



Controversies in the treatment of primary hyperparathyroidism

MARK THIER

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LUND
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DOCTORAL DISSERTATION

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Title: Controversies in the treatment of primary hyperparathyroidism		
<p>Abstract:</p> <p>Background: The surgical treatment of primary hyperparathyroidism (pHPT) and its potential pitfalls are frequently discussed, 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.</p> <p>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.</p> <p>Methods: In paper I, surgical outcome for patients with negative scintigraphy, treated with the intention 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.</p> <p>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 between 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.</p> <p>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.</p>		
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To my beloved parents, family and friends

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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

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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(OH ₂)D ₃	Active vitamin D
25(OH)D ₃	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].

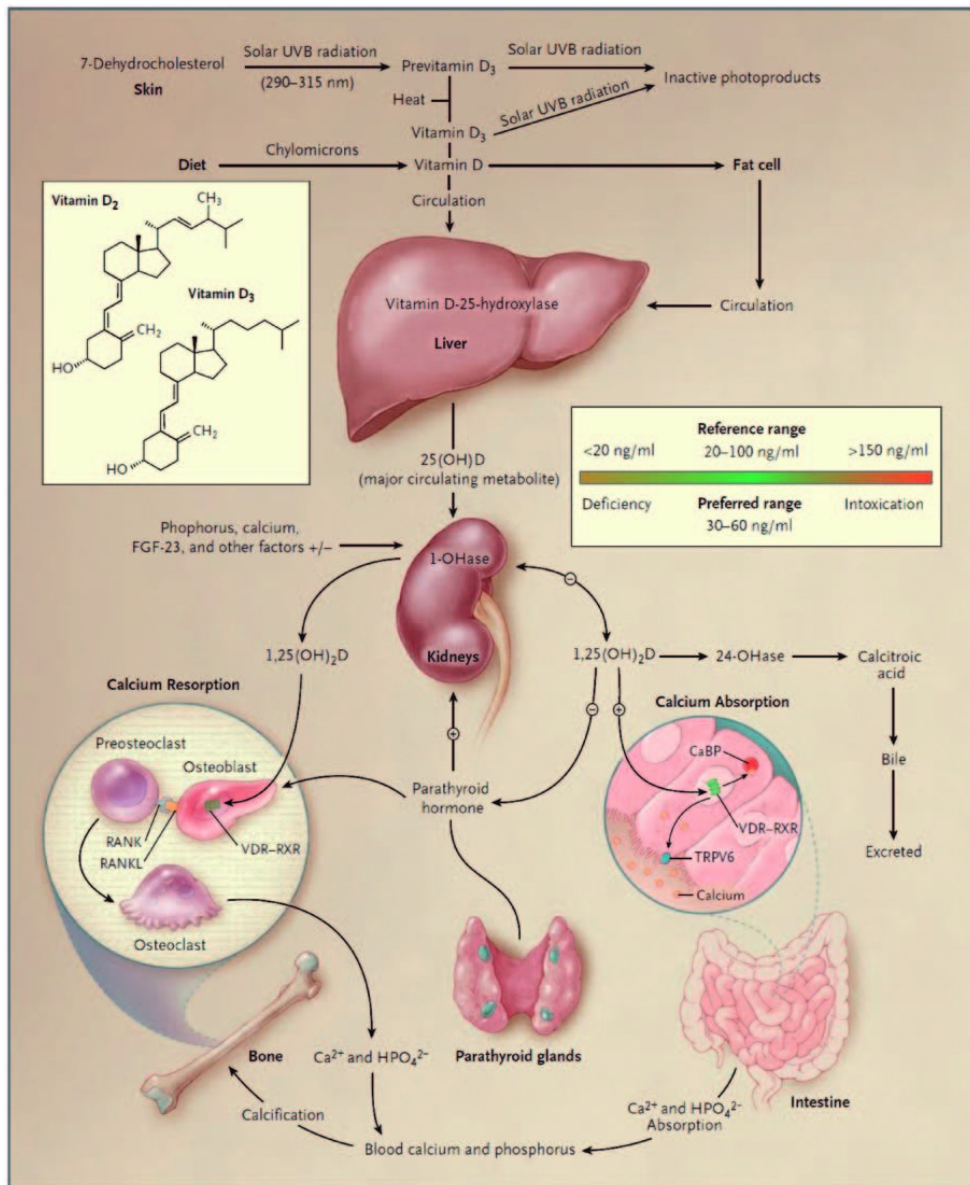


Figure 1.
Calcium hemostasis

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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 Schlagenhauser, 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: glomeruli 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 advocates 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'-methyl-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, iothexol 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, iothexol 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

Time period	All			Women			Men			p		
	1989-1994	1995-2000	2001-2006	p	1989-1994	1995-2000	2001-2006	p	1989-1994		1995-2000	2001-2006
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 -1.70-0.40		0.30	* -0.50 -1.40-0.70	-0.40 -1.60-0.50		0.97	* -0.05 -1.23-0.95	-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 (ρ -0.07; p 0.30), nor in the femoral neck (ρ -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			
	1989-1994	1995-2000	2001-2006	P	1989-1994	1995-2000	2001-2006	P	1989-1994	1995-2000	2001-2006	P
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 52-115	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)	*	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)	-	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)	2.74	2.34	2.31	2.33	2.36	2.35
(median and interquartile range)	2.63-2.85	2.27-2.41	2.25-2.39	2.28-2.39	2.28-2.42	2.27-2.44
S-ionized Calcium (mmol/L)	1.46	1.24	1.22	1.22	1.22	1.23
(median and interquartile range)	1.41-1.52	1.21-1.27	1.2-1.26	1.20-1.25	1.2-1.25	1.20-1.25
P-PTH (pmol/L)	10	5.2	4.65	4.55	4.25	4.7
(median and interquartile range)	7.4-14	3.85-7.3	3.5-6.35	3.55-6.05	3.2-6.2	3.6-5.4
Creatinine	71	-	72	74	70	73
(median and interquartile range)	60-85	60-85	61-83	66-91	62-82	64-87
S-25OHD (nmol/L)	50	45	56	64	*	*
(median and interquartile range)	37-64	38-62	36-69	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 mmol/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, μ kat/L median (i.q.r.)	1.80 (1.30-3.0)	1.70 (1.20-2.40)	0.17
PTH, pmol/L, median (i.q.r.)	9.90 (7.30-13.0)	10.0 (8.50-15.0)	0.09
U-Ca, mmol/L (26%)* median (i.q.r.)	4.44 (2.80-6.60)	3.80 (2.80-5.10)	0.04
Osteocalcin, μ g/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.

Characteristics	Univariate logistic regression		Multivariate logistic regression	
	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	0.13-2.59	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				
1 st tertile	1.00			
2 nd tertile	1.30	0.69-2.44	1.26	0.63-2.49
3 rd tertile	0.57	0.27-1.21	0.34	0.10-1.14
Osteocalcin				
1 st tertile	1.00			
2 nd tertile	3.12	1.51-6.45	3.39	1.75-8.21
3 rd tertile	1.95	0.90-4.22	2.11	1.02-5.48
Iohexol clearance				
1 st tertile	1.00			
2 nd tertile	0.67	0.35-1.27	0.65	0.32-1.35
3 rd tertile	0.68	0.36-1.29	0.57	0.21-1.02
25(OH)D₃				
1 st tertile	1.00			
2 nd tertile	0.93	0.51-1.68	0.86	0.45-1.65
3 rd tertile	0.58	0.29-1.14	0.49	0.22-1.04
BMD Z radius				
1 st tertile	1.00			
2 nd tertile	1.13	0.55-2.32	1.04	0.48-2.24
3 rd 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 revealed 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 than 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 a 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 (SQ RTPAS) 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 SQ RTPAS. 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 flerkörtelsjukdom. 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 förstörade 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. Förstörade bisköldkörtlar avlägsnas och patologen genomför därefter en snabbundersökning av borttagen vävnad medan patienten är sövd för att bekräfta att den avlägsnade bisköldkörteln är förstörad och sjukligt omvandlad.

Eftersom ungefär 85 procent av alla sjukdomsfall av primär hyperparathyroidism är orsakade av en förstörad bisköldkörtel i form av en godartad tumör, så kallat adenom, försöker man numera identifiera förstörade bisköldkörtlar med röntgenunder-

sökningar, 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 förstörad 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 isotopundersökning (skintigrafi) inte kunde påvisa en förstörad 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 flerkörtelssjukdom. 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 nytta 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 förstörade bisköldkörtlar skulle kunna öka antalet patienter som kan opereras med ensidig halsoperation.

Errata:

Paper I:

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

Results: Bilateral group, page 883 in the original article, line 19 “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: it 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 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”

Paper III:

Methods, biochemical variables, it should be: Levels of total serum calcium (2.20-2.50 mmol/L)

Discussion, line 12, it should be: In the present study, cure was defined strictly as calcium levels below the upper limit for normocalcemia (ionized calcium < 1.35 mmol/L and or total calcium < 2.50 mmol/L).

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Surgery for patients with primary hyperparathyroidism and negative sestamibi scintigraphy—a feasibility study

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Abstract

Background We report the surgical treatment of a consecutive series of scan negative patients with the intention of unilateral parathyroid exploration with the aid of intraoperative quick PTH (qPTH).

Materials and methods The study included 35 consecutive sestamibi scan negative patients (27 women, eight men) with sporadic pHPT subjected to first time surgery. Median age was 70 years and median preoperative calcium level 2.8 mmol/L.

Results Thirty-three patients had a histological diagnosis of a parathyroid adenoma (median weight 0.48 g [range 0.12 g–2.5 g]). Nineteen patients were explored bilaterally and 16 patients (46%) were operated unilaterally. The median operation time was 40 min in the unilateral group and 95 min in the bilateral group ($p<0.001$). Three patients were treated for postoperative hypocalcemia after bilateral exploration versus none in the unilateral group ($p=0.23$). With a minimum of 12 months of follow-up, 33 patients (94.3%) were cured. One case of recurrent HPT presented after bilateral exploration with visualization of four glands. One case of persistent HPT was observed after unilateral

exploration. qPTH was predictive of operative failure in both patients.

Conclusion Forty-six percent of the patients in our study could be operated unilaterally with a total cure rate of 94%. Patients in the unilateral group had a significant shorter operation time and a lower incidence of postoperative hypocalcemia. In conclusion our investigation shows that limited parathyroid exploration can safely be performed on patients with negative sestamibi scintigraphy by the aid of qPTH.

Keywords Primary hyperparathyroidism · Sestamibi scintigraphy · Intraoperative PTH · IoPTH

Background

Primary hyperparathyroidism (pHPT) is a common disease that affects 1% of the adult population [1] and some 3% in postmenopausal women.

Classic signs of pHPT include renal lithiasis, cholecystolithiasis, gastrointestinal ulcerations, depression, and osteoporosis.

Despite lack of classical signs, a higher incidence of glucose intolerance, hypertension, hyperlipidemia, and increased morbidity and mortality from cardiovascular disease as well as an increased fracture risk is seen in patients with pHPT [2, 3].

Bilateral neck exploration with visualization of all four parathyroid glands has been regarded as the gold standard in treatment of pHPT. Recently minimal invasive and/or focused approach after preoperative localization studies with the aid of intraoperative measurement of PTH (ioPTH), have challenged bilateral neck exploration [4–6]. It has been shown that limited exploration has advantages

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such as shorter hospital stay, less postoperative pain, and fewer complications, e.g., severe postoperative hypocalcemia [4, 7].

Quick PTH has been proved earlier to be a reliable marker for successful removal of parathyroid tissue [8].

The aim of the present study was to evaluate if it is feasible to perform focused unilateral surgery of pHPT patients with preoperatively negative sestamibi scintigraphy with the aid of ioPTH.

Materials and methods

Patients

Thirty-five consecutive sestamibi scan negative patients (27 women and eight men) with sporadic pHPT, subjected to first time surgery at Lund University Hospital between October 2003 and May 2006 were included in our study. The median age was 70 years (range 37–83 years). The median preoperative serum calcium level was 2.8 mmol/L (range 2.6–3.2 mmol/L). Median preoperative PTH level was 9.7 pmol/L (range 5.3–31 pmol/L).

Exclusion criteria were family history of pHPT, familial hypocalciuric hypercalcemia (FHH), and other planned operations during the surgical procedure including thyroid surgery. The biochemical diagnosis of pHPT was based on a serum calcium level of more than 2.60 mmol/L and a serum PTH level of more than 5 pmol/L with a serum creatinine level of less than 200 μ mol/L. Postoperative hypocalcemia was defined as serum calcium <2.2 mmol/L with typical symptoms of hypocalcemia.

Planned intervention

The patients were subjected to surgery with the intent of limited parathyroid exploration. Surgery commenced with operation of the left side with a minimal transverse incision, 15–20 mm long. If no adenoma was found, the patient was explored bilaterally; this operation was performed by a second lateral incision of 15 to 20 mm with the possibility of conversion to standard open technique (Kocher incision) if needed. Due to the infrequent use of neck ultrasound between 2003 and 2006, we decided to start exploration on the left side of the neck. This approach was once introduced by Sten Tibblin for patients with negative, preoperative localization results, and has a long tradition at the Lund University Hospital.

Sestamibi scintigraphy

Sestamibi subtraction scintigraphy was performed with 30 MBq 99 m Tc and 500 MBq 99 mTc sestamibi [9].

Biochemistry

All blood samples were collected after an overnight fast. Preoperative data were obtained from blood samples collected the day before surgery after an overnight fast. Twenty-four hours urine calcium excretion was routinely evaluated to exclude patients with FHH. Serum ionized calcium concentrations (reference range 2.20–2.60 mmol/L) were analyzed from blood samples normalized to a pH of 7.4 with the ion selective electrode ABL 505 (Radiometer, Copenhagen, Denmark). Serum PTH (reference range 1.0–5.0 pmol/L) was analyzed by using an assay for intact PTH (Inctstar, Stillwater, MN, USA) with a sensitivity of 0.13 pmol/L and a reference range of 1.0–5.0 pmol/L. The inter-assay coefficient of variation (CV) is <11% and the intra-assay variation <6%. The method has a CV of 2.2% at a value of 5 pmol/L.

To shorten the time for intraoperative analysis, the method was modified as previously described [10]. The within-assay variation between 0.8 and 10 pmol/L is less than 8% for the rapid method. The correlation between the two methods is 0.99.

A decrease of ioPTH of >50% after 5 min or >60% after 15 min has been proved earlier to be a reliable predictor for successful removal of pathological parathyroid tissue [8, 10–13].

Follow-up

All patients were followed at least 12 months after surgery. Persistent disease was defined as raised levels of serum calcium before 6 months after surgery. Recurrent disease was defined as raised serum calcium levels after 6 months.

Statistics

Results for continuous variables are expressed as median and range if not stated otherwise. For numeric data, differences between groups were analyzed with the Mann–Whitney test. For categorical data, statistic significance was analyzed using the chi-squared test and the Fishers exact test when frequencies were expected to be less than five. A probability level for a random difference of $p < 0.05$ was considered to be significant. For categorical data, absolute numbers in addition to percentage are given.

Results

Of 35 patients, 16 underwent unilateral surgery and 19 patients were explored bilaterally. One patient had persisting HPT after 12 months follow-up and one patient suffered

from recurrent disease. Thus, the overall cure rate was 94.3%. Among all 35 patients, 33 got the histological diagnosis adenoma. The median weight was 0.48 g (range 0.12–2.49 g). Operation time in the unilateral group was significantly ($p<0.001$) lower compared to the bilateral group. Adenoma weight did not differ significant ($p=0.45$). Three patients in the bilateral group suffered from postoperative hypocalcemia compared to zero patients in the unilateral group ($p=0.23$).

None of the 35 patients suffered from laryngeal nerve damage. There was no significant difference in the complication rate (postoperative bleeding, hematoma, and local discomfort) between the two groups. Cosmetic results were estimated by the patients with the visual analog scale (VAS). Median VAS in the unilateral group was 10 compared to 9 in the bilateral group ($p=0.1$).

The results of both groups are presented in Table 1.

Unilateral group

This group is composed of 16 patients; 12 females and four males with a median age of 71.5 years (range 49–83 years). In all 16 patients autopsy showed solitary adenoma with a median weight of 0.48 g (range 0.15–2.5 g). Median operation time was 39.5 min (range 13–64 min). None of the patients suffered from postoperative hypocalcemia and all patients but one were cured 12 months after surgery with one case of persistent HPT 12 months after surgery.

Intraoperative PTH in this patient declined 48%, 5 min after removal of the lower left gland and 54% after 15 min with an additional decline after 20 min. Therefore, the surgeon decided to terminate operation without bilateral exploration. The final histopathological report showed solitary adenoma. The patient should have become subject to bilateral exploration according to ioPTH protocol.

Bilateral group

This group is composed of 19 patients; 15 females, four males with a median age of 67 years (range 37–83 years)

were operated bilaterally. Seventeen patients histopathological report showed single gland disease (solitary adenoma) with median weight of 0.4 g (range 0.12–1.6 g). Operation time was median 95 min (range 29–266 min). Three patients suffered from postoperative hypocalcemia. Eighteen out of 19 patients (94.7%) were cured with correct prediction by intraoperative qPTH.

In one case of recurrent HPT observed in this group, four enlarged glands could be identified. After removal of three glands, qPTH declined 13% only. The patient was intraoperatively conceived to have hyperplasia, final histopathological report showed however normal glands. FHH or a fifth, not identified gland was discussed as a possible explanation. This patient did unfortunately not collect 24 h urine for further investigation. At 6 months follow-up, the patient was normocalcemic. Twelve months after surgery, the disease recurred.

In one case of hyperplasia, the patient suffered from a large groin. Two glands on the left side were removed without PTH decline. After negative reexploration we converted to bilateral surgery without identifying any glands on the right side. After bilateral exploration, PTH declined to normal levels and operation was executed. The final histopathological report showed hyperplasia.

Operation time was 266 min and the patient suffered from postoperative hypocalcemia that needed treatment. After both 6 and 12 months the patient was normocalcemic and was considered to be cured.

Intraoperative PTH

Thirteen out of 35 patients declined less than 50% of PTH after 5 min (median 59.2%), seven of these 13 patients declined more than 60% after 15 min. Among the remaining six that declined less than 60%, two suffered from persistent or recurrent pHPT.

Intraoperative PTH predicted operative success in 29 of 33 cases (88%). All patients with a surgical failure and persistent or recurrent pHPT were true negative.

The sensitivity was 88% and specificity was 100%.

Table 1 Post-operative results of unilateral and bilateral groups

	Unilateral op $n=16$	Bilateral op $n=19$	p value
Sex m/f	4/12	4/15	
Age (year)	71.5	67	0.82
Preop calcium (mmol/L)	2.78	2.8	0.58
Preop PTH (pmol/L) median	9.7	9.8	0.87
Operation time (min) median	39.5	95	<0.001
Adenoma weight (g) median	0.48	0.4	0.45
Postop. hypocalcemia number(%)	0(0)	3(16.7)	0.23
Hospital stay (days) median	2	2.3	0.2

Discussion

Even in the era of minimal invasive surgery, patients with negative sestamibi scintigraphy are still undergoing open, bilateral exploration as a standard procedure. In this study we compared bilateral, conventional neck exploration with a bilateral procedure by two lateral 15–20-mm incisions on each side in patients with negative sestamibi scintigraphy.

Previous studies have shown that patients with negative sestamibi scintigraphy have smaller adenomas, lower PTH levels, and a lower cure rate than patients with positive scintigraphy results [14, 15].

In our study we could not find any proof for a higher incidence of multiglandular disease in patients with pHPT and negative scintigraphy. Although there were only few patients in this study, we show that unilateral procedure can be performed safely with better cosmetic results, shorter operation time, and less early hypocalcemia with the aid of ioPTH in these patients. Further in 46% of all cases we succeeded with unilateral operation. Patients with negative scintigraphy results have a higher risk of persistent HPT [14, 15]. Cure rate in our study was 94.3%.

In conclusion we showed that limited parathyroid exploration with the aid of intraoperative PTH measurement can be performed in pHPT patients with negative sestamibi scintigraphy with a high cure rate.

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Paper II

Presentation and Outcomes After Surgery for Primary Hyperparathyroidism During an 18-Year Period

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Abstract

Purpose The objective of this study is to analyze whether the trend towards operating on patients with less severe primary hyperparathyroidism (pHPT) than earlier is reflected in a change of preoperative presentation and surgical outcome.

Methods In this longitudinal cohort study, patients with pHPT subjected to first time surgery were compared in three time periods: 1989–1994, 1995–2000, and 2001–2006 in this longitudinal cohort study.

Results There were 404 patients. Median levels of preoperative ionized calcium were lower in 2001–2006 compared to 1989–1994; 1.45 versus 1.50 versus 1.45 mmol/L; $p < 0.001$. Preoperative parathyroid hormone levels in patients with parathyroid adenoma were lower in 2001–2006 than in 1989–1994; 10.0 versus 11.6 pmol/L; $p 0.04$. Median preoperative bone mineral density, BMD, in the whole cohort did not differ between time periods. Median pre- and postoperative glomeruli filtration rate, GFR, and 25-hydroxy-vitamin D₃ remained unchanged between period 1 and period 3. Adenoma weight was lower in 2001–2006 than 1989–1994; 0.70 versus 0.50 g; $p 0.04$. Cure rate did not change during observation time. There was no evidence for differences in change of BMD (femoral neck) after surgery between period 2 and 3 1995–2000 and 2001–2006, 0.798 versus 0.795 g/cm²; $p 0.67$. GFR did not change significantly between 1989–1994 and 2001–2006, 74 versus 77 mL/min; $p 0.43$.

Conclusions A significant change towards operating patients with smaller adenomas and lower preoperative calcium levels was evident throughout the observation period, but this did not correlate with differences in preoperative renal or skeletal function. We found no evidence for a change of postoperative renal function or skeletal function during observation time.

Introduction

The first successful operation for primary hyperparathyroidism (pHPT) was carried out by Mandl in 1925 [1]. Since then, the classic presentation with severe skeletal, renal, and gastrointestinal manifestations has changed. Contemporary patients have milder or no symptoms and

several studies [2–9] have shown a trend over time towards treating patients with smaller adenomas and lower preoperative calcium and parathyroid hormone (PTH) levels. According to some authors, this may lead to a higher number of negative, preoperative localization studies and operative failure [5, 10–12]. It has been shown that parathyroid surgery improves bone density [13–18] and that patient with more severe skeletal disease benefits more from the surgery [19]. It is also known that severe pHPT may be detrimental for renal function [20]. It is not known, however, whether the changing pattern of pHPT presentation over time is associated with a corresponding change in

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skeletal or renal disease, and if there is less benefit for the patients in terms of increase in bone mineral density after parathyroid surgery.

Low vitamin D levels are a common finding among patients with pHPT and are related to skeletal diseases and PTH levels [21]. Thus, it might be hypothesized that a change in preoperative characteristics of pHPT patients over time correlates with a change in vitamin D status, as measured by 25-hydroxy-vitamin D₃ (25(OH)D₃) levels. The aim of this longitudinal cohort study was to investigate whether pre-, and postoperative parameters, such as levels of calcium, PTH, 25(OH)D₃, renal function, bone density and clinical outcomes in patients with pHPT, have changed during 18 years of observation. It is hypothesized that preoperative renal function and bone density may be better preserved in patients with milder increase in serum calcium, and thus that the benefits of surgery may be less obvious.

Our study adds to previous studies, although large and well designed, lacked information about the change in preoperative bone mineral density (BMD), kidney function, and vitamin D levels. The effect of preoperative changes over time is then further investigated by comparing the effect of parathyroid surgery on postoperative outcome variables during the study period.

Materials and methods

Patients

Since 1989, all patients treated for pHPT at Lund University Hospital have been registered in a prospective database. Preoperative parameters, operation details, and data at follow-up until at least 1 year postoperatively are recorded. For this longitudinal cohort study, data were extracted on all patients with sporadic non-hereditary pHPT, independent on histological diagnosis and analyzed in three equal time periods: 1989–1994, 1995–2000, and 2001–2006. Postoperative values were measured 12 months after surgery. Patients that did not complete the 1-year follow-up were excluded from postoperative statistical analysis. Between 1989 and 1994, 11 patients were excluded. Between 1995 and 2000, we excluded 8 patients and between 2001 and 2006, 9 patients had to be excluded. Cure was defined as postoperative ionized calcium <1.35 mmol/L and/or total serum calcium <2.50 mmol/L despite PTH levels at 12 months after surgery.

Surgery

All operations were performed by one of the authors or one of 2 additional specialist endocrine surgeons in our unit.

During the study period, we performed either bilateral neck exploration or unilateral/focused exploration (through a lateral incision or a central Kocher incision), depending on preoperative localization and results of intraoperative PTH measurement (ioPTH). To verify successful removal of all pathological parathyroid tissue, intraoperative PTH measurement (iOPHT) was used in all cases, and cure was predicted according to the MIAMI criterion as earlier described by Irvin et al. [22] e.g., a decrease to <50 % of baseline value.

Biochemistry

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 an assigned value of 1.27 mmol/L. Levels of total serum calcium (reference range 2.20–2.50 mmol/L) and creatinine were measured by a routine laboratory analyzer.

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, we used a correction algorithm between old and new values: new value = 1.4 × 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) which present results in nmol rather than µg/L. We corrected old values by using the algorithm: µg/L × 2.5 = nmol/L, 25-hydroxyvitamin D into new values (reference range 25–125 nmol/L), according to the department of clinical chemistry. The CV for 25(OH)D₃ is 15 % at 50 nmol/L.

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. In 65-year-old subjects, the expected GFR would be about 80 mL/min.

Bone 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

Table 1 Preoperative characteristics in the whole cohort of patients with primary hyperparathyroidism

Time period	All			Women			Men		
	1989–1994	1995–2000	2001–2006	1989–1994	1995–2000	2001–2006	1989–1994	1995–2000	2001–2006
Patients (<i>n</i>)	114	130	160	88	98	128	26	32	32
Age (years)	65	70	67	68	73	68	62	64	62
	55 to 75	55 to 77	59 to 76	57 to 78	58 to 78	59 to 76	49 to 71	49 to 73	51 to 76
P-Calcium (mmol/L)	2.74	2.77	2.76	2.80	2.77	2.76	2.7	2.78	2.8
	2.65 to 2.90	2.67 to 2.88	2.66 to 2.88	2.70 to 2.90	2.70 to 2.90	2.70 to 2.90	2.58 to 2.81	2.67 to 2.92	2.70 to 2.95
S-ionized calcium (mmol/L)	1.50	1.46	1.45	1.51	1.46	1.44	1.45	1.48	1.48
	1.44 to 1.57	1.41 to 1.53	1.40 to 1.52	1.44 to 1.57	1.41 to 1.51	1.40 to 1.50	1.42 to 1.50	1.40 to 1.59	1.41 to 1.55
P-PTH (pmol/L)	11.5	12	11	11.7	12.1	11	11.1	11.3	11
	8.6 to 18	8.6 to 16.6	8.2 to 14	8.6 to 10.4	9 to 16.6	8.3 to 14	9.2 to 16.6	7.4 to 16.6	7.7 to 17
Urinary calcium (mmol/L)	5.0	4.7	4.2	4.6	4.4	4.2	6.5	5.2	5.4
	3.2 to 6.9	2.8 to 6.6	3 to 6	3 to 6.4	2.5 to 6.5	0.6 to 5.6	4.40 to 8.20	4.10 to 7	4 to 6.7
GFR (mL/min)	74	74	77	70.5	72.5	76	89	83	88
	56 to 92	61 to 89	64 to 9	56 to 92	61 to 89	64 to 91	83 to 96	61 to 95	76 to 105
S-25OHD (nmol/L)	53	51	52	52	50	52	56	61	53
	38 to 61	42 to 68	31 to 66	39 to 61	41 to 66	31 to 65	34 to 60	48 to 72	30 to 73
BMD lumbar spine L2–4 (g/cm ²)	*	1.036	1.009	*	0.988	0.991	*	1.189	1.065
		0.883 to 1.209	0.883 to 1.12		0.840 to 1.157	0.837 to 1.111		1.024 to 1.321	0.972 to 1.210
Z-score of BMD lumbar spine, L2–4	*	−0.40	−0.50	*	−0.50	−0.40	*	−0.05	−1.10
		−1.40 to 0.70	−1.70 to .40		−1.40 to .70	−1.60 to .50		−1.23 to .95	−1.90 to 0
BMD femoral neck (g/cm ²)	*	0.796	0.779	*	0.758	0.767	*	0.888	0.829
		0.684 to 0.908	0.694 to 0.855		0.655 to 0.864	0.692 to 0.841		0.778 to 0.980	0.724 to 0.928
Z-score of BMD femoral neck	*	−0.60	−0.60	*	−0.60	−0.50	*	−0.70	−1.20
		−1.0 to 0	1.20 to 0		−1.0 to 0	−1.10 to 0.20		−1.2 to 0	−1.60 to −0.70
Adenoma weight (g)	0.70	0.75	0.5	0.67	0.7	0.51	0.73	0.83	0.5
	0.36 to 1.32	0.41 to 1.46	0.31 to 1	0.38 to 1.3	0.4 to 1.4	0.32 to 1.0	0.27 to 1.3	0.34 to 2.1	0.28 to 1.2

Medians and interquartile range are shown

p values and interquartile range are displayed in italic

BMD bone mineral density, GFR Glomerular filtration rate

* Not measured routinely before 1994

** Few observations

Table 2 Preoperative characteristics in patients with parathyroid adenoma. Medians and interquartile range are shown

Time period	All				Women				Men			
	1989–1994	1995–2000	2001–2006	<i>p</i>	1989–1994	1995–2000	2001–2006	<i>p</i>	1989–1994	1995–2000	2001–2006	<i>p</i>
Patients (<i>n</i>)	108	112	134		83	86	106		25	26	28	
Age (years)	64	70	68	0.24	66	73	69	0.22	61	64	62	0.73
	55 to 74	55 to 77	59 to 76		55 to 76	56 to 78	60 to 79		49 to 71	50 to 70	51 to 76	
P-Calcium (mmol/L)	2.73	2.77	2.76	0.55	2.8	2.77	2.75	0.98	2.7	2.75	2.8	0.07
	2.63 to 2.9	2.70 to 2.90	2.67 to 2.90		2.65 to 2.90	2.66 to 2.88	2.67 to 2.87		2.58 to 2.77	2.65 to 2.89	2.69 to 2.9	
S-ionized calcium (mmol/L)	1.50	1.46	1.45	<0.001	1.51	1.46	1.44	<0.001	1.45	1.44	1.47	0.98
	1.44 to 1.56	1.41 to 1.52	1.40 to 1.51		1.44 to 1.57	1.41 to 1.51	1.40 to 1.50		1.42 to 1.50	1.40 to 1.57	1.41 to 1.54	
P-PTH (pmol/L)	11.6	12	10	0.04	11.8	12	10	0.03	11.4	10.7	11	0.89
	8.70 to 18.7	8.6 to 15.2	7.8 to 14		8.5 to 19.4	8.9 to 17	8 to 14		9.3 to 16.6	7.4 to 13	7.7 to 15	
Urinary calcium (mmol/L)	4.8	4.9	4.2	0.57	4.5	4.8	4.1	0.75	6.3	5	5.2	0.37
	3.2 to 6.6	2.8 to 6.6	3.1 to 6.6		3 to 5.9	2.5 to 6.6	2.7 to 5.9		3.8 to 8.6	3.7 to 6.6	3.9 to 6.3	
GFR (mL/min)	77	74	77	0.47	72	73.5	76	0.50	89	82	89	0.27
	63 to 93	64 to 90	65 to 93		56 to 93	64 to 89	64 to 89		83 to 96	70 to 93	76 to 105	
S-25OHD (nmol/L)	54	50	52	0.46	52	49	52	0.85	57	65	51	0.17
	38 to 61	42 to 68	28 to 65		39 to 61	41 to 63	30 to 65		34 to 60	48 to 72	22 to 73	
BMD lumbar spine L2–4 (g/cm ²)	*	1.044	1.021	0.30	*	1.008	0.993	0.85	*	1.192	1.065	0.04
		0.890 to 1.119	0.874 to 1.119			0.857 to 1.157	0.834 to 1.112			1.011 to 1.353	0.971 to 1.168	
Z-score of BMD lumbar spine, L2–4	*	−0.30	−0.50	0.38	*	−0.40	−0.35	0.96	*	0.20	−1.10	0.02
		−1.25 to 0.70	−1.80 to 0.40			−1.30 to 0.70	−1.75 to 0.60			−1.25 to 1.0	−2.05 to 0	
BMD femoral neck (g/cm ²)	*	0.796	0.768	0.32	*	0.758	0.756	0.66	*	0.890	0.829	0.10
		0.674 to 0.907	0.693 to 0.845			0.652 to 0.858	0.652 to 0.858			0.807 to 0.984	0.716 to 0.89	
Z-score of BMD femoral neck	*	−0.60	−0.60	0.56	*	−0.55	−0.50	0.99	*	−0.60	−1.20	0.07
		−1.0 to 0.10	−1.2 to 0			−1.0 to 0	−1.10 to 0.10			−1.20 to 0.20	−1.60 to −0.60	
Adenoma weight (g)	0.7	0.73	0.5	0.03	0.69	0.7	0.5	0.08	0.73	0.83	0.5	0.31
	0.35 to 1.32	0.4 to 1.48	0.3 to 1		0.36 to 1.3	0.41 to 1.42	0.31 to 1.2		0.27 to 1.3	0.34 to 2.1	0.3 to 1.2	

p values and interquartile range are displayed in italic

BMD bone mineral density, GFR glomeruli filtration rate

* Not measured routinely before 1994

** Few observations

Table 3 Postoperative characteristics 1 year after surgery in the whole cohort of patients operated for primary hyperparathyroidism

Time period	All				Women				Men			
	1989–1994	1995–2000	2001–2006	<i>p</i>	1989–1994	1995–2000	2001–2006	<i>p</i>	1989–1994	1995–2000	2001–2006	<i>p</i>
Patients (<i>n</i>)	114	130	160		88	98	128		26	32	32	
Operation time (min)	115 90 to 155	81 57 to 117	71 40 to 110	<0.001	112 90 to 147	77.5 52 to 15	63.5 39 to 105	<0.001	138 77 to 175	100 78 to 128	97 59 to 119	0.13
P-PTH 1 year (pmol/L)	3.6 2.6 to 4.7	4.1 3.2 to 5.6	4.5 3.4 to 5.9	<0.001	3.6 2.6 to 4.8	4.1 3.15 to 5.8	4.6 3.4 to 6	<0.001	3.7 1.7 to 4.3	3.6 3 to 5.4	4.0 3.2 to 5.1	0.17
S-ionized calcium 1 year (mmol/L)	1.22 1.20 to 1.25	1.20 1.18 to 1.24	1.23 1.20 to 1.27	<0.001	1.23 1.2 to 1.26	1.2 1.18 to 1.24	1.24 1.21 to 1.27	<0.001	1.22 1.21 to 1.24	1.21 1.17 to 1.26	1.23 1.20 to 1.27	0.40
GFR 1 year (mL/min)	**	70 55 to 86	77 62 to 88	0.34	**	70 55 to 85	76.5 62 to 86	0.35	**	70 58 to 88	86 65 to 98	0.32
BMD lumbar spine (g/cm ²) L2–4 1 year	*	1.024 0.871 to 1.221	0.994 0.882 to 1.103	0.43	*	1.021 0.849 to 1.221	0.993 0.875 to 1.102	0.69	*	1.226 1.070 to 1.326	1.126 1.008 to 1.245	0.20
Delta BMD L2–4 (%) 1 year	*	3.48 −0.64 to 9.33	1.58 −0.97 to 7.32	0.09	*	3.48 −0.55 to 9.38	1.35 −0.93 to 6.72	0.08	*	4.48 −0.78 to 9.33	2.77 −1.0 to 9.16	0.46
Z-score of BMD L2–4 1 year	*	−0.25 −1.0 to 1.10	−0.20 −1.30 to 0.60	0.56	*	−0.30 −1.30 to 0.90	−0.20 −1.40 to 0.60	0.71	*	0.25 −1.20 to 1.40	−0.20 −1.15 to 0.60	0.25
BMD femoral neck (g/cm ²) 1 year	*	0.770 0.688 to 0.912	0.793 0.70 to 0.876	0.64	*	0.769 0.673 to 0.907	0.789 0.694 to 0.875	0.95	*	0.895 0.812 to 1.004	0.848 0.741 to 0.923	0.20
Delta BMD (%) femoral neck 1 year	*	2.80 0 to 5.54	2.08 −1.18 to 5.63	0.16	*	3.08 0 to 5.54	1.95 −1.14 to 5.14	0.13	*	2.59 0 to 5.04	2.70 −1.18 to 5.87	0.73
Z-score BMD femoral neck 1 year	*	−0.40 −1.0 to 0.30	−0.50 −0.90 to 0.40	0.57	*	−0.45 −1.0 to 0.3	−0.50 −0.90 to 0.40	0.98	*	−0.30 −0.80 to 0.40	−0.85 −1.40 to 0.05	0.08
Cured 1 year, <i>n</i> (%)	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

Medians and interquartile range are shown. Patients with operative failure were excluded

p values and interquartile range are displayed in italic

BMD bone mineral density, GFR glomeruli filtration rate

* Not measured routinely before 1994

** Few observations

1.72 (Lunar Corp, Madison, Wis). The method has a CV of 1 %. BMD is expressed in gram per square centimeter (g/cm^2) 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: $(\text{BMD 1 year after surgery} - \text{preoperative BMD}/\text{preoperative BMD}) \times 100$, and are presented in per cent.

Statistics

Medians with interquartile range for pre- and postoperative values in three equal periods of time were calculated: (1) 1989–1994, (2) 1995–2000, and (3) 2001–2006, according to operation date. Due to skewed distributions, median values were compared for the three different time periods, using the Kruskal–Wallis test. Patients with operative failure (persistent disease) were excluded from postoperative analysis. The cohort was analyzed in its whole and stratified by gender and histology. Change over time in preoperative calcium levels, PTH, GFR, and postoperative change in BMD were analysed by using Spearman's linear regression model as a sensitivity analysis.

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

Results

There were a total of 435 individuals operated for pHPT during the whole period in the database. Some 404 of these were included in the present study, 314 women (78 %) and 90 men (22 %). The proportion of men and women, and the median age at operation, was similar in the three time periods. Some 354 patients with adenoma (87.6 %), 32 patients with hyperplasia (8.7 %) and 18 patients with unclear histology were diagnosed. The proportion of parathyroid adenoma decreased from 94.7 % (1989–1994) to 86.2 % (1995–2000) and 83.8 % (2001 and 2006). The proportion of bilateral neck explorations was 57 % (1989–1994), 60 % (1995–2000), and 48 % (2001–2006) (Table 5). Overall, there were no differences in the biochemical presentation in patients diagnosed with adenoma or hyperplasia. The cure rate (95 % CI) was 99 % (95–100 %) (1989–1994), 96 % (91–99 %) (1995–2000), and 95 % (90–98 %) (2001–2006). These differences were not significant ($p = 0.48$). Median values and interquartile range for age, preoperative serum calcium, PTH, creatinine, GFR, $25(\text{OH})\text{D}_3$, BMD, and adenoma weight for all patients, for men and women and categorized by histology, are shown in Tables 1, 2, 3, and 4.

Preoperative biochemistry and bone density

In the whole cohort, median preoperative S-ionized calcium was lower in 2001–2006 than 1989–1994, 1.45 versus 1.50 mmol/L ; $p < 0.001$. Adenoma weight followed the same trend, with a median weight of 0.7 g in 1989–1994 compared to 0.5 g in 2001–2006; $p = 0.04$. Preoperative PTH levels in the adenoma cohort were lower in 2001–2006 than in 1989–1994, 10 versus 11.6 pmol/L ; $p = 0.04$. Preoperative PTH levels in the whole cohort did not differ between the time periods, $p = 0.48$; Tables 1 and 2.

Median preoperative BMD of the lumbar spine in male patients diagnosed with parathyroid adenoma was lower in 2001–2006 than in 1995–2000, 1.065 versus 1.192 g/cm^2 ; $p = 0.04$. Further, median preoperative Z-score in the lumbar spine in male patients with parathyroid adenoma was lower in 2001–2006 than in 1995–2000, -1.10 versus 0.20 SD; $p = 0.02$.

There was no difference in median preoperative urinary calcium, GFR, or $25(\text{OH})\text{D}_3$ levels between time periods, Table 1.

Univariate Spearman linear regression with operation year as independent variable showed similar results for preoperative ionized calcium, as the analysis with operation time in three categories; correlation coefficient of -0.16 , $p < 0.001$. There were no significant correlations between operation year and preoperative PTH (correlation coefficient of -0.09 , $p < 0.09$), urinary calcium (correlation coefficient of -0.1 , $p < 0.09$), and GFR (correlation coefficient of -0.03 , $p < 0.63$), respectively, in the linear regression analysis.

Postoperative biochemistry and bone density

Median ionized calcium levels in the whole cohort and in patients with adenomas one year after surgery were higher between 2001 and 2006 compared to 1989–1994 (1.24 versus 1.22 mmol/L ; $p < 0.001$), Tables 3 and 4. Median levels of PTH 1 year after surgery, in the whole cohort, and in patients with adenoma, were higher between 2001 and 2006 than between 1989 and 1994, 4.5 versus 3.6 pmol/L ; $p < 0.001$ and 4.6 versus 3.6 pmol/L ; $p < 0.001$.

Renal function, measured as levels of GFR 1 year after surgery, was similar in all periods, Tables 3 and 4.

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), independent of gender and histology, Tables 3 and 4.

Change over time in delta values of BMD in the whole cohort were also calculated with univariate Spearman's

Table 4 Postoperative characteristics 1 year after surgery in patients with parathyroid adenoma

Time period	All				Women				Men			
	1989–1994	1995–2000	2001–2006	<i>p</i>	1989–1994	1995–2000	2001–2006	<i>p</i>	1989–1994	1995–2000	2001–2006	<i>p</i>
Patients (<i>n</i>)	108	112	134		83	86	106		25	26	28	
Operation time (min)	115	80	62	<0.001	112	78	57	<0.001	135	98	98	0.13
P-PTH 1 year (pmol/L)	90 to 149	55 to 110	38 to 98		92 to 147	52 to 118	38 to 90		77 to 167	76 to 116	59 to 119	
	3.55	4.0	4.5	<0.001	3.5	4.0	4.5	<0.001	3.8	3.7	4.2	0.1
	2.50 to 4.60	3.1 to 5.7	3.4 to 5.8		2.6 to 4.8	3.2 to 5.9	3.6 to 5.8		1.8 to 4.3	3.1 to 5.3	3.4 to 5.4	
S-ionized calcium 1 year (mmol/L)	1.22	1.20	1.23	<0.001	1.23	1.20	1.24	<0.001	1.22	1.21	1.23	0.4
	1.20 to 1.25	1.18 to 1.23	1.20 to 1.26		1.20 to 1.25	1.18 to 1.23	1.21 to 1.26		1.20 to 1.23	1.18 to 1.26	1.20 to 1.27	
GFR 1 year (mL/min)	**	70	78	0.11	**	70	76	0.20	**	79	87	0.48
		59 to 88	63 to 90			55 to 86	63 to 86			66 to 100	68 to 100	
BMD lumbar spine (g/cm ²) L2–4	*	1.102	1.046	0.1	*	1.030	0.994	0.52	*	1.275	1.132	0.18
1 year		0.905 to 1.283	0.886 to 1.140			0.887 to 1.224	0.869 to 1.102			1.070 to 1.326	1.015 to 1.247	
Delta BMD L2–4 (%) 1 year	*	3.31	2.03	0.11	*	3.27	1.39	0.09	*	3.52	4.82	0.44
		−0.47 to 8.53	−0.92 to 7.20			−0.30 to 8.46	−0.93 to 6.29			−0.79 to 8.53	−0.55 to 9.65	
Z-score of BMD L2–4 1 year	*	−0.10	−0.20	0.31	*	−0.25	−0.10	0.75	*	0.80	−0.20	0.12
		−1.10 to 1.27	−1.10 to 0.70			−1.0 to 1.10	−1.10 to 0.70			−1.20 to 1.60	−0.80 to 0.30	
BMD femoral neck (g/cm ²) 1 year	*	0.798	0.784	0.62	*	0.654	0.659	0.95	*	0.907	0.875	0.24
		0.709 to 0.941	0.699 to 0.888			0.554 to 0.804	0.588 to 0.758			0.815 to 1.004	0.763 to 0.940	
Delta BMD (%) femoral neck 1 year	*	2.63	2.18	0.15	*	2.85	1.87	0.11	*	2.52	2.82	0.70
		0 to 5.37	−1.08 to 5.47			0 to 5.50	−2.15 to 5.31			0 to 5.06	0.90 to 5.54	
Z-score BMD femoral neck 1 year	*	−0.40	−0.5	0.60	*	−0.40	−0.50	0.99	*	−0.10	−0.70	0.08
		−1.0 to 0.30	−1.0 to 0.20			−1.1 to 0.40	−1.1 to 0.40			−0.80 to 0.54	−1.30 to 0	
Cured 1 year, <i>n</i> (%)	107 (99)	107 (95)	127 (95)	0.96	82 (98.7)	82 (95.6)	99 (93.4)	0.95	24 (96)	25 (96.7)	27 (96.5)	1.0

Medians and interquartile range are shown. Patients with operative failure were excluded

p values and interquartile range are displayed in italic

BMD bone mineral density, GFR Glomerular filtration rate

* Not measured routinely before 1994

** Few observations

Table 5 Surgical outcome, stratified by exploration type, and pathology report

Time period	1989–1994	1995–2000	2001–2006	<i>p</i>
Bilateral neck exploration <i>n</i> (% of all patients)	49 (42.9)	79 (60.8)	78 (48.8)	
Parathyroid adenoma (<i>n</i>)	43	64	62	
Adenoma cure rate 1 year after surgery <i>n</i> (%)	42 (97.7)	62 (96.9)	56 (90.3)	0.99
Parathyroid hyperplasia (<i>n</i>)	4	14	12	
Hyperplasia cure rate 1 year after surgery <i>n</i> (%)	3 (75)	13 (92.9)	12 (100)	0.98
Unilateral neck exploration (<i>n</i>)	65	51	82	
Parathyroid adenoma (<i>n</i>)	59	47	71	
Adenoma cure rate 1 year after surgery <i>n</i> (%)	59 (100)	44 (97.9)	71 (100)	0.89
Parathyroid hyperplasia (<i>n</i>)	0	1	1	
Hyperplasia cure rate 1 year after surgery <i>n</i> (%)	0	1 (100)	1 (100)	0.32

linear regression model with operation year as independent variable. There was no significant correlation, neither in the lumbar spine, $\rho = -0.07$; $p = 0.30$, nor in the femoral neck, $\rho = -0.09$; $p = 0.17$.

Discussion

The aim of this longitudinal study of patients with pHPT was to investigate whether preoperative variables and the effect of parathyroidectomy regarding biochemistry and bone density have changed over almost two decades.

The results show that preoperative median levels of ionized calcium and PTH in the adenoma cohort and adenoma weight were lower in the later years of observation time. These results are in line with previous studies [2–9], indicating treatment of patients at lower levels of calcium than previously. Despite smaller adenomas in the latter time period, the cure rate did not change. With a median adenoma weight between 500 and 700 mg in our patients, despite decreasing we are still far from the previously described cut-off value of 200 mg with an increased risk for multiglandular disease and consequently risk for lower success rates [5, 23].

Median preoperative GFR was similar in all three time periods for the whole cohort and for men and women separately, despite lower grade of hypercalcaemia in the latter time periods. We expected GFR to be less impaired with lower increase in PTH and calcium. However, this could not be confirmed by our study. A possible explanation for this could be a study published by Tassone et al. [20] that compared PTH levels and glomeruli filtration rate in patients with pHPT. He found comparable levels of PTH in patients with GFR as low as 59 mL/min. He concluded that only severely impaired kidney failure (GFR < 60 mL/min) additionally increases PTH levels significantly.

Differences in median preoperative BMD were only found in male patients diagnosed with parathyroid

adenoma with lower absolute values of BMD in the lumbar spine as well as a lower Z-score in the lumbar spine in patients operated during 2001–2006 compared to patients operated from 1995 to 2000. This was surprising since it could be expected that patients with milder increase in calcium levels, e.g., the last time period, may have a better preserved bone density compared to patients operated at the beginning of the study period. Several observation studies have shown that progression of skeletal disease without surgical treatment of pHPT is rare in patients with mild pHPT [24–27], thus the differences between preoperative PTH and Calcium levels between the three time periods were probably too small to be able to affect preoperative BMD and the observation time too short.

Preoperative 25(OH)D₃-levels were similar in all periods over time despite lower PTH values in period 3. Since levels of 25(OH)D₃ are influenced not only by PTH but also by kidney function, nutrition, exposition to ultraviolet light, and probably by adenoma size [21, 28–30], the reasons for this finding are most probably multifactorial.

Since operations in patients with milder elevations of calcium and with smaller parathyroid adenomas could have implications for short- and long-term outcomes after surgical treatment, postoperative data on biochemistry, bone density, and renal function were evaluated. There were no differences in postoperative change in bone density, measured as delta BMD, among patients operated in the different time periods. This might be expected, since medians of preoperative BMD, except in male patients with parathyroid adenoma, did not differ between the periods. Further, previous studies have shown that patients with pHPT and more advanced bone disease benefit more from parathyroid surgery [19].

Hedbäck et al. showed an increase of glomeruli filtration rate soon after successful parathyroid surgery in patients with mild, moderate, and severe pHPT [31]. Nonetheless, we found no indication on/for? Differences in outcome of renal function, as estimated by GFR, for patients operated

over 18 years, with a preoperative milder increase in calcium and PTH.

In summary, in this cohort of patients with sporadic primary HPT undergoing first time surgery age and gender remained virtually unchanged, as did renal function and bone density. Median levels of ionized calcium and PTH were lower in the later period, as well as adenoma weight. This could mean, that indications for surgery have changed, with a lower threshold in levels of calcium and PTH for operation. There seemed to be no specific benefit in terms of improvement in bone density or renal function with early surgical treatment. This is important since the median age of these patients are above 65 years. The benefit of operating older patients with mild hypercalcaemia remains to be proven. However, reassuringly, the cure rate remained unchanged.

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Paper III

Results of a Fifteen-Year Follow-up Program in Patients Operated with Unilateral Neck Exploration for Primary Hyperparathyroidism

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Abstract

Background Since the introduction of unilateral parathyroidectomy for primary hyperparathyroidism (pHPT) it has been debated whether this approach is associated with greater long-term risk for recurrence compared to bilateral neck exploration.

Methods This is a prospective study based on a structured 15-year follow-up program in patients with non-hereditary, sporadic pHPT, undergoing first time surgery with unilateral or focused neck exploration (unilateral procedures), with the use of intraoperative PTH (iOPTh) between 1989 and 2010.

Results 292 patients were analyzed. The median age of the patients was 66 years [interquartile range (IQR) 57–75], and 234 (80.4 %) were female. The median preoperative level of total calcium was 2.74 mmol/L (IQR 2.63–2.85 mmol/L) and the median PTH level was 10 pmol/L (IQR 7.4–14 pmol/L). The median follow-up time was 5 years (IQR 1–10 years). Some 275 patients were followed for 1 year (94.2 %/275 person-years/5 patients deceased), 164 for 5 years (56.2 %/820 person-years/31 patients deceased), 70 for 10 years (24.0 %/700 patient-years/57 patients deceased) and 51 (17.5 %/765 patient-years/69 patients deceased) for 15 years after surgery. Three patients (1.1 %) had signs of persistent disease. One patient recurred in pHPT at 5 years postoperatively during 15 years of follow-up. Histopathology indicated solitary parathyroid adenoma at primary surgery.

Conclusion Patients with pHPT operated with unilateral procedures and iOPTh, had a low risk for long-term recurrence during a 15 years follow-up program.

Introduction

Some 30 years ago Tibblin et al. introduced unilateral parathyroidectomy in primary hyperparathyroidism (pHPT) due to single adenoma [1, 2]. This approach was initially highly controversial, due to the supposed risk for

short- and long-term recurrence of pHPT [3–7]. The main advantage of a unilateral approach is that, compared to bilateral neck exploration (BNE), it is associated with a decreased risk for complications, especially early postoperative hypocalcaemia [8–12]. The validity and reliability of preoperative localization procedures has been discussed since their introduction. Even though some studies showed that sestamibi scintigraphy had unsatisfactory sensibility for detection of multiglandular disease (MGD) [6, 7, 13], several publications have proven the short-term validity of scan-directed parathyroid exploration in combination with ultrasound and/or intraoperative PTH measurements (iOPTh) [3, 14–18]. The difficulty in differentiating between parathyroid adenoma and hyperplasia based on

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histopathological features implicates the need for long postoperative follow-up and peroperative adjuncts (iOPTH) to verify successful removal of pathological parathyroid tissue and. The unilateral or focused approach for the surgical treatment of pHPT, has gained widespread acceptance during the last decades. In 2012 the Scandinavian Quality Register showed that BNE comprised only 40 % of all parathyroid operations in Sweden (<http://www.thyroid-parathyroidsurgery.com/assets/Årsrapport-2014.pdf>). Even if good results have been shown by a randomized trial at follow-up 5 years postoperatively [19] the long-term risk for recurrent PHPT has been debated. Recently, retrospective studies investigating long-term outcome after unilateral and bilateral exploration have been published [4, 5, 20–26].

It was hypothesized that patients undergoing unilateral parathyroid exploration had a low long-term risk for recurrent disease. In this prospective study results from a structured 15-year follow-up program of patients operated with a unilateral or focused approach between 1989 and 2010 at a single center are reported.

Methods

Study population

Patients operated for pHPT from 1989 to 2010 were included in the study. Exclusion criteria were a family history of pHPT (MEN1, MEN2, or hereditary pHPT), reoperation for pHPT, concordant thyroid surgery and bilateral neck exploration, whether preoperatively planned or peroperatively required. All patients operated for pHPT at the department of surgery at Lund University hospital, Sweden were included in a 15-year follow-up program. The date for last follow-up was December 31, 2013. The length of follow-up was calculated as date for latest biochemical follow-up operation date. The study group consisted of patients with preoperatively localized parathyroid adenoma by (99 m)Tc Sestamibi scanning (MIBI) or by ultrasound complemented by intraoperative PTH (iOPTH). Patients with non-localized adenoma in whom iOPTH measurements confirmed successful excision of pathological parathyroid tissue after unilateral neck exploration, were also included in the study.

Follow-up program

The 15 years structured follow-up program was initiated in 1989. The program was designed to investigate the risk for long-term recurrence in patients with pHPT specifically in patients operated with a unilateral approach.

Results of pre-and postoperative variables, were registered by one of the authors in a database. Registered variables included symptoms and signs of pHPT, medical history and medication, biochemical variables including, among others, calcium and PTH levels, urinary calcium, biochemical markers for bone remodeling, vitamin D status, bone density and renal function. Parathyroid imaging, intraoperative PTH measurements, operation technique and intraoperative findings and histopathology were also recorded.

In the 15 years follow-up program all patients were followed by one of the authors. Follow-up with biochemistry were routinely conducted at 4 weeks, and at 1, 5, 10, and 15 years after surgery. At 1 year after surgery biochemistry were supplemented with investigation of bone density, renal function and Vitamin D status.

Cure was defined as calcium levels below the upper limit for normocalcemia (ionized calcium <1.35 mmol/L/ P-Calcium <2.50 mmol/L), regardless of PTH levels at 12 months after surgery. Persistent disease was defined as calcium levels above the upper limit for normocalcemia within 1 year after surgery.

Surgery

All patients underwent surgery performed under general anesthesia, either with a short 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 [27].

To verify successful removal of all pathological parathyroid tissue, intraoperative PTH measurement (iOPTH) was used, according to the MIAMI criterion as earlier described by Irvin et al. [28] e.g., a decrease to <50 % of baseline value.

Biochemical variables

Preoperative 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 an assigned value of 1.27 mmol/L. Levels of total serum calcium (reference range 2.20–2.60 mmol/L) were measured by a routine laboratory analyzer. Plasma parathyroid hormone (PTH) was analyzed by an assay for intact PTH (Hitachi Modular –E), reference range 1.6–6.9 pmol/L. The analysis has a total CV of 5 % at 100 pmol/L. On 20th

March 2000 the method was changed. The correction formula between old and new values is as follows: new value = $1.4 \times \text{old value} - 0.2$.

High performance liquid chromatography (HPLC) was used for assessment of the level of serum 25-hydroxyvitamin D₃ [25(OH)D₃] (reference range >75 ng/L). The method concerning analyses of 25-hydroxyvitamin D₃ was changed to Nichols Advantage 25-Hydroxyvitamin D, Nichols Institute Diagnostics and all data were transformed. Glomerular filtration rate, GFR, was determined by a technique that measures renal clearance of the contrast agent iohexol. Using this method, the average value for young healthy subjects is 127 ml/min with a reduction in subjects older than 55. Thus, in 65-year-old subjects, the expected GFR would be about 80 mL/min.

Cure was defined as calcium levels below the upper limit for normocalcemia (ionized calcium <1.535 mmol/L/ P-Calcium <2.50 mmol/L) at 12 months after surgery. Persistent disease was defined as calcium levels above the upper limit for normocalcemia before 1 year after surgery.

Statistics

Statistical analysis was carried out using STATA 11 StataCorp LP, 4905 Lakeway Drive College Station, Texas 77845 USA. The association between variables over time was tested with the Spearman rank correlation test. Nominal data are shown as numbers and per cent. All tests were two-sided.

Overall survival data were calculated by Kaplan–Meier survival curves.

A *p* value <0.05 was considered statistically significant.

Results

Preoperative status

There were 570 patients with non-hereditary pHPT undergoing first time surgery, and 292 of these patients were operated with a unilateral approach. The median age of the patients was 66 (range 22–89) years. The median level of total calcium was 2.74 mmol/L (IQR 2.63–2.85 mmol/L).

The results of preoperative localization procedures, is shown in Table 1. Sestamibi scintigraphy was used in 253 patients, indicating single gland disease (SGD) in 219 patients. Sensitivity was 87.2 % for correct prediction of adenoma side. Additional ultrasound was performed in 71 patients, predicting SGD in 61 patients. Sensitivity was 77.0 % for correct prediction of adenoma side. 36 patients had concordant, positive localization results. In 131 of 292 patients (45 %), two parathyroid glands were identified intraoperatively.

Histopathology

Histopathology report showed a solitary parathyroid adenoma in 286 patients with a median gland weight of 730 mg (range 100–9800 mg; IQR 380–1550 mg). In four patients, in whom one gland was excised, the histopathology report suggested parathyroid hyperplasia due to absence of suppressed parathyroid tissue in the specimen. None of these patients, however, showed signs of persistent or recurrent disease.

Follow-up

Results from preoperative biochemical data and follow-up, are shown in Table 2. The median follow-up time was 5 years (range 4 weeks–15 years). Eleven patients were followed for <1 year. Three of these died within the first year of follow-up. During follow-up 69 patients died (Fig. 1). Some 275 patients (94.2 %) were followed for 1 year, 164 (56.2 %) for 5 years, 70 (24.0 %) for 10 years and 51 (17.5 %) for 15 years after surgery. The reason for not taking part in the follow-up program at a particular time point included, patient refusal, medical reasons, and that the patients had moved from the catchment area of the endocrine surgical unit.

None of the patients suffered from postoperative hypocalcemia.

Persistent disease

Three patients (1.1 %) had signs of persistent disease. In two of these patients, two glands were identified and one enlarged gland was removed and histopathology showed a

Table 1 Results of preoperative localization procedures results

	<i>n</i>	Positive	Negative	Not performed	Concordant positive localization studies	Concordant negative localization studies	No localization studies performed	Correctly predicted side	Sensitivity (%)
Scintigrafi	253	219	34	39	36	1	27	191	87.2
Ultrasound	71	61	10	221				47	77.0

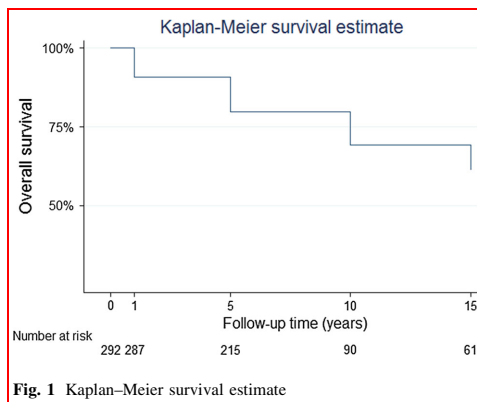
Frequencies are displayed as *n* if not stated otherwise

Table 2 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 (<i>n</i>)	292	292	287	215	90	61
Patients followed-up (<i>n</i>)	292	279	275	164	70	51
Deceased (<i>n</i>)	–	0	5	31	57	69
Missing (<i>n</i>)	–	13 (4.5)	12 (4.2)	51 (23.7)	20 (22.0)	10 (16.4)
(% of pat. at risk)						
Cured <i>n</i> (% of pat. at risk)	–	277 (99.3)	271 (98.5)	163 (99.4)	70 (100)	51 (100)
Persistent disease (<i>n</i>)	–	3	3	–	–	–
Recurrence (<i>n</i>)	–	–	–	1	0	0
P-calcium (mmol/L)	2.74	2.34	2.31	2.33	2.36	2.35
(median and interquartile range)	2.63–2.85	2.27–2.41	2.25–2.39	2.28–2.39	2.28–2.42	2.27–2.44
S-ionized calcium (mmol/L)	1.46	1.24	1.22	1.22	1.22	1.23
(median and interquartile range)	1.41–1.52	1.21–1.27	1.2–1.26	1.20–1.25	1.2–1.25	1.20–1.25
P-PTH (pmol/L)	10	5.2	4.65	4.55	4.25	4.7
(median and interquartile range)	7.4–14	3.85–7.3	3.5–6.35	3.55–6.05	3.2–6.2	3.6–5.4
Creatinine	71	–	72	74	70	73
(median and interquartile range)	60–85	–	61–83	66–91	62–82	64–87
S-25OHD (nmol/L)	50	45	56	64	a	a
(median and interquartile range)	37–64	38–62	36–69	45–80		

^a Not measured routinely 10 and 15 years after surgery

– Not applicable

**Fig. 1** Kaplan-Meier survival estimate

parathyroid adenoma. In the third patient, only one gland was identified and excised with iOPTh decreasing >50 %. Histopathology, however, showed normal parathyroid tissue. This patient had a preoperatively elevated level of Creatinine and developed renal insufficiency at 5 years of follow-up. Intraoperative PTH was false positive in all three patients according to the Miami criteria (21). None of the patients have been re-operated.

Recurrent disease

During 15 years of follow-up one patient was diagnosed with recurrent disease 5 years after primary surgery. This patient had a positive preoperative localization with sestamibi for the upper left parathyroid gland, ultrasound showed an enlarged thyroid gland but no parathyroid adenoma. After removal of the upper left gland, iOPTh decreased by 61 %. In this patient, PTH was in the normal range at 10 min after gland excision, although this was not used for decision-making at the time for the operation. The lower right gland was identified and macroscopically normal. Histopathology showed a parathyroid adenoma with a rim of suppressed normal parathyroid tissue. Post-operatively ionized calcium levels were in the upper normal range with PTH elevated and 25 OHD at 25 nmol/L 1 year after surgery. Supplementation with Vitamin D was initiated, but had to be terminated due to increasing calcium levels. At follow-up 5 years after surgery the patient had clear biochemical signs of recurrent disease with levels of ionized calcium, total calcium and PTH above the normal range. Sestamibi scan 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.

Discussion

The aim of this study was to investigate the risk for long-term recurrence in patients with pHPT operated with a unilateral approach with the use of iOPTH.

In contrast to other authors [6], the results showed that the risk for recurrence during a 15-year follow-up was very low. Due to the unilateral nature of the surgical procedure, there was no patient treated for long-term hypocalcaemia. The long-term success rate of a unilateral approach to pHPT in the present investigation is in agreement with previous retrospective studies, some of them reporting on patients operated without the use of iOPTH [5, 22, 29].

In the present study, cure of pHPT was defined strictly as normocalcemia (ionized calcium <1.35 mmol/L and or total calcium levels <2.50 mmol/L. It may be argued that patients with a normal calcium levels but with an increase in PTH, may suffer from persistent sub-clinical pHPT. However, postoperatively elevated PTH levels after pHPT surgery are not uncommon [30–36], and have been shown to be caused by multiple factors, such as vitamin D insufficiency [32, 34], impaired renal function [33, 35], and decreased peripheral sensitivity for PTH [37]. Patients displaying constantly elevated PTH levels after surgery should probably become subject to an individualized, prolonged follow-up program [33, 34]. In the present study, no patient had persistently elevated PTH levels up to 15 years after surgery.

Two of the three patients with persistent disease, were initially diagnosed with solitary parathyroid adenoma, as was the patient with recurrent disease. The patient with recurrent disease may have a true recurrence or sub-clinical disease. All patients with persistent or recurrent disease had a false positive result of iOPTH, which shows, in agreement with other studies that within the subgroup of multiglandular disease, double adenomas are poorly predicted [38, 39].

In four cases, histopathology report suggested parathyroid hyperplasia due to absence of suppressed, normal parathyroid tissue. All four patients were biochemically cured, without signs of long-term recurrence after removal of 1 parathyroid gland. This clearly illustrates the difficulty in distinguishing between parathyroid adenoma and hyperplasia by histology alone.

For reliable selection and time-effective operation scheduling, ultrasound, and sestamibi scintigraphy was utilized for preoperative localization procedures. 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, and/or concomitant thyroid disease which implicates more extensive surgery and

frequent use of bilateral neck exploration [40–42]. In a previous study [27], it has been shown that some of these patients may be operated with a unilateral procedure with the use of iOPTH, which is substantiated with the results from the present investigation; none of the patients with negative preoperative localization procedures recurred.

There are some limitations to the present investigation. There was an inevitable loss of follow-up due to mortality and co-morbidity in this aging patient population with predominantly mild disease. Data on all patients with non-hereditary pHPT undergoing first time surgery with the intention of unilateral or focused exploration was collected prospectively. Patients that did not decrease $>50\%$ in iOPTH, however, had to be excluded peroperatively. Therefore, the results of this study cannot be applied to other patients groups than those who underwent successful unilateral or focused parathyroid exploration.

However, this was a prospective single center observational study with up to 15-year follow-up. All patients were followed by the attending surgeons. Further, the patient cohort consisted of predominantly localized parathyroid disease but patients with negative localization studies were also included. With increasing numbers of patients with asymptomatic pHPT and some research pointing towards decreasing benefits of surgical intervention [43, 44], future treatment recommendations should be individualized for treatment benefits and to minimize adverse effects and cost of treatment and surveillance.

Conclusions

This study confirms a high success rate with a very low risk for recurrent disease in patients with sporadic pHPT operated with a unilateral procedure with the use of iOPTH. Long-term follow-up of this patient category seems not to add any safety benefits.

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Paper IV

Clinical and biochemical predictors of multiglandular disease in patients with primary hyperparathyroidism

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Abstract

Background

Primary hyperparathyroidism (pHPT) is caused by single or multiglandular disease (MGD). Patients with MGD have an increased risk of complications during surgery and of persistence and recurrence after surgery. The study evaluated whether preoperative clinical and biochemical characteristics could predict MGD in patients with pHPT.

Methods

We retrospectively evaluated patients operated upon in the period 1989-2013 for first-time, non-hereditary pHPT. MGD was defined in patients with more than one pathological gland excised at surgery, or with persistent hypercalcemia after the excision of a single pathological parathyroid gland, confirmed by histopathology. Clinical and biochemical variables were compared in patients with single- and multi-glandular disease. Logistic regression was used to identify variables predicting MGD, yielding odds ratios (OR) with 95% confidence intervals (CI).

Results

There were 707 patients, of which 79 (11 %) had MGD. Patients with MGD were more likely to have negative sestamibi scintigraphy than patients with single gland disease, 15 of 49 (31%) vs. 70 of 402 (17 %; $p=0.03$), to suffer from diabetes (12 of 74, 16%) vs. 45 out of 626 patients (7.2%; $p<0.01$), and had lower preoperative levels of urinary calcium (3.80 mmol/L vs. 4.44 mmol/L; $p=0.04$). Multivariable analysis identified negative scintigraphy (OR 2.42; 95% CI 1.18 to 4.79), diabetes (OR 2.75; 95% CI 1.31 to 4.97) and elevated levels of osteocalcin (OR 3.79, 95% CI: 1.75 to 8.21) as predictors of MGD.

Conclusion

Negative sestamibi scintigraphy, diabetes and elevated osteocalcin levels were predictors of MGD.

Introduction

Sporadic primary hyperparathyroidism (pHPT) is caused by a single gland adenoma in the majority of patients. However, the incidence of multiglandular disease (MGD) has been shown to vary in the range 7-23% [1].

PHPT caused by single gland disease (SGD) is cured by simple resection of the parathyroid adenoma, whereas pHPT caused by MGD requires bilateral neck exploration with increased risks, including postoperative hypocalcemia, neck hematoma and recurrent laryngeal nerve palsy [2]. Additionally, operating times, postoperative pain, average hospital stay and costs are increased following bilateral neck exploration [2]. Furthermore, patients with MGD have a lower likelihood of cure after surgery than patients with SGD [3].

To counsel patients about the risks and benefits of surgery for pHPT, and to plan operations, it would be of great benefit to predict MGD preoperatively.

Neck ultrasonography and sestamibi scintigraphy are the most common modalities to distinguish between SGD and MGD, with reported positive predictive values of 80 – 90 percent [4, 5]. Concordant ultrasonographic and scintigraphic results are highly predictive for solitary adenomas, almost approaching 100 percent [4], whereas negative localization studies are associated with a higher risk for MGD [6].

Several studies have tried to identify further factors that would predict MGD preoperatively [6-9]. The CAPTHUS score combines the results of ultrasound, scintigraphy, serum calcium, levels of parathyroid hormone (PTH) and urinary calcium [10]. The score was found to accurately predict SGD by one group [11], whereas other groups found it reliable only in patients with overt disease and positive imaging studies [7, 12]. Another study found that neurocognitive symptoms could predict MGD in patients with pHPT [9].

The Wisconsin index [7] yields the intraoperative probability of remaining hyperfunctioning gland(s) after the resection of one gland. This index consists of preoperative serum calcium and PTH levels and intraoperative parathyroid gland weight, and inherently, it cannot be used to predict MGD preoperatively.

It has been speculated that SGD and MGD are different disease entities, but little is known about the etiology of MGD.

This study was designed to identify clinical, biochemical, and radiological markers to predict MGD in patients with pHPT.

Methods

Data on consecutive patients operated upon for pHPT at Lund University Hospital have been collected in a database since 1989. The database contains information about clinical variables, and details on surgery, histology and follow-up. For the present study, patients with recurrent pHPT, secondary hyperparathyroidism, ongoing or prior lithium medication, multiple endocrine neoplasia syndrome, familial hyperparathyroidism, familial hypocalciuric hypercalcemia, parathyroid carcinoma and a follow-up time of < 12 months were excluded.

Outcome

Cure was defined as calcium levels below the upper level for normocalcemia (ionized calcium < 1.35 mmol/L or total serum calcium < 2.50 mmol/L) twelve months after surgery, regardless of PTH values.

MGD was defined as a) more than one enlarged parathyroid gland excised at surgery and confirmed by histopathology regardless of cure, or b) when the patient remained hypercalcemic after the excision of a single enlarged parathyroid gland, confirmed by histopathology.

SGD was defined as cured after the excision of one pathological gland.

Biochemistry

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 an assigned value of 1.27 mmol/L. Levels of total serum calcium (reference range 2.20-2.50 mmol/l) were measured by a routine laboratory analyzer.

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

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

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

Urinary calcium was measured after the formation of calcium complexes in two steps, with 5-nitro-5'-methyl-BAPTA (NM-BAPTA) followed by EDTA. The sum of ionized calcium and calcium complexes was 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. No reference range exists for U-Ca, but for tU-Ca the range is 2.5-7.5 mmol/24 hrs.

Plasma PTH, was analyzed by an assay for intact PTH (Hitachi Modular –E), with a reference range of 1.6-6.9pmol/L. The analysis had a total CV of 5.9% at 100 pmol/L. On 20th March 2000, the method was changed to an assay for intact PTH (Hitachi Modular –E), with a reference range 1.6-6.9pmol/L. Due to the change of methods, a correction algorithm was used between the old and new values: new value=1.4 x 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). The CV for 25(OH)D3 is 15% at 50 nmol/l.

The 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. In 65-year-old subjects, the expected GFR is approximately 80 ml/min.

Bone mineral density

Since 1994, bone mineral density (BMD) of the lumbar spine (L2-L4), the femoral neck and shaft, and distal third of the radius has been investigated by dual-energy X-ray absorptiometry (DXA). In this study, measurements were made with Lunar Expert XL equipment, software version 1.72 (Lunar Corp, Madison, Wis). The method has a CV of 1 %. Bmd is expressed in grams per square centimeter (g/cm²) and as age- and gender-specific standard deviations (Z-scores).

Gender and age at the time of operation were noted along with the results of the preoperative localization studies using 99m-Technetium sestamibi scintigraphy. Bone densitometry was carried out preoperatively giving a BMD Z-score for the lumbar spine, femoral neck, and distal 1/3 of the radius. The following biochemical markers were collected preoperatively: calcium, ionized calcium, PTH, phosphate, ALP, osteocalcin, U-calcium, 25(OH)D3, glucose and iohexol clearance. The histopathology of the excised tissue was reviewed and used to classify patients into SGD and MGD.

The results of the scintigraphic studies were encoded as nominal data; positive, negative, or missing.

The BMD Z-score for the distal radius was used.

Missing data

Continuous variables with less than ten percent missing values, except for values of ionized calcium, had missing values replaced with the median [13]. This was done for phosphate, ALP and PTH. For missing values of ionized calcium, a conversion factor (ionized ca/total calcium) was calculated, using values of total calcium, which had no missing data. Osteocalcin, U-Ca, 25(OH)D3, iohexol clearance, and BMD Z-score each had more than ten percent missing values. These variables were categorized into tertiles, with 'missing' as a separate category.

Neck ultrasonography was performed on less than half of the patients and therefore, we opted not to include information on ultrasonography in the study.

Statistical Analysis

All variables were checked for normality, using histograms and box plots. The cohort was analyzed and stratified as SGD or MGD. Medians with interquartile range (IQR) were calculated for continuous data in the two subgroups. Continuous data were compared using the two-sample student's t-test and the Mann-Whitney U test for normal and skewed distributions where appropriate. Pearson's chi-squared test was used to compare categorical data between groups. Univariable 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 scintigraphy (yes or no), diabetes (yes or no), age, ionized calcium, phosphate, ALP, PTH, U-Ca, osteocalcin, iohexolclearance, 25(OH)D3, and BMD z-score for the radius. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A p-value <0.05 was considered statistically significant. All tests were two-tailed. STATA Special Edition version 13.1 was used.

Results

A total of 837 individuals underwent surgery for pHPT at Lund University Hospital during the time period 1989 – 2013. Out of these, 707 patients were included in the present study, 546 women (77 %) and 161 men (23 %). The results revealed that 628 patients had SGD (89 %) and 79 patients had MGD (11 %).

Characteristics for patients with SGD and MGD are shown in table 1. Gender, age, BMD z-score, or biochemical presentation did not differ between patients with MGD and SGD.

Of 85 patients with negative scintigraphy, 15 (18 %) had MGD, compared to 34 of 366 patients (9 %) with positive scintigraphy ($p=0.03$). Patients with MGD were more likely to suffer from diabetes than patients with single gland disease (12 of 79; 15 %) vs. (45 of 628; 7 %; $p<0.01$) and had lower preoperative levels of urinary calcium (median 3.80 mmol/L vs. 4.44 mmol/L; $p=0.04$). Glucose levels did not differ between the groups.

Among the 15 patients with negative sestamibi scintigraphy and MGD, only one suffered from diabetes. Conversely, among 366 patients with positive scintigraphy, 332 had single gland disease. Among those, 311 (94 %) did not suffer from diabetes.

Table 1. 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, μ kat/L median (i.q.r)	1.80 (1.30-3.0)	1.70 (1.20-2.40)	0.17
PTH, pmol/L, median (i.q.r.)	9.90 (7.30-13.0)	10.0 (8.50-15.0)	0.09
U-Ca, mmol/L (26%)* median (i.q.r)	4.44 (2.80-6.60)	3.80 (2.80-5.10)	0.04
Osteocalcin, μ g/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

Logistic regression

Table 2 shows the results of the logistic regression analyses. In univariable analysis, MGD was associated with a negative sestamibi scintigraphy (OR 2.09, 95% CI: 1.08 to 4.05) as well as with osteocalcin, 2nd tertile (OR 3.12, 1.51 to 6.45) and 3rd tertile (OR 1.95, 0.90 to 4.22).

In multivariable logistic regression, diabetes (OR 2.75, 95 % CI 1.31 to 5.80), osteocalcin (2nd tertile OR 3.79, 1.75 to 8.21, 3rd tertile OR 2.36, 95 % CI 1.02-5.48), and negative scintigraphy (OR 2.32, 95% CI 1.40-6.30) were all associated with MGD.

Table 2. 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

Characteristics	Univariate logistic regression		Multivariate logistic regression	
	OR	95% CI	OR	95% CI
Gender				
female	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	0.13-2.59	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				
1 st tertile	1.00			
2 nd tertile	1.30	0.69-2.44	1.26	0.63-2.49
3 rd tertile	0.57	0.27-1.21	0.34	0.10-1.14
Osteocalcin				
1 st tertile	1.00			
2 nd tertile	3.12	1.51-6.45	3.39	1.75-8.21
3 rd tertile	1.95	0.90-4.22	2.11	1.02-5.48
Iohexol clearance				
1 st tertile	1.00			
2 nd tertile	0.67	0.35-1.27	0.65	0.32-1.35
3 rd tertile	0.68	0.36-1.29	0.57	0.21-1.02
25(OH)D₃				
1 st tertile	1.00			
2 nd tertile	0.93	0.51-1.68	0.86	0.45-1.65
3 rd tertile	0.58	0.29-1.14	0.49	0.22-1.04
BMD Z radius				
1 st tertile	1.00			
2 nd tertile	1.13	0.55-2.32	1.04	0.48-2.24
3 rd tertile	1.34	0.66-2.6	1.21	0.56-2.59

Discussion

In this study on 707 patients with sporadic, first-time primary hyperparathyroidism, diabetes was significantly associated with multiglandular disease (MGD), both in univariable and multivariable analysis. We are unaware of any previous report on such an association, but an association between pHPT overall and diabetes type 2 has been described [14, 15]. Also, physical inactivity was recently described as a risk factor for the development of pHPT [16]. The present study cannot answer whether MGD contributes to the development of diabetes, or if diabetes causes MGD. However, the parathyroid glands are closely linked to glucose metabolism. PTH, insulin and osteocalcin interact by modulating insulin secretion, sensitivity and peripheral lipolysis [17-19]. Recent research [20-22] suggests that growth factors, for instance insulin-like growth factor-1 (IGF-1), FGF-23 and vascular endothelial growth factor not only modulate insulin sensitivity but also play a role 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 [21].

Previous studies [23, 24] have suggested that parathyroid adenoma is a predominantly monoclonal lesion, while hyperplasia has been described as an oligo- or polyclonal lesion. It is possible to speculate that the parathyroid glands, due to insulin resistance, the action of insulin-like growth factors or by direct action of glucose levels, are stimulated to grow in a multiglandular fashion.

We also observed MGD in 18 % of patients with negative sestamibi scintigraphy compared to 9 % in patients with positive scintigraphy, which is in line with previous reports [25-32].

We found no difference in the preoperative ionized calcium and intact PTH levels between patients with SGD and MGD. Some groups have reported higher serum calcium and intact PTH levels in patients with SGD compared to MGD [[6, 7, 10], while others could not confirm these findings [33]. In the present study, urinary calcium was significantly lower in patients with MGD, but was not associated with MGD in multivariable logistic regression. Schneider et al. reported a 35 percent incidence of MGD in patients with mild pHPT and low urinary calcium, more than double the rate in patients with overt disease [10]. The patients in our study were defined as having overt disease according to Schneider's criterion, and probably therefore more likely to suffer from SGD.

There is a trend toward earlier surgical intervention in patients with pHPT, leading to fewer symptomatic patients even among patients with single gland disease [34-40]. It remains unclear whether patients with mild disease are diagnosed earlier in

the course of the disease, or if at least some of them belong to a group with a different etiology, caused by MGD.

No single factor, alone or in combination, could reliably predict MGD in patients with pHPT, in the present study, due to overlap. According to the results of the present study, patients with positive scintigraphy and without diabetes, are, however, highly unlikely to be diagnosed with MGD.

Limitations

In the analysis of data, missing data were replaced by medians or treated as a separate category. This might have obscured associations between predictive factors and MGD.

Information on the results of ultrasonography was not included in the analysis since it was performed in less than half of the patients. This being a single – institution study, albeit covering a large time period, the number of patients included in the study could have been too small to evaluate the difference between patients with single gland disease and MGD.

Conclusion

Diabetes and increased levels of osteocalcin were associated with MGD, although negative localization studies remain the most clinically usable predictors.

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