man tolka det som att man antingen upptäcker sjukdomen tidigare eller att fler patienter erbjuds operation. Trots mildare hyperkalcemi skiljde sig inte effekten av operation, d.v.s. det var ingen skillnad mellan patienter opererade mellan tidsperioderna för bentäthet och njurfunktion och Vitamin D nivåer efter kirurgi.

Trots att sjukdomen var mildare och körtelvikten lägre, och därmed potentiellt kunde anses vara svårare att operera, så botades lika många patienter under de tre studerade tidsperioderna.

Delarbete III

I delarbete III undersöktes återfallsrisken upp till 15 år efter ensidig halsoperation mellan 1989 och 2010. Av 292 opererade patienter, blev 289 (98.9 %) botade. Tio år efter operation hade 57 patienter avlidit, efter 15 år ökade antalet till 69 dödsfall.

Enbart en patient fick ett återfall av sjukdomen, fem år efter operationen. Studien bevisar att ensidig halsoperation är en operationsmetod med mycket hög chans till bot samt en låg risk för återfall under långtidsuppföljning. Längre uppföljning av patienter som opererats med ensidig halsoperation med normalt kalcium och PTH under de först 6-12 månaderna tillför ingen ytterligare säkerhet ur patientsynpunkt.

Delarbete IV

I delarbete IV undersöktes möjligheten att förutse flerkörtelsjukdom hos patienter med överfunktion i bisköldkörtlar. Sammantaget undersöktes 707 patienter opererade vid kirurgiska kliniken i Lund mellan 1989 och 2013. Patienterna delades in i två grupper, enkörtelsjukdom eller flerkörtelsjukdom. Indelningen gjordes på basen av operationsfynd, vävnadsundersökning och uppföljning med kalcium och PTH. Resultat av isotopundersökning (skintigrafi) samt blodprover före operationen jämfördes mellan grupperna. Statistisk analys, så kallad multivariabel regressionsanalys, utfördes med hänsyn tagen till samtliga ingående variabler för att identifiera möjliga riskfaktorer för flerkörtelsjukdom.

Förekomst av negativ isotopundersökning samt lägre kalciumvärden i urinen och diabetes var vanligare hos patienter med flerkörtelsjukdom. Multivariabel analys bekräftade negativ isotopundersökning, diabetes samt stegrade nivåer av osteokalcin, en markör för ökad skelettomsättning, som oberoende riskfaktorer för flerkörtelsjukdom.

Resultat av isotopundersökning styr till en del valet av operationsmetod och en negativ undersökning är därför en användbar markör för flerkörtelsjukdom. Tidigare studier har visat att mild sjukdom med lägre kalciumnivåer är förenad med ökad förekomst av flerkörtelsjukdom vilket också resultaten från delarbete 4 visar. Däremot har inte diabetes och ökade osteokalcinivåer tidigare beskrivits som riskfaktorer för flerkörtelsjukdom. Osteokalcin är ett protein som tillverkas av celler som bidrar till nybildning av ben och används bland annat som markör för benomsättning hos patienter med benskörhet. Proteinet uppvisar också flera andra intressanta verkningsmekanismer; osteokalcin ökar känsligheten för insulin, och sänker därmed blodsockernivåerna och ökar dessutom nedbrytning av fettvävnad. Även diabetes var en oberoende riskfaktor för flerkörtelsjukdom. Vi förslår därför, att orsaken till flerkörtelsjukdom kan vara en annan jämfört med enkörtelsjukdom, åtminstone hos en del av patienter. Resultaten antyder att patienter med flerkörtelsjukdom tillhör en annan sjukdomsgrupp där diabetes och andra metabola rubbningar förekommer i högre utsträckning jämfört med enkörtelsjukdom.

Summering av resultat och framtida forskningsområden

Forskningsresultaten i denna avhandling visar att ensidig halsoperation har utmärkta långtidsresultat med mycket låg återfallsrisk över tid och kan även användas på upp till hälften av patienter med negativ isotopundersökning om man samtidigt mäter PTH under operationen. Patienter med överfunktion i bisköldkörtlar har idag lägre kalcium och PTH värden och mindre uttalad körtelförstoring än tidigare. Detta har dock inte påverkat möjligheten till bot av sjukdomen men verkar inte heller ge några större positiva effekter på njurfunktion och mineralhalt i skelettet.

Flerkörtelsjukdom är svår att förutse innan operationen, förekomst av diabetes samt förhöjda osteokalcinnivåer i blodet var förenad med ökad förekomst av flerkörtelsjukdom. Det kan bero på att utvecklingen av en- och flerkörtelsjukdom skiljer sig åt.

Det behövs fler studier för att öka vår förståelse i hur flerkörtelsjukdom skiljer sig i detalj från enkörtelsjukdom och varför den uppstår. Negativa isotop-undersökningar är fortfarande den mest användbara markör för flerkörtelsjukdom. Framtida studier borde även undersöka effekten av operation på sjuklighet och dödlighet hos patienter med mild sjukdom. Utveckling av röntgenundersökningar som tillförlitligt kan identifiera förstorade bisköldkörtlar skulle kunna öka antalet patienter som kan opereras med ensidig halsoperation.

Errata:

Paper I:

Biochemistry: The reference range for serum ionized calcium is supposed to be 1.15-1.35 mmol/L

Results, bilateral group; page 883 in the original article, line 19: it should be "the patient suffered from a large goiter"

There was no statistically significant difference in the frequency of postoperative hypocalcemia (p 0.23) between the groups. Stated otherwise in the abstract of the article and in the results section on page 883, line 8.

Paper II:

Abstract; results, line 2 should be: "Median levels of preoperative ionized calcium were lower in 2001-2006 compared to 1989-1994; 1.45 versus 1.50 mmol/L; p<0.001.

Results, page 362, line 7 stated incorrectly "32 patients with hyperplasia (7.9%)" but it should be 8.7 %.

Discussion, page 363, line 37 "Nonetheless, we found no indication for differences in outcome of renal function, as estimated by GFR, for patients operated over 18 years"

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