

Primary hyperparathyroidism: nonclassical symptoms and benefits from parathyroidectomy

Encircling the invisible



Anna Koman



**Karolinska
Institutet**

From department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

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Primary hyperparathyroidism: nonclassical symptoms and benefits from parathyroidectomy

av

Anna Koman

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Principal Supervisor:

Inga-Lena Nilsson
Karolinska Institutet
Department of Molecular Medicine and Surgery

Opponent:

Oliver Gimm
Linköpings Universitet
Department of Biomedical Clinical Science

Co-supervisor(s):

Robert Bränström
Karolinska Institutet
Department of Molecular Medicine and Surgery

Examination Board:

Peter Stålberg
Uppsala Universitet
Department of Surgical Science

Ylva Pernow
Karolinska Institutet
Department of Molecular Medicine and Surgery

Lisa Juntti-Berggren
Karolinska Institutet
Department of Molecular Medicine and Surgery

Richard Bränström
Karolinska Institutet
Department of Clinical Neuroscience

Ewa Lundgren
Uppsala Universitet
Department of Surgical Science

Utan tvivel är man inte riktigt klok.

Tage Danielsson

Mission invisible and to end up in research

Sometimes the invisible is obvious, still just as difficult to grasp. To wonder is to take a step into research, to give the invisible contours. The connection between my research studies and my concern for my patients has appeared to me with time, hand in hand with my clinical practice.

This thesis has been created in an era with advanced methods and biochemical benchmarks available. Nevertheless, to understand primary hyperparathyroidism (PHPT) with non-classical symptoms requires a different form of navigation. PHPT is a common disease, sometimes associated with symptoms that significantly impair the conditions for preserving a good physical and mental health. Depression, muscle pain, fatigue and impaired memory are sometimes the only symptoms of the disease but are also common features of other medical conditions. Not all patients are helped by curative surgery – parathyroidectomy. However, many patients with nonclassical symptoms that are related to the disease itself experience relief and find that their lost spark for life returns. The dilemma remains, to then ascertain as to which individuals will benefit from a parathyroidectomy?

Nonclassical symptoms are rarely detectable using conventional examination methods and, in the decision-making process, the patient risks ending up “in limbo” with treatment being withheld. The surgeon is left to interpret the patient's story and a battery of slightly deranged blood samples. Risk (costs) and benefit must be taken into consideration. The outcome - surgery or not surgery – is often arbitrary and depends upon the decision maker's (surgeon's) experience.

The rule of thumb -"sometimes cure, not hurt, always comfort and never harm" - has guided physicians for more than two millennia. However, all endocrine surgeons have at times experienced little guidance when dealing with mild PHPT and nonclassical symptoms. To diagnose and surgically take on a sick parathyroid gland can be anything between heaven and hell, from very simple and to extremely challenging.

The overall aim of this thesis has been to explore the nature of non-specific symptoms related to PHPT and to sharpen the tools in order to promote a correct and fair treatment of each patient concerned.

Anna Koman

OVERVIEW OF THE THESIS

Paper	Aim	Objectives	Methods	Results
I	To explore the use of short-term calcimimetic treatment as a diagnostic tool in primary hyperparathyroidism (PHPT) to predict the outcome of nonclassical symptoms after parathyroidectomy (PTX).	To analyze the accuracy of normalization of hypercalcemia by medication to predict effects after PTX on cognitive function, muscle strength and Quality of Life (QoL).	Observational intervention study. A panel of tests during calcimimetic treatment was compared with the postoperative results.	Improvements in cognition, mental health and muscle strength during study medication correlated well with the long-term outcome after PTX (Positive Predictive Values [PPV] 74-96%).
II	To analyze the feasibility and accuracy of calcimimetic treatment as a diagnostic tool used specifically for patients age ≥ 50 years with cognitive decline.	To analyze the accuracy of diagnostic short-term medication to predict effects on cognitive function, muscle strength and QoL in patients without obligate indications for PTX.	Sub-analysis including 35 (19) patients age ≥ 50 (≥ 70) years identified from Study I with mild cognitive dysfunction (MoCA < 26).	Predictive values for improvement were high (PPV 80- 94%). The method was inferior for excluding potential effects (NPV 22-92 %). 17 patients (10 age ≥ 70 years) achieved normal cognitive scores (MoCA ≥ 26) postoperatively.
III	To investigate any impact of PHPT on neuropsychiatric morbidity and the effects of curative treatment in a population perspective.	To analyze neuropsychiatric comorbidity in PHPT and explore the utilization of psychotropic drugs, before and after PTX in comparison to the general population.	A registry-based population study analyzing drug use in 8279 patients subjected to PTX during 2008-2017 compared with a matched (1:10) population.	The use of drugs for treating mental depression, anxiety and sleep was more widespread in patients 3 years before PTX (benzodiazepines OR: 1.40 and SSRI ;OR: 1.38). A decreasing trend was found but the utilization remained elevated up to 3 years after PTX.
IV	To investigate possible impact of untreated PHPT on dental health in comparison to the general population.	To analyze the annual incidence rate ratios of dental care consumption in untreated PHPT in comparison to the general population.	A population study. Dental intervention in patients subjected to PTX (n=982) were compared to a population cohort (n=2944).	Patients belonging to the highest quartile (ionized calcium level ≥ 1.51 mmol/L) had an 85% increased risk for tooth extraction. Female gender independently amplified the risk.

POPULAR SCIENCE SUMMARY OF THE THESIS

Primary hyperparathyroidism (PHPT) is characterized by blood analysis featuring relatively elevated concentrations of calcium and parathyroid hormone. PHPT is usually caused by an enlarged parathyroid gland (*parathyroid adenoma*) that produce an excess of parathyroid hormone thus causing a disturbed calcium balance. The disease is often discovered by chance in connection with investigation of other disorders or during a standard health check-up. Around 1% of the population is affected.

The parathyroid glands are normally four in number, each a few millimeters in size and are usually located deep within the neck on back of the thyroid gland. The only curative treatment for PHPT is to surgically remove the diseased gland (s); a so-called *parathyroidectomy*.

Classically, PHPT may cause complications such as osteoporosis and kidney stones. Furthermore, PHPT is sometimes associated with a wide range of *nonclassical symptoms*; such as fatigue, depression, concentration difficulties, impaired memory, muscle weakness and diffuse pain.

Surgical treatment is recommended in all patients younger than 50 years of age or when complications (such as osteoporosis, kidney stones or kidney failure) have occurred and in cases of very high calcium levels. However, most commonly PHPT patients are older than 50 years of age, lack classical symptoms and are often classified as asymptomatic. The majority are therefore not obvious candidates for surgery. Nevertheless, nonclassical symptoms are sometimes substantial and yet difficult to distinguish from symptoms related to other diseases or normal aging and can easily be overlooked. Previous studies have shown that recovery from nonclassical symptoms after surgery often occurs. Yet the dilemma remains; to individually predict who will or will not benefit from an operation.

The aim of this thesis was to explore the nature of nonclassical symptoms related to PHPT and to map out the consequences of the disease and the potential benefits of parathyroidectomy.

Study I describes a method for predicting the effects on nonclassical *symptoms* after surgical treatment. Various tests used to assess muscle strength, mental status, cognition and Quality-of-Life (QoL) were performed by 110 patients before and during four weeks of treatment using a drug that reduces the calcium concentration in blood to normal levels. The results were then compared with the results six weeks and six months after the parathyroidectomy.

The study showed that improvements in muscle strength and mental status corresponded well with improvements following curative surgery. The sensitivity was worse to rule out the potential for cognitive improvement.

Study II is a deep analysis of Study I, aiming to evaluate the model when used in elderly patients with cognitive decline. 35 patients aged ≥ 50 years with mild cognitive impairment were included. Fifty percent of the patients achieved normal cognitive scores six months after surgery. Improvements during medication correlated well with the outcome after surgical treatment but the precision was worse with regards to ruling out any potential for improvement. The study medication was well tolerated and the diagnostic test model in Studies I and II was found feasible when used as a tool to aid in the decision as to whether to perform parathyroidectomy or not.

Study III is a population study aiming to investigate the use of medications for treating psychiatric conditions and dementia in patients with PHPT. The drug consumption for a period of three years *before* and three years *after* surgery in 8279 patients was compared with 82,790 matched individuals from the general population. The study revealed that the use of antidepressant and tranquilizing drugs was more extensive in patients with untreated PHPT than in the general population while treatment for dementia was less common. New introduction of drugs for treating depression and anxiety decreased after surgery. However, the consumption of antidepressant drugs remained higher in the PHPT patients, also after surgery. The study results suggest that the existence of psychiatric symptoms should be taken into consideration in patients with PHPT and highlights the importance to re-evaluate the need for psychiatric drug treatment even following curative surgical treatment.

Study IV. The impact of untreated PHPT on dental health in the population has so far been unexplored. Study IV is a registry-based analysis of 982 patients with untreated PHPT compared to 2944 individuals from the general population. This study showed that the overall consumption of dental health care in the patients was equal to the control population. However, patients with the highest calcium levels had increased risk of tooth loss by extraction. Furthermore, the frequency of tooth extractions among female patients was higher than in men independent of calcium levels. This study sheds light on possible detrimental effect of PHPT on dental health and the need for more knowledge in this field.

ABSTRACT

Primary hyperparathyroidism (PHPT) is characterized by an inadequate increase in calcium and parathyroid hormone levels in blood. The cause is usually a benign tumor, parathyroid adenoma, and the only curative treatment is parathyroidectomy (PTX). PHPT is sometimes associated with a spectrum of neuropsychiatric and musculoskeletal so called *nonclassical symptoms*. The aim of this thesis was to explore the impact of nonclassical symptoms and to validate the benefits of PTX with a focus on PHPT patients without obligate indication for surgical treatment. **Paper I.** Observational study including 110 patients (median age 62 years; 82.7% [n=91] females) aiming to evaluate a method for predicting the outcome of nonclassical symptoms after PTX. Intervention: Calcimimetic treatment, four weeks, 30-60 mg daily. Outcome Measures: A panel of tests assembled to assess psychiatric status, cognitive function and muscle strength performed: at baseline, during study medication, six weeks and six months after PTX. Study medication resulted in normocalcemia and improvements of nonclassical symptoms that correlated well with the postoperative outcome (positive predictive values (PPV)74-96%). The positive effects increased over time. **Paper II.** A sub-analysis of 35 patients with cognitive decline defined in Study I. Seventeen patients achieved normal cognitive scores six months postoperatively. PPV ranged from 80 to 94%. NPV varied between 22-92%. Short-term calcimimetic treatment was found feasible to predict improvements of nonclassical symptoms after PTX. **Paper III.** A retrospective case-control study and a prospective cohort study aiming to map out psychiatric comorbidity as reflected by dispensing of symptomatic medication. Data from national registries in 8279 cases of PTX between the years 2008-2017 and a population cohort matched (1:10) were analyzed. The results revealed a more comprehensive drug dispensing within 3 years before PTX (benzodiazepines OR:1.40 and selective serotonin reuptake inhibitors (SSRI) OR:1.38) with a decreasing trend postoperatively but still remained higher than in the control cohort also after PTX. This study implies that psychiatric comorbidity should be considered in PHPT patients and continued medication for mental symptoms should be reevaluated after PTX. **Paper IV.** A case-control study of dental comorbidities in patients treated with PTX 2011-2016 (n=982) compared to a population cohort (n=2944). The number of interventions were similar in the cohorts but PHPT patients with calcium levels in the upper quartile (≥ 1.51 mmol/L) had an increased risk for tooth loss by extraction (IRR 1.85; 95% CI 1.39-2.46). Female gender was an independent risk factor for tooth loss by extraction (IRR 1.34). Paper IV draws special attention to PHPT patients with high calcium levels and poor dental health. Further research is needed in this field.

LIST OF SCIENTIFIC PAPERS

- I. Koman A, Ohlsson S, Bränstrom R, Pernow Y, Bränstrom R & Nilsson IL.
Short-term medical treatment of hypercalcaemia in primary hyperparathyroidism predicts symptomatic response after parathyroidectomy.
British Journal of Surgery 2019.

- II. Koman A, Bränstrom R, Pernow Y, Bränstrom R & Nilsson IL.
Prediction of cognitive response to surgery in elderly patients with primary hyperparathyroidism
British Journal of Surgery Open 2020.

- III. Koman A, Bränstrom R, Pernow Y, Bränstrom R, Nilsson IL & Fredrik Granath.
Neuropsychiatric comorbidity in primary hyperparathyroidism before and after parathyroidectomy – a population study
Submitted manuscript.

- IV. Koman A, Näsman P, Discacciati A, Ekbohm A, Nilsson IL, Sandborgh-Englund G.
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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
AUC	Area Under Curve
BMD	Bone Mineral Density
CaSR	Calcium Sensing Receptor
CDC73	Cell Division Cycle 73
CYP3A4	Cytochrome P450 3A4 enzyme
DHR	The Swedish Dental Health Register
DRN	Dorsal Raphe Nucleus
FGF23	Fibroblast growth factor 23 protein
FHH	Familial Hypocalciuric Hypercalcemia
HbA1c	Glycated hemoglobine
HPT-JT	Hyperparathyroidism Jaw Tumor syndrome
5-HT	5-Hydroxytryptamine receptor (serotonin receptor)
GRF	Glomerular Filtration Rate
HADS	Hospital Anxiety and Depression Scale
IRR	Incidence Rate Ratio
LISA	Statistics Sweden's Longitudinal integrated database for health insurance and labor market studies
MDRD	Modification of Diet in Renal Disease
MEN1	Multiple Endocrine Neoplasia 1
MoCA	Montreal Cognitive Assessment
mRNA	Messenger Ribonucleic Acid
NA-LC	Noradrenaline-containing Locus Coeruleus
NPR	The National Patient Register
NYH	New York Heart Association
OR	Odds Ratio
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PHPT	Primary hyperparathyroidism
PSOM	Positive States of Mind

PTH	Parathyroid hormone
PTX	Parathyroidectomy
QLQ C-30	Quality-of-Life Questionnaire Core 30
QoL	Quality of Life
r (rho)	Correlation coefficient
ROC	Receiver Operating Characteristics
RTB	The Population Register
SCB	Statistics Sweden (SCB)
SF-36	36-Item Short Form Health Survey
SPECT-CT	Single photon emission computed tomography
SQRTPA	Scandinavian Quality Register of Thyroid, Parathyroid and Adrenal surgery
^{99m} Tc	^{99m} Technetium
TSH	Thyroid stimulating hormone
TST	Timed-Stands Test
VDR	Vitamin D receptor

1 INTRODUCTION

1.1 THE HISTORY OF PRIMARY HYPERPARATHYROIDISM

The parathyroid glands was first described in the mid-19th century by the anatomist and zoologist Sir Richard Owen. During the dissection of a rhinoceros who died after a fight with an elephant at *The Zoological Society* in London, Sir Owen noted some structures on the neck that differed from other previously known tissue. Since then, the rhinoceros has been the symbol of endocrine surgery. In a human, the parathyroid glands were not recognized as organs until the late nineteenth century. By this time, surgeons and pathologists in Europe had described structures of a few millimeters in size situated near the thyroid gland without any speculation as to any physiological significance.

The discovery of the parathyroid glands is usually attributed to the twenty-five year old Swedish medical student Ivar Sandström who practiced as an assistant teacher at the Department of Anatomy in Uppsala during his studies. His work involved dissection of both humans and animals. After his first discovery on a dog, in 1877, he established that the parathyroid glands were found close to the thyroid gland in both humans and most animals. By means of systematic anatomic and histologic examination, he stated that the glands consisted of a cellular structure that differed from the thyroid gland and thus constituted unique and separate organs. Based on their location, they were named *glandulae parathyroideae* (1).

The journey towards understanding the function of the parathyroid glands involved many of history's most prominent physicians, surgeons and pathologists. Decades of theories and trials would be carried out until the physiology of the parathyroid glands and its significance was understood.

Ideas as to their purpose raised from two main paths over a period of 50 years. The first path was through years of tragic experiences following the severe complications of tetanus after goiter surgery. These, often fatal, were later understood to be caused by hypocalcemia due to iatrogenic *hypoparathyroidism*. The second path was by means of the condition *hyperparathyroidism*. Freidrich Daniel von Recklinghausen suspected that the parathyroid glands could be the culprit in 1891 following a series of simultaneous autopsy findings of severe cystic skeletal deformities and brown tumors in bone alongside enlarged parathyroid

glands (later named *parathyroid adenoma*), suggesting that the conditions were directly related.

At the beginning of the twentieth century a series of fairly obscure trials were carried out. By this time, Jacob Erdheim (1874-1937) was however on the right track by noticing that removal of all parathyroid glands in rats caused seizures, while injection of parathyroid extract interrupted the normal development and growth of the rat's teeth. The link between the parathyroid glands and calcium and the connection between enlarged parathyroid glands, bone disease and tetani was finally clarified.

However, it was not until 1915, when Friedrich Schlagenhauer (1866-1930) stated that the bone disease described by von Recklinghausen was caused by a parathyroid tumor (*parathyroid adenoma*), and that surgical removal (*parathyroidectomy*) of the adenoma was the appropriate treatment for *osteitis fibrosa cystica*. In 1925, the first successful parathyroidectomy was performed on a World War I soldier by Felix Mandl (1892-1957) in Vienna. This particular soldier had been discharged from the Austrian army after he developed severe bone deformations and progressive generalized weakness. The message about the soldier's miraculous recovery following the removal of the tumor spread and the procedure gained ground on the other side of the Atlantic. Primary hyperparathyroidism (PHPT) became known as a severe disease with pronounced skeletal deformities, brown tumors in the jawbone, stone disease and calcification of internal organs and with pronounced lethargy. Parathyroid surgery became an accepted procedure and yet was occasionally carried out on relatively inconclusive grounds. However, the mystery of the underlying mechanisms still remained to be ascertained (2).

Medical breakthroughs during the first decades of the 20th century laid the foundation for understanding of the parathyroid function. In 1808, Humphry Davy of *The Royal Institution of Great Britain*, and Sidney Ringer (1835-1910, London) isolated calcium by means of electrolysis, and concluded among other things, that calcium played a central role in human physiology. The parathyroid hormone itself remained undetected for a long time.

Experiments with parathyroid extracts gave results but were difficult to interpret and it was not until 1952 that the parathyroid hormone consisting of 84 amino acids was isolated. Ten years later, following the invention of the radioimmunoassay technique (3), a method for measuring the parathyroid hormone in the blood at last became available.

From that point on, biochemical analyzes have become easily available and relatively cheap. Imaging techniques such as ultrasound, computerized tomography and functional imaging (^{99m}Tc -MIBI scintigraphy/SPECT/CT and PET/CT) have enabled less invasive surgical techniques to evolve. However, the only curative treatment for PHPT is still parathyroidectomy and still the anatomic knowledge established by Ivar Sandström, is crucial for a successful outcome after parathyroidectomy.

1.2 EPIDEMIOLOGY AND CLINICAL PRESENTATION

Today PHPT is recognized as an endemic disease and constitutes the third most common endocrine disease after diabetes mellitus and thyroid disorders. PHPT is three times as prevalent in women than in men and the incidence increases with age. The overall prevalence is estimated to be about 1% (4, 5). In a population-based longitudinal study carried out in 2008 by Siilin et al that included 1900 females screened for serum (s)-calcium in connection with routine mammography, the prevalence was estimated to be as high as 5.1% in females between 40-50 years of age (6).

The incidence in the general population has continuously increased over the past decades, mainly due to both a raised awareness of the diagnosis itself and to the increasingly available and inexpensive blood analysis. The disease is often discovered *en passant* during the examination of unrelated conditions or in standard health check-ups. The analysis of serum calcium is obligate in the investigation of osteoporosis and nowadays is usually included in investigations of psychiatric disorders and cognitive impairment(7, 8).

The existence of a solitary parathyroid adenoma constitutes the cause of PHPT about 80% of cases, hyperplasia accounts for 10–15% and multiple adenomas for 5% whereas parathyroid cancer is rare, <1% of cases. The basic preoperative evaluation of PHPT should include analysis of serum phosphate and serum creatinine, 25-hydroxyvitamin D and 24h urine calcium in order to rule out secondary hyperparathyroidism or familial hypocalciuric hypercalcemia (FHH) (9, 10).

Most commonly, PHPT appears in sporadic form (90%). About 10 % are hereditary of which some mechanisms have been clarified; for example, mutations of *MEN1* (11q13) and *CDC73*, (1q31.2; hyperparathyroidism-jaw tumor syndrome, HPT-JT) and the calcium receptor gene *CASR* (3q21.1, familial hypocalciuric hypercalcemia, FHH) have been identified (11).

Radiation therapy early in life and lithium treatment have been detected as risk factors for the development of PHPT over time (12).

In Stockholm region, the surgical treatment of PHPT is centralized at the *Karolinska University Hospital* where more than 250 parathyroidectomies are performed annually. The cure rate following surgery varies between 95 and 97%. The complication rate is low even in patients with fairly extensive comorbidities and parathyroidectomy can be safely performed on patients of advanced age.

Nowadays, the symptoms are rarely dramatic although PHPT can still lead to an abnormal bone metabolism, “brown tumors” of the jaw and calcification in parenchymal organs or collapse due to severe hypercalcemia (12). The impact of untreated mild PHPT on oral health has hardly been studied and is largely unexplored area. Results from small studies and case reports have demonstrated typical periodontal lesions in patients with PHPT thus indicating a direct connection (13).

Mild disease without complications is commonly considered to be asymptomatic and does not require active mandatory treatment (14-16). Although, complaints of cognitive impairment, psychiatric and musculoskeletal symptoms are relatively common, but yet not specific for the disease and can consequently be difficult at times to distinguish from symptoms related to other conditions or even to the natural aging process.

1.3 GUIDELINES FOR TREATMENT

The indications for parathyroidectomy in symptomatic patients are fairly clear. **Figure 1.** The fulfillment of one or more of the criteria should raise the question of the need for surgical treatment. Patients with solely nonclassical symptoms are not obligate candidates for surgery and may instead be more suitably followed by biochemical observation. An optimal follow-up time so as to avoid complications has been debated and has still not been conclusively decided upon.

Figure 1. Indications for parathyroidectomy.

- Calcium in blood >0.25 mmol/L (>1 mg/dL) above upper limit of normal
- Bone mineral density (BMD) < -2.5 standard deviations compared to young healthy individuals (osteoporosis)
- Vertebral fracture on radiological examination
- Creatinine clearance <60 ml/min
- 24-h urine Ca > 10 mmol/d
- Nephrolithiasis or nephrocalcinosis (X-ray, CT or ultrasound)
- Age <50 years

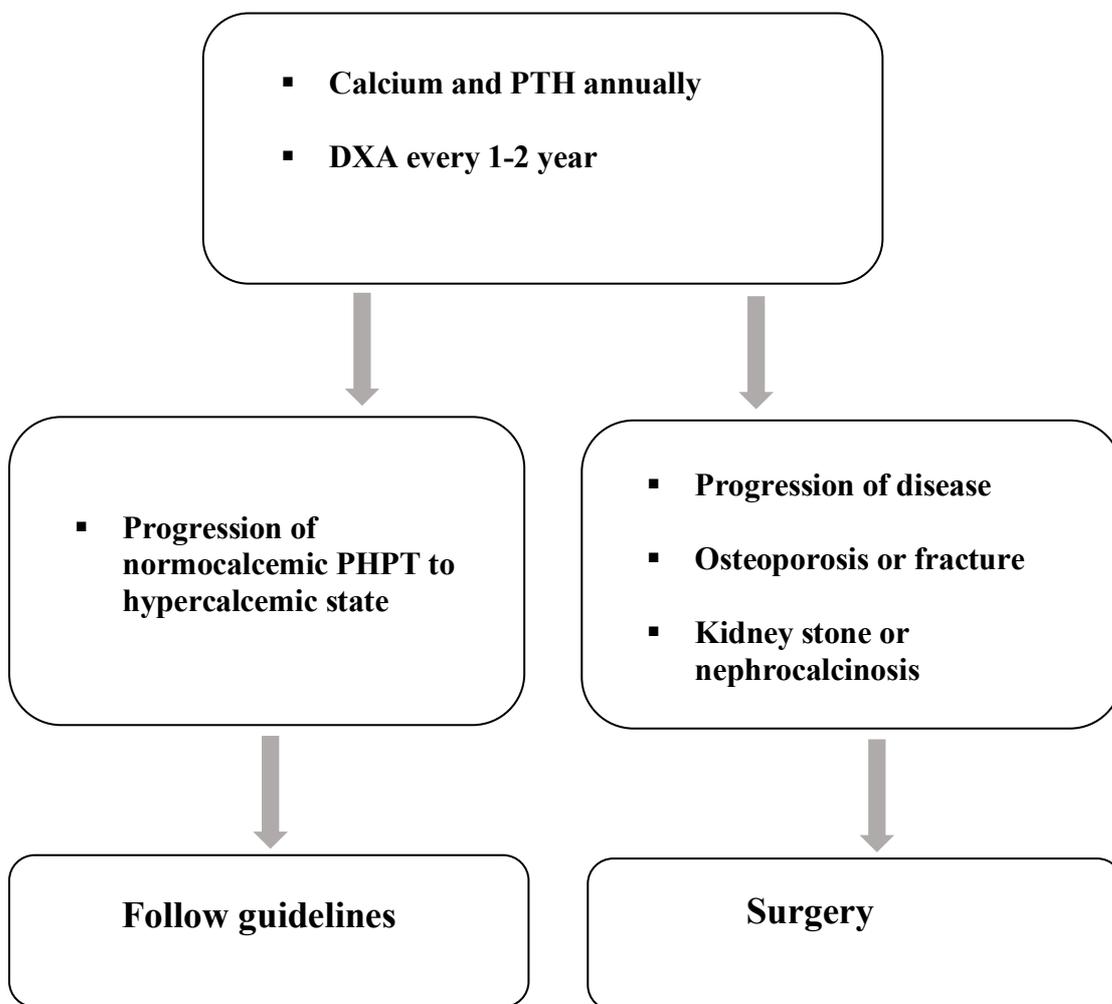
In Florence, Italy in 2013, an international expertise gathered in the three-day *Fourth international workshop* aiming to extract the latest scientific updates in order to convey more clear *Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism*.

Explicit recommendations with regards to the monitoring of untreated disease included a more extensive imaging and biochemical investigation at base-line and by regular follow-up.

Figure 2. Areas recommended for investigation included non-traditional aspects of PHPT and the natural history and pathophysiology in normocalcemic hyperparathyroidism.

Prospective studies, randomized trials and controlled cohort studies of neurocognitive and vascular function before and after parathyroidectomy were called for in order to be able to determine predictive indices (5, 17). Guidelines regarding treatment and indications for surgery are being continuously revised (18).

Figure 2. Guidelines for untreated primary hyperparathyroidism.



1.4 THE SURGICAL PROCEDURE AND LOCALIZATION

Parathyroidectomy is typically performed through a midline transversal incision on the neck. The strap muscles are separated in order to reach the thyroid lobe which is then retracted anterolaterally to expose the prevertebral area and enable the visualization of the parathyroid glands. Classically, all four parathyroid glands were explored and visually assessed before the excision of the affected adenoma/adenomas. Today, as the preoperative imaging techniques have advanced, a focused approach with a small incision and a local dissection is the dominating practice (70% registered in the Scandinavian Quality Register of Thyroid, Parathyroid and Adrenal surgery, SQRTPA) (19-21).

Most humans have four parathyroid glands of a few millimeters each. The number and location may vary which can constitute a surgical challenge. The parathyroid adenoma is usually larger than the normal parathyroid gland and darker related to a lower fat content. The size of the adenoma usually correlates well with biochemical severity (22).

The understanding of parathyroid anatomy and embryology is of great importance in performing parathyroid surgery. The parathyroid glands start developing and migrating caudally within the fifth and sixth week of gestation. The superior parathyroid glands start derive from the fourth brachial pouch along with the thyroid while the inferior glands develop and migrate from the third brachial pouch along with thymus. The superior glands are commonly found posterior of the upper part of the thyroid lobe or close to the crossing of the recurrent laryngeal nerve (RLN) and the inferior thyroid artery (ITA), The inferior glands are usually located along the posterior surface of the inferior part of the thyroid lobe or occasionally in the tip of the thymus, but can also due to the longer distance of migration be located anywhere laterally between the jaw and into the mediastinum (23).

Normally the operation is preceded by ultrasound (**Figure 3**) and/or imaging combining nuclear medicine and computed tomography e.g. Single Photon Emission Computed Tomography (SPECT) using the tracer ^{99m}Tc-sestamibi (**Figure 4**) in order to localize the adenoma and guide in decision of the surgical approach. All preoperative imaging is for guidance in surgery only and should not be used for diagnostic purposes.

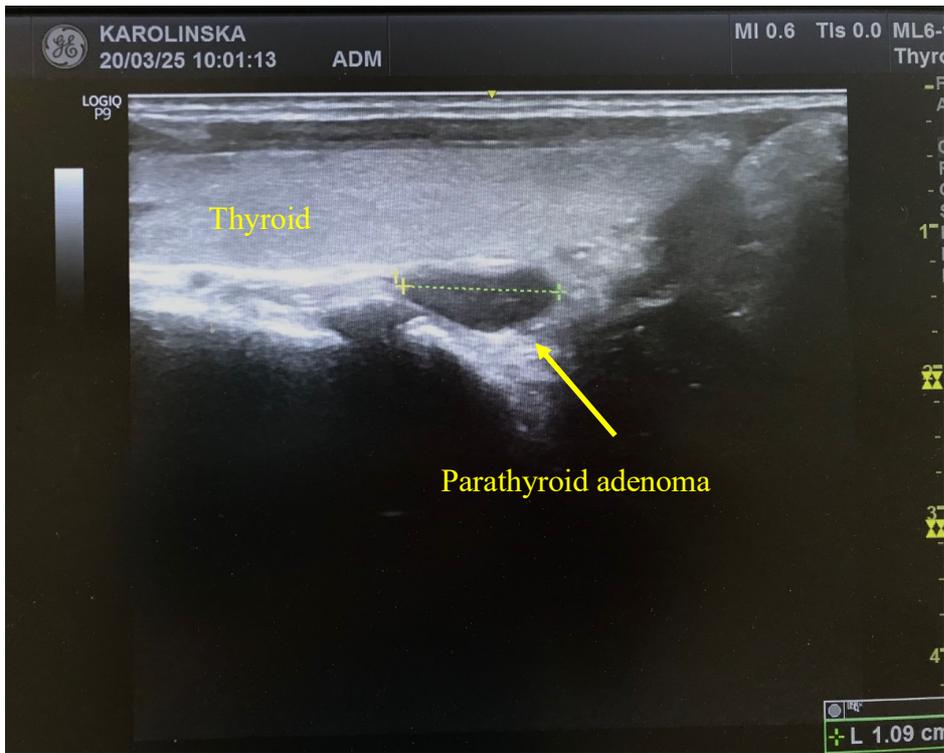


Figure 3. *Ultrasound imaging of the inferior parathyroid adenoma.*



Figure 4. *SPECT CT-scan of a parathyroid adenoma (inferior right side).*

On suspicion of multiglandular disease (about 15 % of PHPT), an exploration of both sides of the neck should be performed. If the surgeon expects the operation to be complicated (e.g. reoperation, multiglandular disease, inconclusive imaging), intraoperative parathyroid hormone measurement can be a useful tool to confirm that the proper gland(s) was removed. Approximately 50 % drop of plasma-PTH levels within ten minutes after excision confirms an adequate removal of tissue (24, 25). A remaining elevated PTH is an indication of either multiglandular disease or that the removed tissue did not correspond to the pathologic adenoma.

1.5 PHYSIOLOGY OF THE PARATHYROID GLANDS AND PRIMARY HYPERPARATHYROIDISM

Parathyroid hormone secretion is normally tightly regulated by a complex endocrine signal transduction involving the calcium-sensing receptors (CaSR) at the surface of the parathyroid cells, vitamin D and fibroblast growth factor 23 (FGF23). In the process of calcium

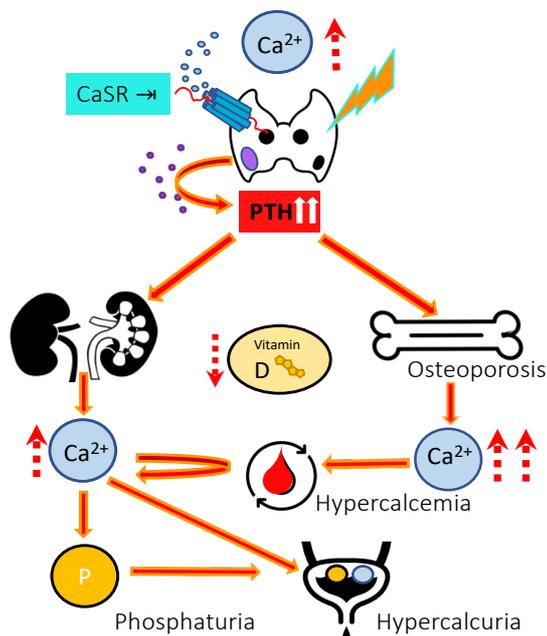


Figure 5. Redistribution of the calcium deposits initiated by the CaSR in PHPT

metabolism, parathyroid hormone acts to increase the concentration of circulating calcium ions (Ca^{2+}) by means of three major pathways; by renal tubular reabsorption of calcium, by adjusting the release of Ca^{2+} from the bone mineral component and by conversion of vitamin D to its active form thus increasing the intestinal uptake of Ca^{2+} . An increased Ca^{2+} concentration in serum in healthy individuals will induce a nearly instantaneous decrease in parathyroid hormone excretion and vice versa in the case of reduced Ca^{2+} concentration thus maintaining optimal calcium homeostasis (26).

PTH exerts both anabolic and catabolic effects on bone tissue by means of a balanced activation of osteoblasts and osteoclasts, stimulating continuous physiological regeneration of degraded bone tissue. PHPT leads to a redistribution of the body's calcium deposits which

can eventually cause complications such as osteoporosis, renal stones and a wide spectrum of unspecific symptoms. **Figure 5.** A recovered means of skeletal regeneration following surgical cure enables the renewal of the bone tissue and a reduced risk for nephrolithiasis and calcification of parenchymal organs.

There are indications that an increased risk of fracture lasts for up to one year after parathyroidectomy, which then decreases to levels equivalent to healthy controls (27). However, results from observational studies and conclusions drawn through meta-analysis of existing literature regarding the effects on bone density have varied (27-29).

1.6 THE CALCIUM SENSING RECEPTOR (CASR) AND SIGNALING TRANSDUCTION PATHWAY

Parathyroid hormone consist of 84 amino acids, is produced by so-called chief cells in the parathyroid glands and constitutes the most important regulator of S-Ca²⁺ (30). The mRNA transcription of parathyroid hormone is negatively regulated by an increase of extracellular calcium ions which binds to the type II G-coupled protein calcium sensing receptor (CaSR) which inhibit the release of parathyroid hormone (31). The CaSR is abundant in the chief

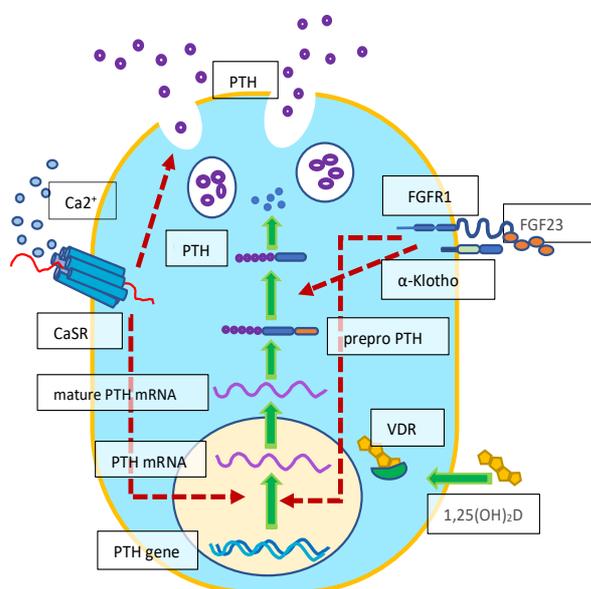


Figure 6. Intracellular calcium signal transduction within the chief cell.

cells of the parathyroid glands and the cells lining the renal tubules. The CaSR also is expressed in cells of other organ systems including the cardiovascular, nervous and the respiratory system and have been found even in the dental pulp cells where it may be involved in physiological functions that are not yet fully understood (32-34). **Figure 6.**

PHPT was found to be associated to an elevated set-point for Ca²⁺-mediated parathyroid hormone release and a reduced expression of CaSR. In a study including thirty-six patients with sporadic PHPT, the *in vivo* set-point of calcium

Ca²⁺-regulated PTH release was analyzed and investigated in relation to various clinical measures and to the expression of the CaSR of the parathyroid adenomas. The individual set-

point was found to be significantly correlated to preoperative Ca^{2+} levels and to the adenoma volume itself. The set-point was inversely associated to the intensity of immunostaining of the CaSR thus suggesting that a reduced CaSR content in the parathyroid chief cell might play an important role in the pathogenesis of PHPT (35).

The CaSR is widely expressed throughout the nervous system; in nerve terminals, myelin-producing oligodendrocytes, astrocytes and microglial cells to name but a few. Based on an in vitro mice model it has been proposed that the CaSR plays a significant role in the embryologic neuronal migration and development of the hippocampus and cerebellum (36). Furthermore, it has been suggested that the CaSR modifies the neuronal excitability within the hippocampus by regulation of the sodium leak from potassium (K^+) channels (37). A dysfunctional CaSR has been implicated in cognitive disorders such as Alzheimer's disease, ischemic brain injury and epilepsy. In a cohort study including 692 patients and 435 controls, a significant association of polymorphic dinucleotide repetitions within the CaSR gene and the occurrence of Alzheimer's disease was found (OR 1.62; 95% CI: 1.27–2.07). The susceptibility to Alzheimer's disease induced by the CaSR was suggested as a consequence of both systemic and local calcium dysregulation within the nervous system itself by initiating transduction cascades promoting Alzheimer's disease pathogenesis (38).

1.7 THE CALCIUM HOMEOSTASIS

Calcium hemostasis is crucial for adequate neuropsychiatric functioning, yet the mechanisms behind PHPT are dynamic, multifactorial and complicated to pinpoint. It has not been possible to demonstrate any general correlation between calcium levels or parathyroid hormone per se and the extent of non-specific symptoms.

PHPT is three times more common in women thus suggesting that female sex hormones might be involved in the pathophysiology. Substitution with estrogen and medroxyprogesterone in postmenopausal women has been shown to increase bone density and reduce calcium levels but not parathyroid hormone levels (39, 40). However, epidemiologic studies have shown associations with an increased risk of malignancies in patients with PHPT, such as breast cancer where tumoral growth might even be enhanced by hormonal therapy implicating that caution should be applied (41).

1,25-dihydroxyvitamin D enters through the intracellular vitamin D receptor (VDR) and acts by inhibiting the expression of parathyroid hormone mRNA. Vitamin D might be a target of

significance although conflicting results concerning the general impact on the neuropsychiatric aspects have been presented in literature (42, 43). However, vitamin D should always be prescribed in vitamin D deficiency-induced secondary hyperparathyroidism. Patients with PHPT frequently exhibit vitamin D deficiency driven by the disease itself. Preoperative vitamin D substitution has been debated, however, observational studies have shown that it rarely carries any risk of exacerbation of hypercalcemia (26, 40).

Fibroblast growth factor (FGF-23) acts by inhibiting the transcription of parathyroid hormone mRNA. The concentration of FGF-23 has been found to be reversibly increased in PHPT and is suggested to comprise a risk factor for metabolic disease yet the relevance for developing neuropsychiatric symptoms is unknown (44). A recent mouse model study revealed that mice deficient in either the ligand FGF-23 or the co-receptor Klotho, displayed effects on the hippocampus that induced a cognitive impairment indicating that FGF-23 may also primarily be involved in the pathophysiology of the brain (45).

Biochemical mechanisms in PHPT affecting the central and the peripheral neural system are indeed complex. There is a certain amount of evidence that CaSR is one of the key factors in PHPT featuring neuropsychiatric symptoms, although the mechanisms involved have not yet been fully identified. Other but not yet discovered pathways are likely to be involved and remain to be further investigated and mapped out.

2 ASSESSMENT OF NONCLASSICAL SYMPTOMS

2.1 NONCLASSICAL SYMPTOMS - A TANGLED NETWORK

Patients without classic symptoms (e.g. renal stones and osteoporosis) and signs of PHPT are often regarded and classified as asymptomatic. The majority of these patients are not obvious candidates for surgery according to current guidelines and may instead become subject to long-term biochemical follow-up until eventual complications occur. It has not been previously possible to predict, on an individual basis, as to who will experience the benefits of a parathyroidectomy and who will not (46).

Nonclassical symptoms of PHPT, namely depression, mental and muscular fatigue, mild cognitive impairment and oral health are indeed interrelated and constitutes a tangled network of conditions that affects and reinforce each other. The number of publications featuring connections between mental illness, cognition and physical activity is large and exceeds the scope of this thesis. A few relevant relationships will be mentioned and discussed.

Inevitably, we all begin to age soon after we have reached adulthood. The nervous system is not the exception, which does not mean that the intellect as a whole necessarily deteriorates, at the same time experiences, strategies and knowledge are built up over time (47). The incidence of PHPT increases with age, in our material the median age of the patients was just over 60 years. With increasing age, the homeostatic reserve decreases and the nervous system becomes more vulnerable to endogenous and/or exogenous stressors (48). Polypharmacy is common among older and more frail persons leading to an increased risk for side effects and drug interactions (48). However, it is today well established that development of cognitive decline in relation to age is multifactorial (49). Genetic inheritance, environmental and life-style factors as well as previously built-up reserves in form of education and social networks all play a role for our mental health later in life (50).

Most reports state that the majority of elderly PHPT patients experience positive general symptomatic effects on over-all quality of life (QoL) and cognitive function after biochemical cure by means of parathyroidectomy. The surgical procedure has, furthermore, been shown to be safe in old age (51-55).

Though the occurrence of nonclassical symptoms related to PHPT is today uncontroversial, the underlying pathophysiology is still unclear. It still remains difficult to distinguish mental symptoms and cognitive decline related to natural aging from the potentially reversible symptoms of PHPT (51, 53, 56-58). Recent studies have revealed that elderly patients with

increasing age are less frequently referred for parathyroidectomy, suggesting that surgical treatment is underused (52). Sufficient prospective studies of neuropsychiatric function before and after parathyroidectomy are requested to determine predictive indices (4).

2.2 ORAL MANIFESTATIONS OF PRIMARY HYPERPARATHYROIDISM

The balanced bone turnover in PHPT is disturbed leading to a catabolic state and a reduced bone mineral density of both trabecular and cortical bone (26). General osteopenia is a relatively common sign, also in biochemically milder PHPT (17). Historically, PHPT was associated with severe bone disease with osteolytic lesions located anywhere in the body, in advanced stages sometimes presented as expansile granulation tissue masses, brown in color due to hemosiderin deposition, so called brown tumors (46).

The presence of brown tumor of the jaw associated with PHPT are today rare and should raise suspicion for a genetic disorder (hyperparathyroidism- jaw tumor syndrome) caused by a mutation in the *CDC73 gene* (11, 59).

Quality studies of the impact on dental health in untreated PHPT in milder disease are few and the field is sparsely studied. A number of publications, mostly case reports, were recently summarized in a review paper including 205 articles and a total of 245 patients written between 1975 and 2016 (60). A variety of oral signs and symptoms were outlined with the most common findings being associated with expansile bone lesions and the second most common symptom being oral pain. In a cross-sectional case-control study, Padbury and co-authors found a significant difference in subtle periodontal pathological processes measured by reduced radicular lamina dura, interdental alveolar bone density and a greater likelihood of developing torus (bony growths in the upper or lower jaw) compared to controls. The previously considered pathognomic sign of gross loss of the lamina dura or osteolytic lesions were not observed. This study did also not prove any significant difference regarding the number of teeth, attachment loss or in other periodontal parameters affecting the patients' general oral health (13).

3 RESEARCH AIMS

The aim of this thesis was to increase the understanding of nonclassical symptoms associated to PHPT with a focus on neuromuscular, neuropsychiatric, cognitive disorders and oral health. The four studies aim to explore and cover different levels and aspects of comorbidity in PHPT, on both an individual as well as a population level.

- **Study I** was aimed to evaluate if medical normalization of calcium levels can be a useful as a diagnostic tool in decision of treatment for predicting the outcome of nonclassical symptoms after parathyroidectomy.
- **Study II** was aimed to evaluate if the diagnostic method described in Study I, was applicable in elderly patients with cognitive deficiency for predicting the effect of parathyroidectomy on cognition.
- **Study III** encompasses two parts. The first part (case-control study) aimed to map the presence of neuropsychiatric comorbidity in untreated PHPT as reflected by the use psychotropic medication. The second part (cohort study) aimed to analyze the effects of parathyroidectomy on psychotropic drug utilization.
- **Study IV** aimed to investigate the presence of dental comorbidities in patients with untreated PHPT as reflected of tooth loss by extraction and dental care utilization in comparison to the background population.

4 PATIENTS AND METHODS

4.1 STUDIES I AND II

Study I and II were based on a prospective clinical trial, designed as an observational interventional study with each patient serving as their own control object. The purpose of the design was to measure the individual effects of normalization of ionized serum calcium on nonclassical symptoms during medical treatment as compared with the effects after parathyroidectomy. **Figure 7.**

Based on the hypothesis that the effects would be similar, the aim was to assess the method as a tool used to determine which patients would most benefit from parathyroid surgery and which would not.

A panel of tests was performed at the point of inclusion, during ongoing short-term medication and at six weeks and six months postoperatively. In this way, an individual comparison of the effects measured on each occasion was made possible, which was the purpose of the study. 110 patients scheduled for parathyroidectomy were included after informed consent.

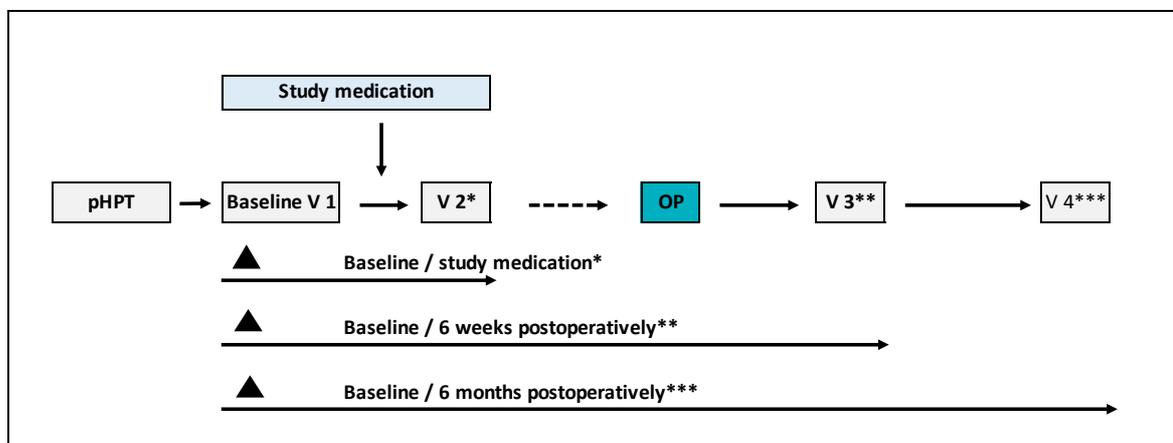


Figure 7. The study design in Studies I and II. Each patient served as its own control.

In the absence of the study's exclusion criteria (kidney failure, epilepsy, severe liver impairment and heart failure (New York Heart Association class III-IV) and drugs contraindicated for calcimimetic treatment; tricyclic antidepressant; oral ketoconazole) males and females from all ages were eligible to participate.

4.2 BIOCHEMICAL ANALYSES AND HISTOPATHOLOGY

Blood samples were collected in the fasting state prior to each visit and were delivered to the laboratory within one hour and centrifuged within two hours according to routine methods by the Karolinska University Laboratory in Stockholm. The biochemical analysis included ionized and total plasma calcium, serum phosphate, serum creatinine, serum albumin, 25-OH vitamin D, TSH and blood glucose. Baseline glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula; $175 \times (\text{S-Creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$. The weight of the excised adenoma and the histologic diagnose retrieved from the pathology report were included in the analysis in study I.

4.3 CALCIMIMETIC STUDY MEDICATION

The pharmaceutical form used as study medication, Cinacalcet was registered in 2006 by Amgen (Mimpara®) (61). The active agent has been found to be effective in treating hypercalcemia. Cinacalcet is an allosteric modulator that affects the CaSR on the surface of the parathyroid cells by increasing the sensitivity to activation by extracellular calcium. Following administration, a direct reduction of PTH synthesis and excretion is achieved with a concomitant decrease in serum calcium levels. Its empirical formula is $\text{C}_{22}\text{H}_{22}\text{F}_3\text{N}$ with a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base) (62).

Figure 8.

Following the oral administration of cinacalcet, maximum serum concentration is achieved within approximately 2 to 6 hours. The concentration increases proportionally over the dose range of 30 to 180 mg once daily. After absorption, cinacalcet concentrations decline with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady-state drug levels are achieved within 7 days. Cinacalcet is metabolized by multiple enzymes, primarily CYP3A4, CYP2D6, and CYP1A2. The hydro cinnamic acid metabolite and glucuronide conjugates have minimal or no calcimimetic activity (61).

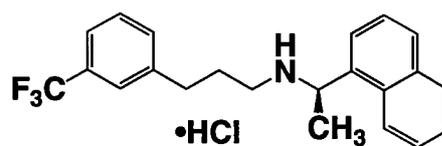


Figure 8. The calcimimetic agent cinacalcet.

Cinacalcet is mainly indicated for the treatment of secondary hyperparathyroidism in adult dialysis patients with chronic kidney disease and in patients with disseminated parathyroid

carcinoma. Calcimimetic treatment can also be useful for patients with PHPT who fulfill the criteria for parathyroidectomy but are unable or unwilling to undergo surgery (63). In PHPT, cinacalcet is effective in reducing hypercalcemia and phosphate loss, however, there is weak evidence as to its effects on bone density, the fracture risk or altered concentrations of biomarkers for bone remodeling (64, 65). Furthermore, the treatment is expensive, side-effects are common and the effect only lasts for as long as the treatment is given (64).

In the trial, short-term calcimimetic treatment was evaluated as a prognostic tool. Our hypothesis was that the effects on nonclassical symptoms that could be achieved during four weeks of Calcimimetic treatment (normocalcemia) would directly correspond with the clinical effects (on neuropsychiatric symptoms, muscle strength and cognitive functioning) after curative surgery (56).

4.4 THE MEASUREMENT OF NONCLASSICAL SYMPTOMS

Nonclassical symptoms; depression, fatigue, muscle weakness and cognitive decline, are mentioned in the international guidelines for treatment and should be taken into consideration when making treatment decisions (17). However, any unanimous recommendations as to how to assess, measure and evaluate unspecific clinical symptoms have not yet been defined. The assessment of nonclassical symptoms is highly subjective as is only based on the patient's presentation and the physician's interpretation. The tests described below were selected for this study because they are frequently used and well established scales to perform with sufficient validity and reliability. Further, they cover the different aspects to be studied and for the fact that they are relatively easy to perform in a clinical context. **Figure 9.**

Quality-of-Life Questionnaire Core 30 (QLQ C-30) covers all aspects of physical, emotional and social well-being (66). In order to record changes that occur during a short period of time, the QLQ C-30 questionnaire aims to concretize the physical and emotional perceptions during the final week in contrast to the final four weeks for Short Form Health Survey 36 (SF-36). QLQ-C-30 was initially developed for use in clinical cancer trials but has also been found to be reliable for the assessment of benign disorders (67). This self-assessment form includes 30 questions divided into six domains: physical functioning (PF), role function (RF), emotional function (EF), cognitive function (CF), social function (SF) and global health (GH). Scoring algorithms are used to transform the results into one total score ranging from 0

to 100 for each domain. A perception of a better QoL generates a higher score and vice versa. QLQ-C30 is fully validated and is recognized as one of the most widely used questionnaires in cancer research.

The Montreal Cognitive Assessment (MoCA) is a validated screening test for the evaluation of cognitive functioning. The test is widely used in the initial investigation of cognitive impairment and dementia. Previous studies have shown a higher sensitivity and equal specificity compared to the Mini-Mental State Examination (68, 69). The test is performed following instructions given by the examiner and takes approximately 10 minutes. Visuospatial and abstraction capacity, memory, executive capability, attention, language and orientation of time and space are evaluated. The maximum score is 30 points. Age and education have an impact on the results. One point is added to the total score for individuals with ≤ 12 years of education.

A score of < 26 points was suggested as the cut-off for mild cognitive impairment in previous Canadian studies and, in the event of a score of < 22 points, Alzheimer’s disease should be considered (69). Normative scores, based on a large Swedish population of individuals aged 65–85, were recently published (70).

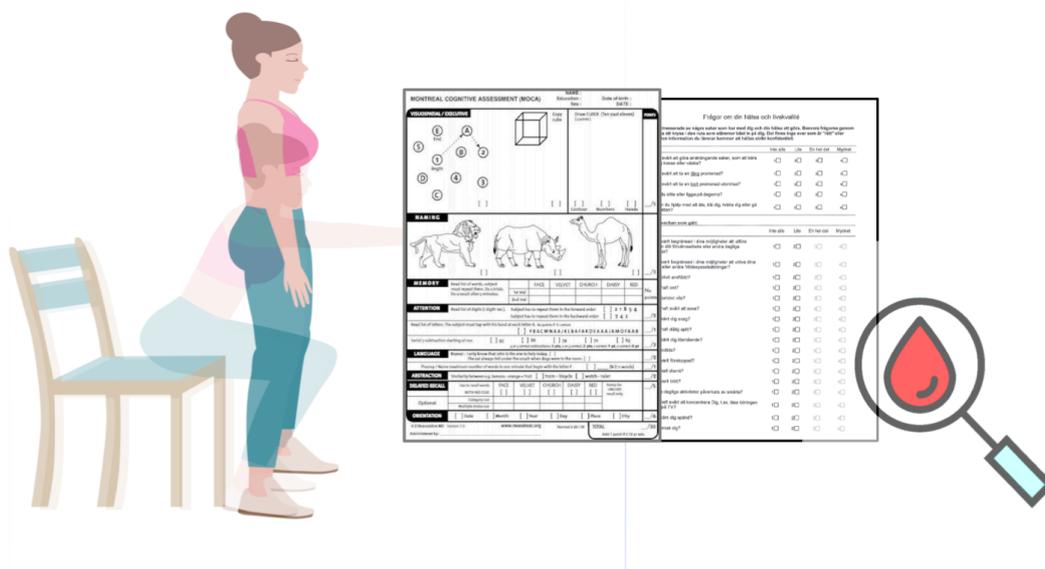


Figure 9. The test panel in Studies I and II.

Hospital Anxiety and Depression Scale (HADS) questionnaire comprises two domains (anxiety and depression) including seven questions for the detection of anxiety and seven for depression. Each question is scored on a scale of 0–4, lower scores being favorable. The

results are traditionally calculated both in total and separately as applied in the study (71, 72). The questionnaire is very easy to perform and usually requires only a few minutes to complete.

The Positive States of Mind (PSOM) questionnaire is a six-item-form designed to evaluate the level of the subjective positive state of mind. Each question is scored on a scale of 1–5 with a maximum total of 30 points and a minimum of 6 points. A higher score reflects a more positive state of mind. A low frequency of positive states of mind would seem to enhance the negative influence of stress on symptoms of anxiety and depression (73).

The Timed-Stands Test (TST) estimates muscle performance by measuring the change in the time required to as quickly as possible complete ten full stand-ups initiated from a sitting position. The recorded time is rounded off to the nearest tenth of a second. A decrease in time spent performing the test indicates an improvement in proximal muscle strength (74). This test is easy to instruct and to understand. The only equipment needed is a stool and a timer. However, the test assume that the patient has the physical strength to get up from a chair and can sometimes be difficult to complete for very weak patients.

4.5 STATISTICS IN STUDY I AND STUDY II

Each patient served as his/her own control. Based on the distribution which did not meet the assumption of normality, nonparametric methods were used for the statistical analysis. All tests were two-tailed and the statistical significance levels were defined by probabilities of < 0.05. Data is presented as the median, quartiles, and range.

Wilcoxon's signed rank test was used for intra-individual comparisons of data from repeated observations in order to investigate any change in scores.

The Mann-Whitney U (Wilcoxon rank-sum test) test was used for comparisons of the test results at a group level.

Spearman's rank-order test was used to analyze bivariate strength and direction of associations (correlation coefficients).

For analyzing the outcome in each test, the results were transformed into dichotomous variables; improved scores or no change or no improvement. For QLQ C-30, a difference in median scores of 10 or more was considered clinically relevant and defined as improvement

Figure 10. Sensitivity, specificity, and positive and negative predictive values were calculated using cross tabulation.

(75, 76).

	<i>Positive test</i>	<i>Negative test</i>
<i>True positive</i>	<i>a</i>	<i>b</i>
<i>True negative</i>	<i>c</i>	<i>d</i>

$$\text{Sensitivity} = a / (a+b)$$

$$\text{Specificity} = d / (c+d)$$

Predictive values of each diagnostic test domain were further determined by means of the Receiver Operating Characteristics (ROC) and Area under the Curve (AUC). The ROC curve illustrates a plot of the true positive rate against the false positive rate for the possible cut-points of the test. Each plot on the curve demonstrates the trade-off between sensitivity and specificity. The area under curve reflects the accuracy of the test. An area greater than 0.9 is considered as high accuracy, while 0.7–0.9 indicates moderate, and 0.5 up to 0.7 as low accuracy. The closer the curve comes to the 45-degree diagonal (AUC 0.5), the less accurate is the test (77). **Figure 11.**

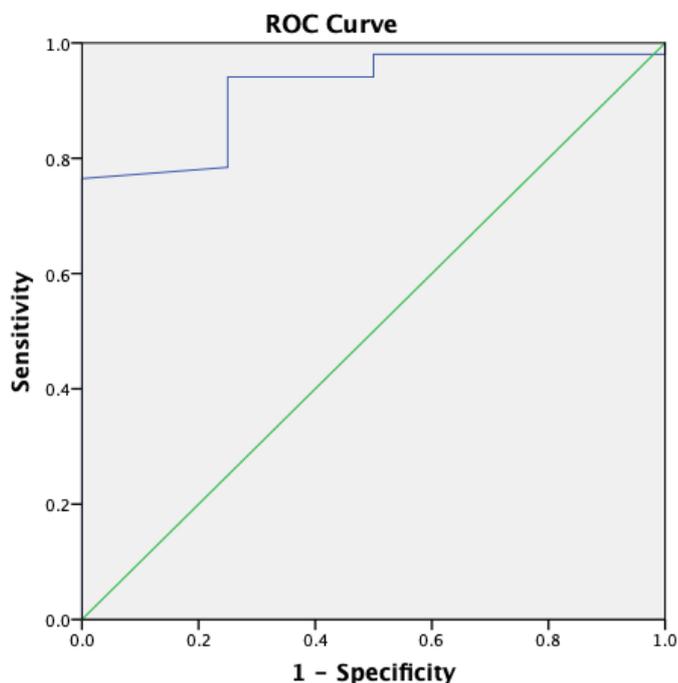


Figure 11. Predictive values of the tests were determined by means of the Receiver Operating Characteristics (ROC).

5 STUDY III AND STUDY IV

5.1 NATIONAL REGISTERS

All Swedish residents are assigned a unique personal identity number either at birth or upon immigration. The personal identity number is used in all health registries and allows for a linkage between national registries which enables comprehensive epidemiological research in Sweden.

The Scandinavian Quality Register of Thyroid, Parathyroid and Adrenal surgery (SQRTPA) is one of the first quality registers for endocrine surgery and was founded in 2004 (21). The register is well validated and normally covers about 95% of all parathyroidectomy procedures performed in Sweden. Regular audits have been carried out, normally annually at 4-6 different clinics, validating data since the start of the register. Unfortunately, no audits were performed during the Covid-19 pandemic and the coverage was drastically compromised. SQRTPA comprises detailed information on biochemical measures, surgical complications, pathology reports and lead times from the time of referral to 6 months postoperatively. Furthermore, the indications for surgery are included, as reported by the surgeon.

The Total Population Register (RTB) is an individual register at Statistics Sweden (SCB) managed by the Swedish Tax Agency and covers data on, for example, relocations, births, deaths and change of civil status of nearly all Swedish citizens. The register was established in 1968 with the intention of producing statistics on the demographic data of the Swedish population for research and statistical purposes. Information on education, unemployment, health insurance on an individual level was collected from the Statistics Sweden's Longitudinal integrated database for health insurance and labor market studies (LISA).

The Swedish Prescribed Drug Register (Läkemedelsregistret), established in July 2005 and administered by the Swedish National Board of Health and Welfare, contains continuous information on all prescribed medication dispensed at Swedish pharmacies. The reporting first passes the Swedish Health Agency that checks the quality of data before it is included in the register. Drugs administered at hospitals and care facilities are not included; neither drugs

sold directly to the consumer without prescription. However, very few drugs in Sweden are administered over the counter, mostly only non-opioid analgesics and medications treating mild symptoms. The drug register is updated every month and is therefore a reliable source when analyzing drug consumption (78).

The National Patient Register (NPR) managed by the National Board of Health and Welfare include all in-patient care since 1987 and since 2001 also out-patient doctor visits and provides data on ICD-10 diagnosis codes, number of inpatient and specialized outpatient visits procedures and length of stay. However, diagnoses registered during outpatient visits to general practitioners are not included (79, 80).

The Swedish Cancer Register was established 1958. Besides malignant diagnoses, this register also covers some benign hormone-producing tumors including parathyroid adenomas.

The Swedish Dental Health Register (DHR) was initiated in July 2008 and includes information on dental care under the National Dental Care Benefits Scheme. The register contains information regarding all dental diagnoses and all procedures approved by the Swedish Social Insurance Agency covered by state dental care support (long-term treatments and unavoidable dental care). The dental care register does not include dental care provided free of charge (children and adolescents up to 23 years of age), maxillofacial surgery or short-term dental treatment (81).

5.2 PATIENTS AND REFERENCE POPULATION IN STUDY III

All patients (n = 8,626) registered after parathyroidectomy between 1st January 2008 to 31st December 2017 in the Scandinavian Quality Register of Thyroid, Parathyroid and Adrenal surgery (SQRTPA) and/or in the National Swedish Patient and Cancer Registers were collected by the National Board of Health and Welfare (78, 82). For each patient, Statistics Sweden (SCB) selected 10 individuals from the Total Population Register (RTB) matched by year of birth, gender and county (n = 86,260). To allow a complete analysis of drug dispensing up to 3 years prior to parathyroidectomy, 347 patients registered between January

and June 2008 and their respective controls (n=3,470) were excluded from the analyses thus resulting in a study population of 8,279 PHPT patients and 82,790 controls.

5.3 STATISTICAL MODELS IN STUDY III

The retrospective case-control study aimed to analyze untreated PHPT as a risk factor for neuropsychiatric disease as reflected by drug dispensing. The analysis included data collected from up to three years before the index date, defined as the time of parathyroidectomy in the cases and the corresponding time point for the matched controls, in order to adjust for duration of exposure.

All data were analyzed longitudinally. The cohorts were stratified into age groups: <50 years, 50-64 years, 65-79 and >80 years. At least one administration of the drug within each 6 months period were considered as ongoing treatment.

The odds ratios (OR) within three years before the index date were calculated by conditional logistic regression. The exposure was untreated PHPT. The primary outcome measure was the dispensing of drugs according to ATC codes designated to match the treatment of depression, anxiety, sleep disorders and dementia (ICD10).

Diagnostic data and socioeconomic status from the year before the index date itself were analyzed cross-sectionally.

Interactions in relation to the calcium levels, age and gender of the patients were all analyzed separately within the patient cohort.

Base-line characteristics are presented as median and interquartile range for the continuous variables and as Odds Ratio (OR) for categorical variables.

In the prospective cohort study, the incidence rates for dispensing of psychotropic drugs 3 years after the index date were analyzed longitudinally (Risk Ratio, RR). In this part the exposure was parathyroidectomy and cure of disease. The primary outcome measure was dispensing of drugs used to treat depression, anxiety, sleep disorders and dementia after exposure to parathyroidectomy.

In order to define a change in drug dispensing, the Poisson regression model was used to analyze the RR in comparison with the control cohort. Due to the broken match in the prospective part, age, gender, region and education were considered confounders and were thereby adjusted for.

The statistical software programs SAS and SPSS version 27, were used to conduct all analyses. All results are presented with a 95% confidence interval (95% CI). P values less than 0.05 were considered significant.

Power calculations were based on the assumption of a Poisson distribution of events and a 25% reduction of follow-ups due to mortality and emigration. The population was estimated to guarantee 80% statistical power at a 95% confidence level for the presence of risk factors between 0.5-30% among controls in the retrospective case-control analyses and an incidence of 0.5-10% in the prospective cohort study. **Figure 12.**

Figure 12. Power calculations for Study IV.

Case control study		Prospective cohort study	
Risk factor, prevalence in controls	Detectable Relative Risk	Incidence 1/1000/person year in controls	Detectable Relative Risk
0.5%	1.81	0.5	2.26
1%	1.51	1	1.83
5.0%	1.23	2	1.57
10%	1.16	5	1.34
30%	1.10	10	1.23

5.4 PATIENTS AND REFERENCE POPULATION IN STUDY IV

Study IV included all patients registered in the Swedish Quality Register of Thyroid, Parathyroid and Adrenal surgery (SQRTPA), who underwent parathyroidectomy during the period 2011-2016. By matching on age and gender (matching ratio 1:3), the control population was selected from a cohort of normal population which formerly had served as controls in a research study on head and neck cancer and oral health at the Institution of Odontology, Karolinska Institutet.

5.5 STATISTICAL MODEL IN STUDY IV

In this observational cohort study Fixed-effect Poisson regression models (conditioned on the matching strata) were used to analyze longitudinal data featuring the number of events (dental care visits and interventions) in PHPT patients compared with a cohort from the background population. All models were adjusted for age, index year and number of teeth. Time in the study was included as an offset variable after logarithmic transformation. The PHPT cohort was further categorized into quartiles based on the preoperative S-Ca²⁺ in order to investigate any effect related to the severity of hypercalcemia. IRRs for tooth extractions, periodontal interventions and total number of visits were calculated for each S-Ca²⁺ quartile versus the reference cohort.

Furthermore, a complementary sensitivity analysis was performed restricted to the PHPT cohort in order to estimate the IRRs for the same outcome variables related to a 1 gram increase in weight of the excised parathyroid adenoma (defined as postoperative verification proxy for severity and duration of disease) (22). All statistical analyzes were performed by the co-author statistician using the statistical program Stata (version 15, Stata Corp LP, College Station, TX).

6 RESULTS

6.1 STUDY I

The clinical characteristics of the study cohort are presented in **Table 1**. 110 patients (91 women) were included in the study. Eight patients had multiglandular disease and the cure rate was 97%.

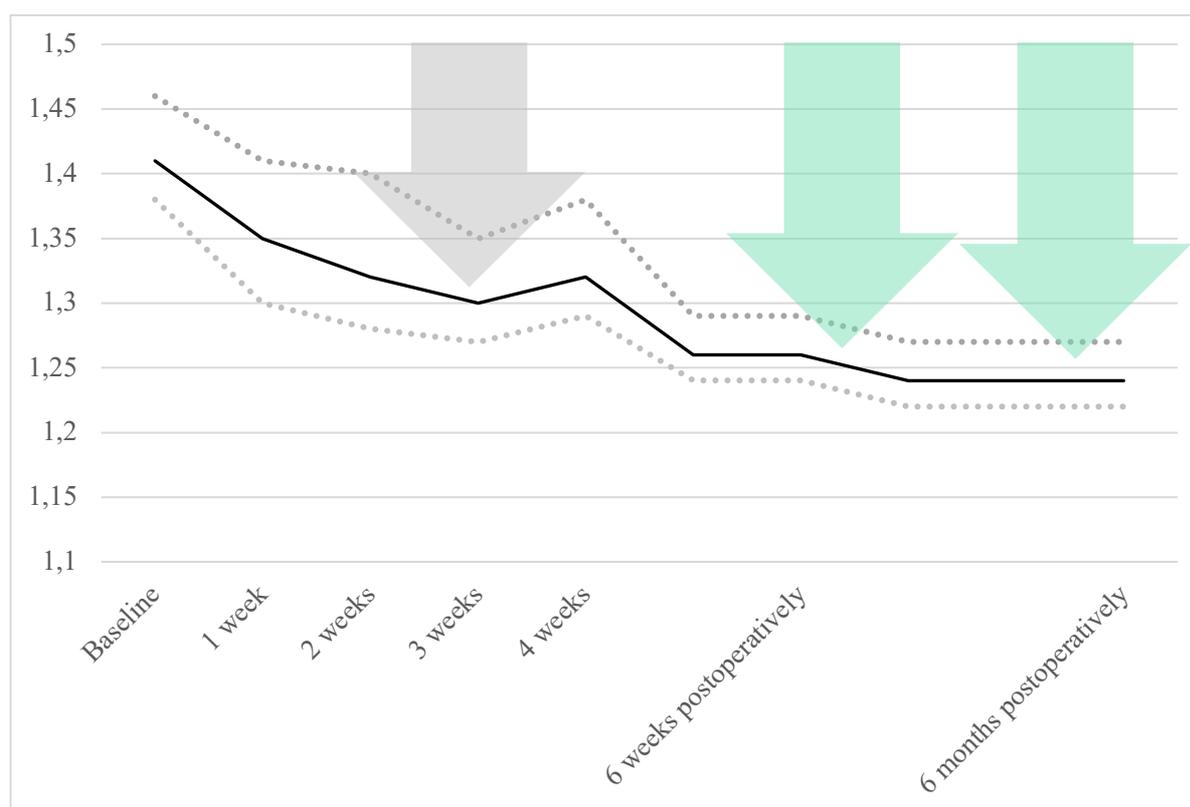
13 patients did not fulfill the whole study protocol. Two patients were excluded because of a previously unrecognized exclusion criterion (history of epilepsy and tricyclic medication respectively). One patient exhibited persistent disease after the first operation. Five patients ceased the medication due to side effects, two women discontinued medication following intercurrent disease (stroke, upper respiratory tract infection) and three patients missed any of the visits.

Table 1. Clinical characteristics in Study I.

Clinical characteristics	median	quartiles 25th;75th
n=110 (91 women)		
Age (years)	62	53;72
BMI (kg/m ²)	26	23.0;29.0
P-Calcium (2.15 - 2.50 mmol/L)	2.60	2.51;2.68
P-Albumin (< 41 years 36 - 48 g/L, 41 - 70 years 36 - 45 g/L, > 70 years 34 - 45 g/L)	38	36;39
P-Calcium corrected for albumin (2.15 - 2.50 mmol/L)	2.65	2.57;2.74
S-Ca ²⁺ (1.15-1.33 mmol/L)	1.41	1.38;1.46
P-PTH (1,6-6,0 pmol/L)	10	7.9;13.0
P-Phosphate (0.8 - 1.5 mmol/L)	0.86	0.78;0.95
P-Creatinine (female <90 mikromol/L, male <100 mikromol/L)	68	62;78
GFR (>60 mL/min/1.73 m ²)	82	75;93
S-25-OH-D (50 - 250 nmol/L)	66	52;81
TSH (0.3 - 4.2 mE/L)	1.8	1.2;2.6
fb-Glucose (4.0 - 6.0 mmol/L)	5.6	5.3;5.9
Weight of adenoma (mg)	356	260;633

The study medication induced a significant decrease of ionized calcium levels to a median of 1.35 [1.30;1.41] mmol/L after one week compared to 1.41 [1.38;1.45] mmol/L; $P < 0.001$ at baseline. Calcium levels continued to decrease during the second (1.32 [1.28; 1.40] mmol/L) and third weeks of treatment (1.30 [1.27; 1.35] mmol/L); $P < 0.001$). **Figure 13.**

Figure 13. Normalization of the calcium concentration during the study period (IQR).



39 patients required double doses of calcimimetic (60 mg per day) to reach normal calcium levels. Mild to moderate side effects were frequently reported, mostly gastrointestinal in character. No serious adverse event related to the study medication was observed.

The group of patients that required an increased dose was characterized by higher preoperative calcium (1.46 [1.44; 1.49] vs 1.39 [1.37-1.42] mmol/L) and PTH-levels (11 [8.6-14] versus 9.8 [7.3;12.6] pmol/L) and larger parathyroid adenomas (440 [276;1100] versus 344 [200;515]) mg; $P < 0.05$. In total, 97 patients completed the full study protocol and were included in the analyses.

During the study medication, a significant increase of self-assessment scores in four of six functional domains of QLQ C-30 including GF, EF, CF and SF, scales was reported which then correlated well with the postoperative outcome ($r=0.478-0.625$; $P<0.001$).

Cognitive ability (MoCA score) improved during the medication, which also significantly correlated to the long-term postoperative results. ($r=0.389$; $P < 0.01$).

The proximal muscle strength improved significantly during medication which likewise correlated with the postoperative outcome ($r=0.738$; $P<0.01$).

The observed changes did not correlate with preoperative PTH or the calcium levels.

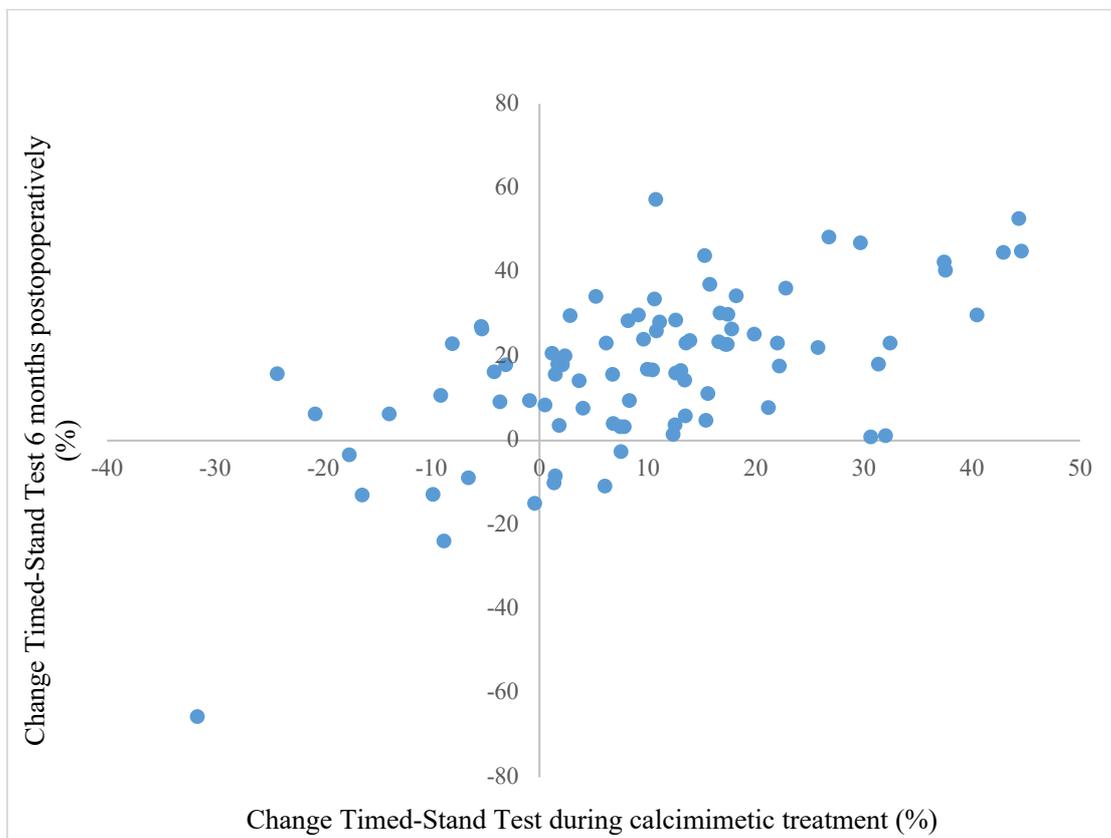


Figure 14. The correlation of improvement (%) of TST during treatment with the study medication and six months postoperatively.

The predictive values were based on dichotomous values, whether or not there was an improvement of the different components of the test protocol. **Table 2.**

The TST showed the highest numeric sensitivity and PPV. A quarter of the participants reduced the time spent on the test by more than 20% during medication and furthermore continued to improve during the follow-up period. The correlation between the change in TST during medication and six months after parathyroidectomy is illustrated in **Figure 14.**

Table 2. Predictive values of each test included in the test panel in Study I.

Prediction of improvement at follow up 6 months after PTX*	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	Δ Score Calcimimetic AUC (CI 96%)
QLQ-C30					
Global health status	85.0	53.7	64.2	78.6	0.708 (0.599;0.817)
Physical functioning	95.5	76.9	63.6	97.6	0.786 (0.679;0.893)
Role functioning	90.0	76.6	62.1	94.7	0.708 (0.570;0.845)
Emotional functioning	88.8	65.8	71.1	84.0	0.746 (0.646;0.843)
Cognitive functioning	74.2	60.5	57.5	76.5	0.691 (0.583;0.799)
Social functioning	88.0	81.4	73.3	92.1	0.794 (0.691;0.894)
Corresponding test panel					
Timed stand test	95.3	28.6	85.9	57.1	0.836 (0.727;0.944)
MoCa	86.0	32.6	54.4	71.4	0.599 (0.465;0.733)
HAD A	84.0	61.5	73.7	75.0	0.722 (0.594;0.849)
HAD D	87.2	68.3	75.9	82.4	0.746 (0.619;0.872)
PSOM	80.4	44.1	68.3	60.0	0.710 (0.606;0.814)

*cut off for improvement in QLQ-C30; 10 points

6.2 STUDY II

35 PHPT patients (median 77 [72;82] years of age) were detected featuring mild cognitive impairment defined by MoCA-score < 26 (median 23 [20-24]). 35 patients were ≥ 50 years (19 patients ≥ 70 years) of age.

All but three patients completed the full study protocol. Two patients discontinued medication due to gastrointestinal side effects and one due to an upper respiratory tract infection.

A total of 15 patients (9 patients age ≥ 70 years) required higher dose calcimimetic treatment (60mg/day) to achieve normal calcium levels. Parathyroidectomy was performed at a median of 6 (4-12) weeks after the final dose of study medication.

Calcimimetic treatment resulted in normalization of calcium levels and significant improvements in MoCA (2 [0-3]; $P < 0.001$), (HADS -2 [0- -3]; $P = 0.020$) and TST (-3s [0- -9]); $P = 0.004$). Seventeen patients reached normal MoCA scores (≥ 26) six months postoperatively.

Ionized calcium concentration at inclusion and improvement in MoCA score during calcimimetic treatment were recognized as independent predictors for a favorable long-term outcome. In patients aged ≥ 70 years, the decrease in ionized calcium level correlated with long term improvement in MoCA score following parathyroidectomy ($r = -0.536$; $P = 0.022$).

The predictive values of the test panel are presented in **Table 3** (PPV/NPV, specificity, sensitivity).

HADS showed the highest accuracy with PPV and NPV around 90% and was found predictive for a later improvement of cognitive functioning, namely 6 months after parathyroidectomy ($r: -0.488$; $P = 0.047$).

MoCA and TST had a PPV around 80% but were inferior when ruling out any potential for improvement. Half of the patients (17/35) attained normal MoCA scores (≥ 26) six months postoperatively (57). **Figure 15.**

Table 3. Predictive values of each test included in the test panel in Study II.

Prediction of improvement at follow up 6 months after parathyroidectomy by in patients over fifty years of age and with Montreal Cognitive Assessment score <26 at baseline					
	PPV %	NPV %	Sens %	Spec %	AUC for Δ score calcimimetic
Age ≥ 70 years, n=19					
Montreal Cognitive Assessment	82	33	69	50	0.596 (0.263;0.929)
Timed-stands test	89	25	73	50	0.569 (0.209;0.930)
HADS anxiety	94	56	68	90	0.669 (0.394;0.945)
HADS depression	80	88	89	78	0.833 (0.629;1.000)
HADS total	90	100	100	89	0.944 (0.891;1.000)
Age ≥ 50 years, n=35					
Montreal Cognitive Assessment	86	22	72	40	0.560 (0.273;0.847)
Timed-stands test	94	33	74	75	0.745 (0.474;1.000)
HADS anxiety	94	56	68	90	0.791 (0.626;0.956)
HADS depression	75	83	88	67	0.775 (0.603;0.946)
HADS total	80	92	94	75	0.846 (0.700;0.991)

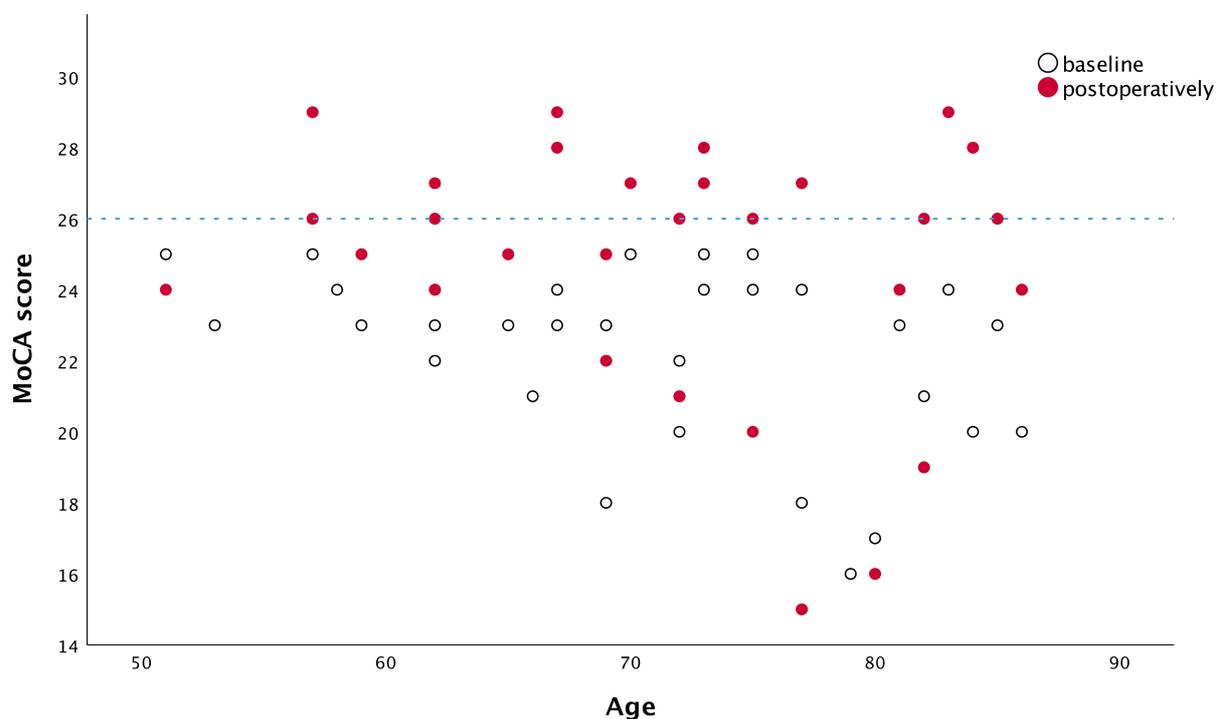


Figure 15. The MoCA scores at inclusion compared with six months postoperatively in patients ≥ 50 years of age with mild cognitive impairment in Study II.

6.3 STUDY III

Baseline characteristics at index date including age distribution, information with regards to education, employment and health insurance and country of birth are outlined for patients and controls in **Table 4**.

Table 4.

Characteristics of 8279 patients with primary hyperparathyroidism subjected to parathyroidectomy and 82790 controls from the background population matched for age, gender and region

Characteristics	PHPT patients (n=8279)		Control population (n=82790)	
Median age at index date, IQR	62 (53, 71)		62 (53, 71)	
<i>Age</i>	n	%	n	%
<30	186	2.2	1860	2.2
30-39	337	4.1	3370	4.1
40-49	942	11.4	9420	11.4
50-59	1820	22.0	18220	22.0
60-69	2451	29.6	24510	29.6
70-79	1943	23.5	19430	23.5
80+	598	7.2	5980	7.2
<i>Gender</i>				
female	6374	77.0	63740	77.0
male	1905	23.0	19050	23.0
<i>Education</i>	n	%	n	%
Elementary school	1972	23.8	20643	24.9
Upper secondary school	3598	43.3	35418	42.8
Post-secondary education	2612	31.6	25347	30.6
Data not available	106	1.3	1382	1.7
<i>Occupational status</i>	n	%	n	%
Employed				
<65 years	3385	75.6	34949	78.1
65+ years	503	13.2	5008	13.2
Unemployed, declared				
<65 years	248	5.5	2508	5.6
<i>Country of birth</i>				
Sweden	6897	83.1	69063	83.4
Nordic countries (except Sweden)	445	5.4	3809	4.6
Europe (except Nordic countries)	475	5.7	5224	6.3
Outside Europe	480	5.8	5224	5.3
Unknown	0	-	2	-

Abbreviations: PHPT, primary hyperparathyroidism

After a review of the characteristics of patients registered in SQRTPA (n= 7,177), it was found that the degree of hypercalcemia was generally mild; serum ionized calcium 1.44 (1.39,1.50) mmol/L and parathyroid hormone was moderately increased; P-PTH 10 (7.9;13.0) pmol/L. Reported as indications for surgery were osteoporosis or fracture in 14-20%, kidney

stones in 3-6% and hypercalcemia with a total calcium level > 2.75 mmol/L in 13% of the patients. Psychiatric symptoms and fatigue were recorded as prevalent in 10-12% and 28-33% of the patients respectively.

The case-control analysis revealed that dispensing of psychotropic drug over-all, were more extensive in patients with untreated PHPT compared with the background population cohort within 3 years prior to parathyroidectomy.

Table 5.

Users by age groups and gender within 3 years prior to index date in the PHPT patients compared to the control population*

		PHPT patients (n=8279)		Control population (n=82790)		OR	95% CI	
		n	%	n	%			
SSRI	N06AB, N06A All	1316/8279	15.9	10004/82790	12.1	1.38	(1.30-1.47)	
	Age	<49	278/1465	19.0	1677/14650	11.4	1.81	(1.57-2.09)
		50-64	516/3012	17.1	3627/30120	12.0	1.53	(1.38-1.70)
		65-79	424/3204	13.2	3730/32040	11.6	1.17	(1.05-1.30)
		80+	98/598	16.4	970/5980	16.2	0.98	(0.78-1.23)
	Sex	M	189/1905	9.9	1414/19050	7.4	1.37	(1.17-1.61)
	F	1127/6374	17.7	8590/63740	13.5	1.38	(1.29-1.48)	
Anxiolytic, benzodiazepin N05BA	All	1097/8279	13.3	8261/82790	10.0	1.40	(1.31-1.50)	
	Age	<49	157/1465	10.7	800/14650	5.5	2.09	(1.74-2.52)
		50-64	349/3012	11.6	2452/30120	8.1	1.51	(1.33-1.70)
		65-79	464/3204	14.5	3784/32040	11.8	1.28	(1.15-1.42)
		80+	127/598	21.2	1225/5980	20.5	1.06	(0.86-1.31)
	Sex	M	181/1905	9.5	1224/19050	6.4	1.58	(1.34-1.87)
	F	916/6374	14.4	7037/63740	11.0	1.37	(1.27-1.48)	
Sleep, benzodiazepine N05CF	All	1861/8279	22.5	14589/82790	17.6	1.38	(1.30-1.46)	
	Age	<49	208/1465	14.2	1229/14650	8.4	1.82	(1.55-2.14)
		50-64	604/3012	20.1	4438/30120	14.7	1.47	(1.34-1.62)
		65-79	816/3204	25.5	6909/32040	21.6	1.25	(1.15-1.36)
		80+	233/598	39.0	2013/5980	33.7	1.25	(1.05-1.49)
	Sex	M	294/1905	15.4	2127/19050	11.2	1.48	(1.29-1.70)
	F	1567/6374	24.6	12462/63740	19.6	1.36	(1.28-1.45)	

*at least one dispense of the prescribed drug within the observation time

Abbreviations: PHPT, primary hyperparathyroidism; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitors

The most common medications were benzodiazepines (OR 1.40, 95% CI 1.31-1.50) and SSRIs (1.38, 95% CI 1.30-1.47). **Table 5.** OR's for SSRIs were highest among patients <50 years of age (19% users as compared to 11% in the background population) and among patients with lower calcium levels; P<0.001. No gender-specific difference between the cohorts was observed.

Among the oldest patients (80 years of age and older), dispensing of antidepressant medication was similar in both the patients and controls but the use of benzodiazepines to

induce sleep was higher also among elderly patients compared to controls of same age group (OR 1.25, 95% CI 1.05-1.49).

Psychiatric disorders (ICD-10; F06-F99) were registered more than twice as common in patients within the year before parathyroidectomy, 8.7% as opposed to 3.7% among the controls during the corresponding period (OR 2.51, CI 95% 1.31-2.73. The difference was less pronounced during the period of five years before index date (OR 1.67, CI 95% 1.56-1.79). Furthermore, somatic diagnoses were overrepresented in the patient cohort. Contrarily, treatment for dementia were less common among patients compared to controls (OR 0.53, CI 0.39-0.73).

After curative parathyroidectomy, psychotropic drugs dispensing remained elevated with a significant trend of normalization of RR's for some substances but not all. The relative use of antidepressant medication (SSRI) remained higher with no significant change. **Figure 16.**

The use of Lithium was markedly overrepresented in the patient cohort (OR 5.74, 95% CI 4.76-6.93) and remained unchanged postoperatively.

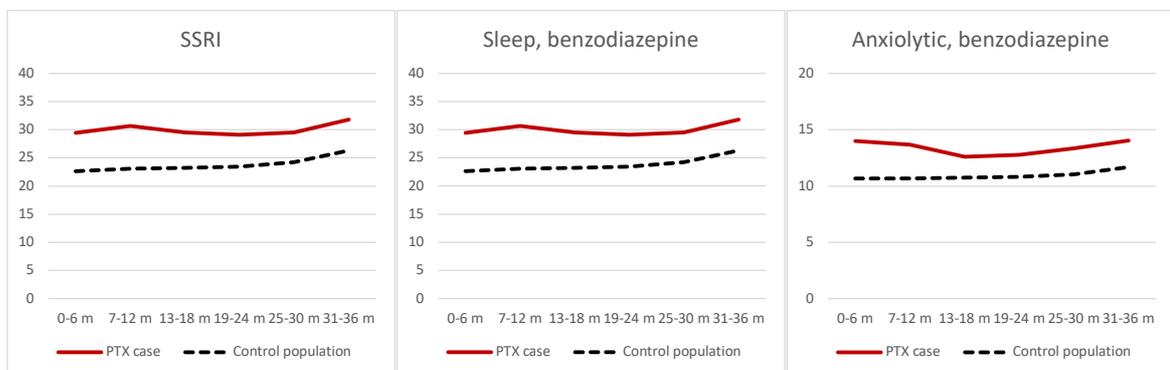


Figure 16. Dispensing of SSRI and benzodiazepines within 3 years from the index date in patients compared to the background population; incidence/100 persons/year within three years of follow-up.

6.4 STUDY IV

The patient cohort included 982 PHPT patients (748 females) at a median age of 62 years with a preoperative median S-Ca²⁺ of 1.45 mmol/L. The reference cohort consisted of 2944 Stockholm County residents matched using age and gender. **Figure 17.**

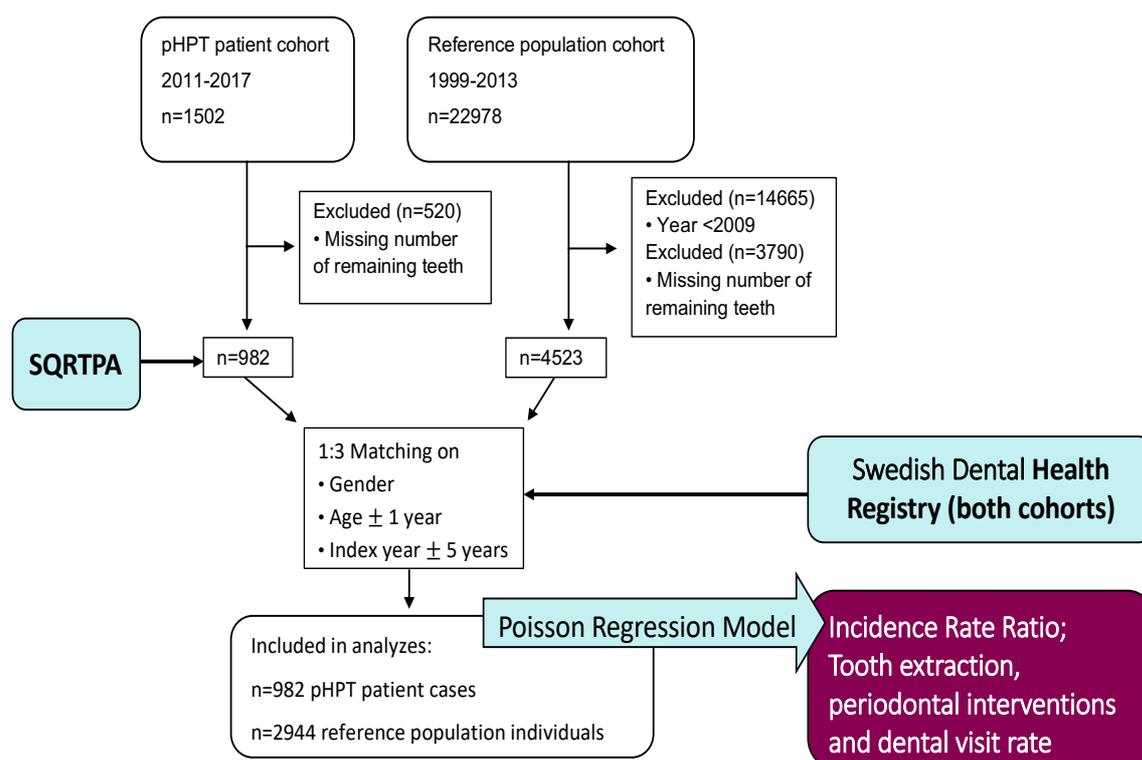


Figure 17. Flow-chart of study IV.

Overall, there were no significant difference between the cohorts regarding the incidence of the primary and secondary outcomes, e.g. tooth extractions, periodontal interventions and total number of dental physician visits. PHPT patients with highest calcium concentration (belonging to the fourth quartile with S-Ca²⁺ levels ≥ 1.51 mmol/L) had a markedly increased risk for tooth extraction (IRR 1.85; 95% CI 1.39-2.46) Female gender independently entailed an amplified risk (IRR 1.341, P = 0.027). After adjustment for S-Ca²⁺, the adenoma weight seemed to be an independent risk factor for tooth extractions (IRR 1.047, P <0.030).

7 DISCUSSION

Firstly, this thesis has come about in an attempt to give each patient a fair treatment that is most beneficial with realistic expectations. To better understand the nature of nonclassical symptoms in PHPT has an increasing relevance given that PHPT is becoming a more common disease. The population has not only become older but also healthier and thus the demands on maintaining health and the ability to participate in society have increased. This thesis hopefully shed light, from several perspectives, on nonclassical symptoms associated with PHPT and the importance of a proper treatment for each patient with a proper underlying indication.

The general perception among scientists internationally is above all that the increased incidence of PHPT is driven by a raised awareness among both doctors and patients. Results from a retrospective cohort study performed in Edinburgh, Scotland by Andrew Collier et al. showed that the incidence of PHPT increased around three-fold during the 21st century. Furthermore, they found that increased social deprivation was associated with decision for a conservative approach rather than curative treatment; among the deprived 59.6% were managed “conservatively” as compared with 48.7% in lesser deprived areas ($p < 0.01$) (83).

Accumulating epidemiological publications reveals that PHPT often goes undetected or underdiagnosed, especially among elderly and frail individuals (84-87). One stipulated reason is the lack of knowledge with regards to mild hypercalcemic or normocalcemic disease which are often incorrectly assumed to cause no or negligible symptoms (88-90). This was further confirmed in a recently published population study carried out by Seib et al which looked at adherence to consensus guidelines for treatment. They showed that less than 30% of patients who fulfilled at least one criterion were treated with parathyroidectomy within the year following diagnosis. Comorbidity, frailty and increasing age had a strong inverse correlation with the chance for surgical treatment (91).

It is therefore appropriate to stipulate that a considerable number of patients have gone undetected or received inappropriate treatment meant for other diagnoses.

To date, treatment guidelines are still ambiguous, particularly concerning older patients (≥ 50 years of age) with non-disease-specific symptoms. According to international consensus more research in the field is warranted and guidelines are to be continuously revised regularly (92). However, cumulative literature agree that curative parathyroidectomy often

exerts a positive effect on QoL, in a proportion of patients also in biochemically mild disease and unrelated to the serum calcium levels (56, 57, 93).

In our **Paper I** and **II** we could state that the study medication exerted positive effects on mental status, muscle strength and cognition. Although cinacalcet was found efficient means of reducing hypercalcemia, we found that the effects on nonclassical symptoms were minor compared with the effects of parathyroidectomy. Furthermore, the calcimimetic treatment is expensive, side-effects are common and the effect only lasts for as long as the treatment is given (64). Our studies support that calcimimetic treatment should be reserved for PHPT patients who fulfill the criteria for PTX but are unable to undergo surgery (61).

The availability of biochemical analyzes for diagnostics and imaging is good in developed countries such as Sweden. Yet, there are at the same time a lack of tools in clinical praxis for prediction of the effect of parathyroidectomy on nonclassical symptoms on an individual level. Furthermore, with increased demands on efficiency in health care, the time spent on the consultation of each patients have become scarce and despite any doctor's solid clinical experience, it is difficult to capture what our patients express "between the lines". Inevitably, as with other diagnoses worldwide, there are also disparities in the approach to treatment depending on age, gender, demography, ethnicity and socioeconomic status (83, 86, 94).

A diagnostic tool of using short-term calcimimetic treatment to predict effects of parathyroidectomy is presented in **Papers I** and **II**. Improvements in the test results were significant both during ongoing medication and postoperatively and the effects increased over time. The main results in **Papers I** and **II** were that the method was found feasible to use and improvements in QoL- aspects, cognitive function and muscle strength during study medication correlated well with the postoperative outcome (PPV 74-96%). The study medication was well tolerated without serious side effect and normocalcemia was achieved.

Paper II presents the diagnostic method described in **Paper I** applied specifically on older adults defined with mild cognitive impairment. Short-term treatment was found to be equally effective to predict improvements for this group, but was found to be inferior when ruling out any potential benefit on cognitive function.

Secondly, we could ascertain that half of the patient attained normal scores in the cognitive test 6 months postoperatively. The long-term effect on cognition was also found to be preceded by an improved mental status during the study medication period.

Furthermore, the time required to perform the TST changed significantly from a median of 33(29;40) to 27(23;30) seconds from the point of inclusion in the study till 6 months postoperatively (median change 5.3 [1.8;10.0]) seconds ($P=0.006$). The improvement in muscle strength was found correlated to results of the MoCA test 6 months postoperatively ($r=0.413$; $P=0.04$). This is in line with emerging literature providing strong evidence of interrelationships between muscle strength and cognition in the elderly is which will be further discussed below.

Despite the fact that the population as a whole has become healthier, the consumption of antidepressant drugs has increased markedly (95). This is a worrying signal that mental health in society has deteriorated over recent years, especially in elderly for whom mental symptoms and a more extensive use of antidepressants and sedatives entail an underlying risk for general frailty, increased side effects, drug interactions and falls (96). The epidemiological analysis presented in **Paper III** showed that the dispensing of drugs to treat depression, anxiety and sleep disorders was significantly more extensive among untreated PHPT patients when compared with the background population. The dispensing of antidepressants and anxiolytic drugs (except Lithium) increased during the five years of observation prior to parathyroidectomy which indicates a clear progression of mental symptoms related to untreated PHPT.

When the cohorts were stratified into age groups, the disparities in the dispensing of antidepressant medication between cases and controls were found to be mainly represented by patients of up to 65 years of age. In the elderly, the use of SSRI in PHPT patients was equal to the controls whereas sleep medication was slightly more common. However, neuropsychiatric symptoms registered in SQRTPA were equivalent regardless of age, which in light of previous knowledge was interpreted possibly due to the fact that somatic symptoms tend to be more in focus among older patients (97-100).

From the results in **Paper III** we saw that females in both cohorts consumed more drugs for the treatment of depression, anxiety and sleep disorders compared with males (Table 3, manuscript **Paper III**) This finding corresponded with a cross-sectional study of health care consumption for 1.6 million inhabitants of western Sweden (Region Västra Götaland) during 2012. Friberg and co-authors found that the consumption of health care for mental, behavioral and musculoskeletal disorders were the dominating causes in women (after adjustments for care related to reproduction and gender-specific diseases). The cost ratio (female/male) for mental disorders and diseases of the musculoskeletal system were 1.30 and 1.48, respectively. It was furthermore noted that men consumed more specialist care (101, 102).

Mild rather than severe hypercalcemia seemed to be associated with a higher prevalence of medication requirement for the treatment of psychiatric symptoms whereas a decrease in calcium concentration correlated with cognitive improvement in Study II. Previous studies have not shown any link between calcium levels and decreased QoL so this is of interest. (89).

One contributing factor behind this is possibly the detection of PHPT in connection with diagnostic work-up for psychiatric symptoms in some individuals which might have entailed a selection bias that may have amplified the epidemiological findings in **Paper III**.

The clinical effect of the biochemical modulations of the nervous system is not yet fully understood. Lithium consumption/medication is a risk factor for the development of PHPT and is mainly used in the treatment of chronic psychiatric diseases such as depression and bipolar disorder (103). No predisposition for mental illness linked to PHPT is known, beyond the secondary effects of lithium treatment and the effects of the disease itself. As expected, lithium therapy was overrepresented among PHPT patients (2.1% in PHPT patients vs. 0.4% in the background population) and remained unchanged during pre- and postoperative observation.

Following parathyroidectomy, the consumption of anxiolytics and sleeping pills tended to decrease whereas the consumption of SSRIs remained elevated. In patients without treatment before parathyroidectomy, the introduction of SSRI and benzodiazepines was equal to controls at least three years after parathyroidectomy, which advocate that a significant proportion of patients were genuinely asymptomatic.

Given that the presence of neuropsychiatric symptoms and fatigue were reported in 40% of the patients who had undergone surgery registered in the SQRTPA, it proves that there is an awareness and a commitment concerning nonclassical symptoms among endocrine surgeons (Table 2, **Paper III**). The question is how and by whom follow-up should be addressed.

7.1 THE CONCEPT OF FRAILTY

Frailty is a description of a multidimensional syndrome, namely a of loss of reserves (physical, cognitive, health, energy). The concept of frailty is a frequently used concept for describing an individual's vulnerability to exogenous and endogenous stressors. The 7-point Clinical Frailty Scale, published by Rockwood et al in The Canadian Medical Association

Journal 2005, is a widely used predictive tool to estimate the risk for death or need for institutional care (104).

I would argue that the concept of frailty is highly applicable in the context of nonclassical symptoms of PHPT and worthwhile to discuss in this thesis (48). There is a plethora of publications that shows the obvious fact that frailty has a negative impact on health outcomes (105). Among well-documented risk factors that are also well recognized as non-classical symptoms in some PHPT patients are, for example, mental illness, impaired muscle strength, and mild cognitive impairment (106). This chain of symptoms often leads to isolation, which in turn reinforces the symptomatology (107, 108). Cesari et.al. recently summarized the concept of cognitive frailty in the article *The Controversial Condition of Cognitive Frailty: What It Is, What It Should Be?* which emphasizes the importance of looking at frailty as a multidimensional phenomenon. The number of published studies in the field of cognitive frailty specifically related to other diagnoses is emerging rapidly. However, interventional studies looking at protective factors are still relatively few. In these, the authors pay attention to the danger of narrowing the analyzes and called for a holistic approach to avoid limiting assessment to a single organ (e.g. brain) or function (e.g. cognition) and to identify potentially reversible causes (unidentified diagnoses, life-style factors, lack of physical activity) in order to pave the way for preventive strategies (105, 109).

It is therefore also reasonable to assume that also nonclassical symptoms related to PHPT may constitute risk factors for frailty, which in turn enforces the importance of developing methods to identify individuals at risk and who can benefit from parathyroidectomy.

7.2 COGNITIVE DECLINE, MUSCLE STRENGTH AND PHYSICAL ACTIVITIES

The evidence for a link between mild cognitive impairment, lack of physical activity and impaired muscle strength is accumulating. Decreased muscle strength is a proven predictor for later cognitive decline and frailty whereas physical activities have been shown to exert a protective effect (76, 109-111). It is therefore worth recalling the results in **Paper II**, which showed that a lack of effect of calcimimetics does not exclude long-term positive effects on cognitive functioning or muscle strength following parathyroidectomy.

Results from a prospective observational cohort study of 750 cognitive intact persons during 12 years across Chicago showed that physical frailty (grip strength, timed walk, body

composition, and fatigue) was associated with a 63% increase in the risk of mild cognitive impairment (hazard ratio 1.63; 95% CI 1.27-2.08) and faster rate of decline. The association persisted for at least 1 year and after adjustments for depressive symptoms, disability, vascular risk factors, and vascular diseases (112). In line with this, Sipilä et.al. stated that physical activity combined with cognitive exercise exerts synergic protective effects on mental health (109).

7.3 COGNITIVE DECLINE AND EMOTIONAL STATUS

In the analysis presented in **Paper II**, we found that long-term improvement of cognition was preceded by improved emotional status at an earlier stage. Reduced psychiatric symptoms were thus a predictor of the long-term effect on cognition.

Similar results were found in both observational and population-based studies (113). In the Kungsholmen Project, analysis of depression and anxiety in relation to future development of Alzheimer in elderly persons of 75 to 95 years of age were carried out. Elderly persons with mild cognitive impairment (n=47) and cognitively intact persons (n=185) were followed over a period of 3 years. The authors found that psychiatric symptoms occurred more frequently in individuals with mild cognitive impairment compared with cognitively intact elderly individuals. In patients with mild cognitive impairment and combined anxiety, 83.3% developed Alzheimer's disease versus 6.1% among cognitively intact persons with symptoms of anxiety. In cognitive intact subjects, mainly depressive symptoms were found to be related to later AD development (114).

In **Paper III**, we found that the incidence of reported fatigue and depression was equivalent in the age quartiles, however, antidepressant medication was not as extensively prescribed in patients older than 65 years of age. Under-diagnosis or somatization may be one explanation. It is well established that pain is a common and sometimes the only manifestation of depression especially in women older than 50 years of age (88, 115). Patients with PHPT often report chronic musculoskeletal pain sometimes leading to the deterioration of sleep quality and mental status and subsequently affecting everyday life and the ability to participate in social activities (116-118). In *A key to dissect the triad of insomnia, chronic pain, and depression* a vicious circle including several clinical links and pathophysiological mechanisms are compiled and depicted (97).

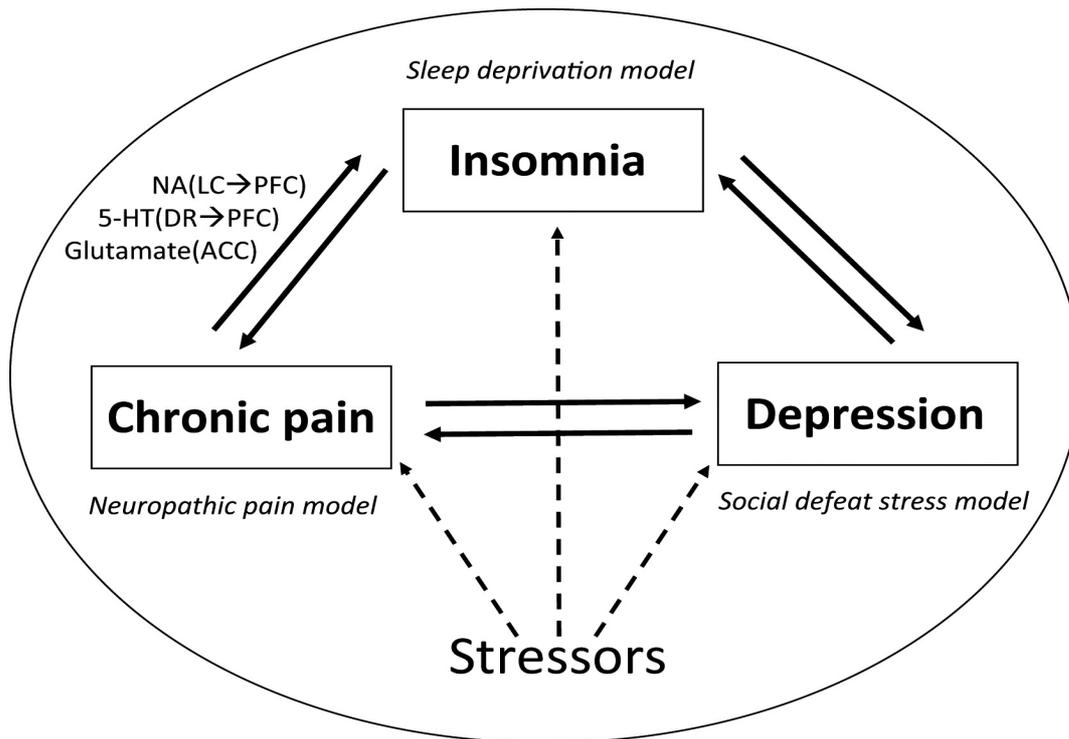


Figure 18. *The viscous pain circles*

Senba E. A key to dissect the triad of insomnia, chronic pain, and depression. *Neurosci Lett.* 2015;589:197-9. Epub 20150107. doi: 10.1016/j.neulet.2015.01.012. PubMed PMID: 25576841.

7.4 PHPT AND THE IMPACT ON ORAL HEALTH

The rationale behind **Paper IV** was partly the previously described associations between PHPT and lesions in the oral cavity and the jaw (13, 60) and furthermore, on the fact that merging studies suggest that osteoporosis is a risk factor, which obviously is an occasional complication in PHPT (119-122). In addition to that, it has been proven that mental illness and mild cognitive impairment negatively affect dental health and vice versa (123-125). Thus, even in this field, the causal relationships are complex and far from fully understood (51).

Judging from the results in **Paper IV**, we could not detect any overall difference between patients and the controls in terms of total dental care visits, number of remaining teeth or dental interventions.

Periodontitis is a major cause of tooth loss in adults (126). Consistent with previously described observations of periodontal lesions associated with PHPT that mainly occurring in the advanced stages of PHPT, we found that patients belonging to the highest S-Ca²⁺ quartile had a markedly increased risk of tooth loss by means of extraction. This would further indicate a connection between the disease severity and oral disorders. It is worth noting, however, that the calcium concentrations generally were not exceptionally high; 1.41(1.45-1.51) mmol/L, which means that patients with moderate hypercalcemia and without mandatory indication for parathyroidectomy were also included in the upper quartile.

Female gender was found to be a risk factor for tooth loss by means of extraction, regardless of serum calcium levels. Many factors may possibly be involved, for example, sex hormones, osteoporosis related to PHPT, more extensive consumption of drugs affecting the oral cavity and socioeconomic aspects that are all beyond reach of our analysis (127).

Paper IV, however, provides new and relevant perspectives in a sparsely studied field and points to beneficial effects through earlier detection of PHPT. By means of this study we aim to encourage further interdisciplinary research in order to increase an awareness of oral comorbidity in PHPT patient and promote the development of preventive routines.

8 STRENGTHS AND LIMITATIONS

Science is a race to capture the truth, sometimes on the run. Based on an as clear hypothesis as possible, variables are studied as precisely as possible to be interpreted and presented as accurately as possible. Studying nonspecific symptoms, by definition involves obvious difficulties.

The main strength in **Papers I and II** is the systematic approach which enabled the analysis of both the effects based on each individual's starting point and of any relationships on a group level. Another advantage was that the panel of validated tests included both subjective and objective measurements. Furthermore, the design also enabled us to analyze the different domains (mental status, cognitive functioning and muscle strength) in relation to each other and we could consequently visualize patterns of how the domains were related. An example of this is how the early improvement of mental state was preceded by long-term effects and improvement on cognition and muscle strength that went hand in hand. The studies' composition also gave us a certain amount of validation of the different tests as it turned out that the results for each domain of the corresponding tests were congruent and pulled in the same direction (HADS, QLQ-C30, PSOM and MoCA). The test model proved to be feasible in clinical praxis and most patients completed the entire protocol.

There are obvious limitations in **Papers I and II**. Most important is the fact that the participants were already planned for parathyroidectomy at the time of inclusion. The indications for surgery varied and nonclassical symptoms were not an explicit criterion for participation. However, after a review of the records, neuropsychiatric symptoms, muscle pain or weakness was reported by the surgeon in a majority of the patients. Furthermore, all patients had already been assessed and judged eligible to benefit from surgical treatment which most probably led to some degree of selection bias. This also limits the generalizability. Furthermore, patients' own expectations of improvement may lead to bias, as well as any potential learning effect after the repeated visits which in turn entails a risk of strengthening the results. Even the referral to a surgeon itself involves a selection and possibly raises expectations. However, the tendency towards better results at follow-up and after as long as six months would advocate against significant inductive bias. Ideally, a randomized study involving multiple disciplines should be performed exclusively on patients with PHPT and non-specific symptoms. However, still the proportion of undiagnosed PHPT cases are difficult to catch (128).

A recent prospective multicenter study revealed a significant long-term overall recovery from non-disease-specific symptoms after parathyroidectomy, in both normocalcemic and hypercalcemic PHPT patients. Physical component scores improved significantly in both groups compared with the preoperative scores, whereas the mental component summary only improved significantly in the hypercalcemia group (51). However, another large study did not show as convincing results. The Scandinavian Investigation on Primary Hyperparathyroidism (SIPH) study is a robustly conducted multicentric prospective randomized study of patients with PHPT aiming to study health effects in patients who have undergone parathyroidectomy or been treated conservatively. Recently published data from the SIPHs material regarding the outcome of QoL pointed in favor of surgical treatment, however the clinical significance was considered minor and insufficient to motivate any changes of current guidelines. Although the study is well conducted, the analysis for this purpose has its shortcomings, partly due to the overall aim of the project which was to study death and a wide range of comorbidities and partly due to a limited cohort size and a relatively large drop-out (15).

The strength of **Paper III** is the large-scale highly comprehensive and valid population data of the population. The longitudinal study design allowed analysis of both the natural course of neuropsychiatric morbidity in untreated PHPT as well as the effects of treatment. The overlapping linkage between several well-validated national population registers, enabled a credible handling of socioeconomic and demographic confounders (78, 82). Dispensing of medication is considered to be a valid proxy to estimate prevalence and incidence of disease in population-based studies (129). Furthermore, the access to information with regards to both diagnoses and drug dispensations combined, provide an overview of the congruence between morbidity and treatment.

There are shortcomings in **Paper III**. Most importantly, which again applies to all four studies, the patients were already selected for treatment by various indications for parathyroidectomy. Investigation or surveillance due to neuropsychiatric conditions or other health problems are likely to lead to selection bias. Low odds for dispensing of treatment for dementia also point towards some bias. For these reasons, the generalizability is limited. This aside, one can expect that a minor proportion also of the controls actually had PHPT which most likely would have weakened the results. Furthermore, since data regarding the doses or the size and number of packages was not available we were not able to carry out an analysis of the magnitude of treatment. Although dispensing of medication has been found to be a valid proxy for morbidity, we cannot say with any degree of certainty that the medications

actually had been consumed, which may lead to misclassification. However, as this fact does not differ between patients and controls, the risk of affecting the results is small.

The main strength of **Paper IV** is that the results of the study provide a completely new knowledge of a topic that has not previously received much attention. In addition, another important strength is that the majority of our patients represented the milder form of PHPT that today constitutes a common disease which makes the results relevant to contemporary characteristics of the disease. The size of the study-population, the validity and the coverage of the registries contributed to the results being reliable (130).

The conclusions that we could draw from the results in **Paper IV** are limited. The observation time was relatively short bearing in mind that long-term complications take time to develop and the frequency of dental health care visits may have affected the results. Neither were the analyses adjusted for comorbidities such as osteoporosis, cardiovascular disease and diabetes or for socio-economics and education, which have probably affected the general trend in the utilization of both dental care and health care. Based on the fact that these are risk factors linked to both PHPT and deteriorated oral health they must be considered confounders and are therefore likely to bias the results (126, 131, 132).

Analyzes of causation or possible biochemical mechanisms are far beyond the scope of this study. **Study IV** primarily makes its contribution as a pilot study that points out the direction towards new areas left to explore in the field of PHPT and oral health.

9 ETHICAL CONSIDERATIONS

Ethical aspects have been considered and discussed at all stages of the studies. The studies have been preceded by planning, definition of research questions and statistical estimations of the number of study participants needed to achieve valid results (133).

Studies I and II required quite extensive and active participation of the study patients. The study medication occasionally caused side effects; none were severe but were sometimes experienced as uncomfortable. Careful handling of both the test performances and data management was required in order to guard the personal integrity of the study participants.

Written informed consent was mandatory for inclusion in **Studies I and II** and the participants were then closely followed to identify eventual adverse effects. Only the individuals in charge of the study, namely one research nurse, two physicians and an external monitor were, following contract signature on *good clinical scientific practice*, permitted to review the identified records.

Studies III and IV included registry-based anonymized data comprised from the national registries and retrieved from the quality register SQRTPA.

Data was pooled by the *National Board of Health and Welfare* and compiled into an anonymised data file in order to ensure the protection and integrity of the individuals involved. This was especially important in the case of **Study III** which contained sensitive information on psychiatric diagnoses, drug use and emigration status etc. For safety reasons, original data for all four studies was kept in a locked storage unit in accordance with the regulations at the *Karolinska University Hospital* and *Karolinska Institutet*. Statistical analysis reports were all based on anonymized data.

10 CONCLUSIONS

- From **Paper I** we concluded that the medical normalization of calcium levels is an appropriate tool that can be used to predict the outcome of non-classical symptoms after parathyroidectomy and can therefore be used in the surgical decision-making process.
- The conclusion from **Paper II** was that the medical normalization of calcium levels is an applicable diagnostic tool for predicting the effect of PTX on cognitive functioning in older adults (≥ 50 years of age) with cognitive deficiency. Our analysis confirms that the potential for cognitive functioning improvement in some elderly patients with PHPT is substantial.
- From the results in **Paper III** we concluded that PHPT contributes to the burden of neuropsychiatric symptoms in some patients. Since the dispensing of medications remained higher, yet with a decreasing trend after parathyroidectomy, we suggest that medication for psychiatric conditions should both be preoperatively assessed and reconsidered following curative surgery.
- In **Paper IV** we concluded that PHPT patients with moderate to severe hypercalcemia, especially women, have increased risk for tooth loss by means of extraction and should thus receive special attention when it comes to oral health. More high-quality research is required in this field.

11 POINTS OF PERSPECTIVE

- The calcimimetic prognostic tool needs to be implemented and validated in terms of clinical routine, ideally with the involvement of endocrinologists and general practitioners. The protocol probably needs to be simplified and optimized to get the most out of it, with the least effort due to lack of time in the clinical everyday life which is the reality in which we operate.
- Nonclassical symptoms of PHPT such as depression, mental and muscular fatigue, mild cognitive impairment and oral health as discussed above are indeed interrelated and constitutes a tangled network. More prospective studies are required to better understand the characteristics of PHPT patients affected by mental symptoms mild cognitive decline and the clinical results of both conservative treatment as well as treatment with parathyroidectomy.
- In addition, randomized studies that compare treatment with parathyroidectomy and alternative interventions such as physical and social activity could be of great value. Multicentric and multidisciplinary collaborations would be ideal for these type of studies.
- Furthermore, continued epidemiological studies of nonclassical aspects of PHPT should continue. Swedish registers, when used correctly, constitute a goldmine for epidemiological research. The relationships between treatment choice and outcome related to socioeconomic, geography, gender, age and related comorbidity such as mental illness and pain are largely unexplored. Increased knowledge would potentially affect the indications for treatment and contribute to improved preventive treatment strategies.

- A goal is to increase the knowledge about nonclassical symptoms among colleagues from all specialties who treat patients with PHPT and to promote more homogeneous assessments and more individually tailored treatment of patients with PHPT and nonclassical symptoms.
- Available and consistent patient information about the disease and alternative treatments as well as what expectations are reasonable after parathyroidectomy or conservative treatment.
- More pre clinical studies on the molecular biological impacts of the disease on the nervous system in particular are of interest. A greater understanding of the condition may lead to a better identification of risk factors that can be targeted for treatment.
- The impacts of oral manifestations in PHPT remain largely an unexplored area of research. There are large gaps to be filled. Future epidemiological and prospective observational studies need to look at relevant comorbidities, socioeconomic variables and drug exposure in order to explore any possible connections and causes.

12 SAMMANFATTNING PÅ SVENSKA

Studie I

Bakgrund: Primär hyperparatyroidism (PHPT) orsakas vanligen av en godartad bisköldkörteltumör som resulterar i en störd kalciumomsättning och förhöjda kalciumnivåer i blodet. Den enda botande behandlingen är paratyroidektomi (PTX) vilket rekommenderas vid svår sjukdom, ålder <50 år eller utveckling av komplikationer, t.ex. osteoporos eller njursten. PHPT är ofta behäftat med försämrad livskvalitet till följd av ospecifika symtom i form av nedstämdhet, nedsatt ork samt muskelsvaghet som också kan bero på andra orsaker. Att adressera dessa och förutsäga nyttan med paratyroidektomi avseende kognition, psykisk ohälsa och muskuloskeletala symtom är därför ett diagnostiskt dilemma.

Syfte: Att utforska om normalisering av kalcium genom korttidsbehandling med kalciumsänkande läkemedel (kalcimimetika) kan utnyttjas som ett diagnostiskt verktyg för att förutsäga effekterna efter paratyroidektomi.

Metod: Interventionell observationsstudie. 110 patienter planerade för paratyroidektomi inkluderades. En testpanel bestående av validerade tester genomfördes före operation under pågående studiemedicinering samt 6 veckor och 6 månader efter paratyroidektomi för bedömning avseende förändring av symtom och livskvalitet. Resultaten under studiemedicineringen jämfördes med de kort- och långtidsresultaten efter kirurgisk behandling.

Resultat: Alla patienter normaliserades i sina kalciumnivåer under pågående studiemedicinering. Lättare biverkningar var vanliga, ingen drabbades av allvarlig biverkning. Förbättring av kognition, psykisk hälsa och muskelstyrka under studiemedicinering överensstämde väl med de postoperativa resultaten (positiva prediktiva värden 74 - 96%).

Studie II

Bakgrund: Det åldrade nervsystemet är sårbart och ospecifika symtom av PHPT är svårvärderade och kan lätt förväxlas med naturligt åldrande. Potentialen till förbättring av förekommande kognitiv svikt och nyttan med paratyroidektomi hos äldre patienter har varit omdiskuterad.

Syfte: Att utvärdera korttidsbehandling med kalcimimetika som ett prognostiskt verktyg samt analysera effekter på kognitiv funktion efter paratyroidektomi hos äldre patienter med mild kognitiv svikt.

Metod: Subanalys av resultaten hos 35 patienter i åldern ≥ 50 (19 patienter ≥ 70 år) med mild kognitiv svikt, *The Montreal Cognitive Assessment* < 26 (MoCA) identifierade från studie I.

Resultat: 17 patienter (10 ålder ≥ 70 år) uppnådde normala poäng (MoCA ≥ 26) sex månader postoperativt. Förutsägbarhet till förbättring varierade mellan 80% och 94%. Metoden var sämre (22 - 92% träffsäkerhet) för att utesluta möjlig förbättring efter paratyroidektomi.

Studie III

Bakgrund: Psykiska symtom och mild kognitiv svikt förekommer ofta vid PHPT.

Omfattningen av psykisk ohälsa och nedsatt kognitiv förmåga relaterade till obehandlad PHPT i befolkningen är okänd.

Syfte: Att undersöka användandet av läkemedel mot psykiska symtom och demens hos patienter med obehandlad PHPT i relation till bakgrundsbefolkningen och att studera eventuella effekter på läkemedelsanvändningen efter kirurgisk behandling.

Metod: Registerbaserad tillbakablickande (före paratyroidektomi) fall-kontrollstudie respektive framåtblickande (efter paratyroidektomi) kohortstudie. Genom logistisk regression och Poisson regressionsmodell analyserades läkemedelsanvändning före och efter kirurgisk behandling hos 8279 patienter som opererats med paratyroidektomi under åren 2008 - 2017 i jämförelse med 82 790 individer ur bakgrundsbefolkningen matchade till kön, ålder och landsting (1:10).

Resultat: Användningen av psykofarmaka var tilltagande mer omfattande hos patienter med obehandlad PHPT. Läkemedelskonsumtionen kvarstod förhöjd men stabiliserades eller tenderade att minska efter paratyroidektomi.

Studie IV

Bakgrund: Förändringar i tandbenet och destruerande tumörer i käken är historiskt kända komplikationer till svår PHPT. Vilken inverkan obehandlad, numera vanligen biokemiskt mild PHPT har på tandhälsan har hittills varit okänt.

Syfte: Att analysera incidensen av odontologisk samsjuklighet och tandvårdskonsumtion vid obehandlad PHPT jämfört med normalbefolkningen.

Metod: Registerbaserad kohortstudie. Tandvårdsingrepp och besöksfrekvens (IRR) hos patienter som opererats med paratyroidektomi (n = 982) jämfördes med kontroller från bakgrundsbefolkningen (n = 2944).

Resultat: Konsumtionen av tandvård var likartad hos patienter och kontroller. Patienter med joniserat kalcium $\geq 1,51$ mmol / L hade en markant ökad risk för tandextraktion (IRR 1,85

(1.40-2.46)). Kvinnor med PHPT genomgick tandextraktion i högre utsträckning än manliga patienter (IRR 1,34 [1.03-1.74]).

Avhandlingens slutsatser i korthet

- Korttidsbehandling med kalciumsänkande läkemedel hos patienter med PHPT är ett tillämpbart verktyg för att förutsäga långtidseffekterna på kognition, psykisk hälsa och muskelsvaghet efter paratyroidektomi inför beslut om kirurgisk behandling alternativt att avstå operation.
- Medicinsk normalisering av kalciumnivåer är ett tillämpligt diagnostiskt verktyg för att förutsäga långtidseffekterna av paratyroidektomi på kognition hos äldre med kognitiv svikt. Vår analys bekräftar att potentialen för förbättring av kognitiv funktion är betydande även hos äldre patienter.
- PHPT är hos en del patienter förenat med en förhöjd börda av psykiska symptom i jämförelse med bakgrundsbefolkningen. Eftersom uttagen av läkemedel mot psykiska symptom förblev högre, med en minskande trend efter paratyroidektomi, föreslår vi att medicinering mot psykisk ohälsa bör utvärderas hos patienter med PHPT och omprövas efter botande kirurgi.
- PHPT-patienter med måttligt till kraftigt förhöjda kalciumnivåer, i synnerhet kvinnor, förefaller ha en ökad risk för tandförlust genom utdragning och bör därför ägnas särskild uppmärksamhet när det gäller munhälsa. Mer högkvalitativ forskning behövs inom detta område.

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