Impact of Surgery for Primary Hyperparathyroidism

Nilsson, Martin

2024

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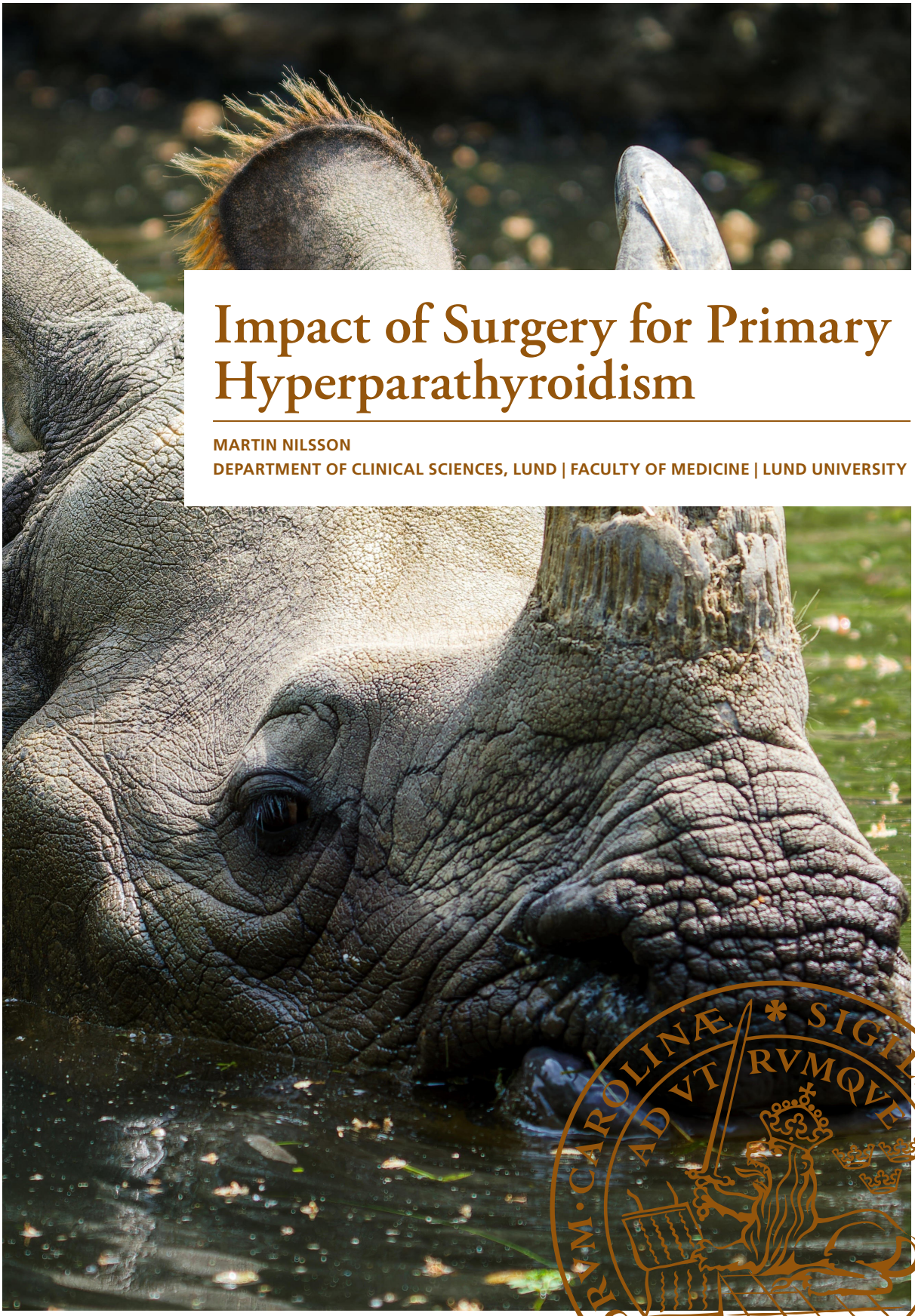

Impact of Surgery for Primary Hyperparathyroidism

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Impact of Surgery for Primary Hyperparathyroidism

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

at the Faculty of Medicine at Lund University
to be publicly defended at Skåne University Hospital, Lund
Entrégatan 7, Föreläsningssal 1,
5th of April at 13.00.

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Organization: LUND UNIVERSITY, Faculty of Medicine, Department of Clinical Sciences, Lund

Document name: Doctoral Dissertation **Date of issue:** 2024-04-05

Author(s): Martin Nilsson, MD **Sponsoring organization:**

Title and subtitle: Impact of Surgery for Primary Hyperparathyroidism

Abstract:

Primary hyperparathyroidism, pHPT, is an endocrine disease with complications that range from osteoporosis and fractures, nephrolithiasis, cardiovascular disease, to neuromuscular, neurocognitive and neurobehavioral symptoms. The presentation of pHPT has shifted towards milder disease, with few overt complications. It is unclear whether patients with mild pHPT benefit from surgery. This thesis primarily aims to evaluate disease complications in relation to surgery for pHPT. Secondly, to establish predictors for treatment effect following surgery.

Paper I: A registry-based nation-wide investigation of mortality following surgery for pHPT in Sweden by cross-linking a cohort of 5009 patients operated for pHPT 2003–2013 from SQRTPA and 14983 controls with the National Board of Welfare. Patients with pHPT did not have increased mortality compared to controls. Among patients, total serum calcium was associated with mortality.

Paper II: The national cohort described in Paper I was investigated for fracture incidence before and after surgery, finding increased fracture incidence among patients with pHPT up to four years before surgery, which normalized postoperatively.

Paper III: A local cohort of 709 consecutive patients operated for pHPT 1989–2013 and 2112 controls were cross-linked with the National Board of Welfare, finding that 24-hour urine calcium predicted reduced fracture incidence and BMD recovery postoperatively.

Paper IV: The national cohort described in Paper I was investigated for the incidence of cardiovascular diseases before and after successful surgery, finding increased incidence of transient ischemic attacks, heart failure, mitral valve stenosis, which all were reduced after surgery, and aortic aneurysms. Total serum calcium was associated with acute myocardial infarction, coronary artery disease and heart failure postoperatively.

In summary, contemporary patients benefit from surgery in terms of fractures and cardiovascular morbidity, and survival is equal to population controls. Serum calcium predict mortality and cardiovascular morbidity postoperatively, whereas 24-hour urine calcium predict reduced fractures and BMD recovery.

Key words: primary hyperparathyroidism, parathyroidectomy, mortality, fractures, bone mineral density, cardioavscular disease, calcium, parathyroid hormone, adenoma, multiglandular disease

Classification system and/or index terms (if any) Supplementary bibliographical information

Language: English **ISSN and key title:** 1652-8220

ISBN: 978-91-8021-530-5

Recipient's notes **Number of pages:** 118

Price Security classification

Signature Date 2024-02-22

Impact of Surgery for Primary Hyperparathyroidism

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UNIVERSITY

Faculty of Medicine, Doctoral Dissertation Series 2024:37
Department of Clinical Sciences, Lund

ISBN 978-91-8021-530-5
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2024

Till Selma, Kerstin, Vidar & Gro

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Abstract

Primary hyperparathyroidism, pHPT, is an endocrine disease with complications that range from osteoporosis and fractures, nephrolithiasis, cardiovascular disease, to neuromuscular, neurocognitive and neurobehavioral symptoms. The presentation of pHPT has shifted towards milder disease, with few overt complications. It is unclear whether patients with mild pHPT benefit from surgery. This thesis primarily aims to evaluate disease complications in relation to surgery for pHPT. Secondly, to establish predictors for treatment effect following surgery.

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In summary, contemporary patients benefit from surgery in terms of fractures and cardiovascular morbidity, and survival is equal to population controls. Serum calcium predict mortality and cardiovascular morbidity postoperatively, whereas 24-hour urine calcium predict reduced fractures and BMD recovery.

Populärvetenskaplig sammanfattning

Primär hyperparathyroidism, pHPT, är en relativt vanlig endokrinologisk sjukdom som karaktäriseras av förhöjd utsöndring av bisköldkörtelhormon, PTH, i förhållande till kalciumnivån i blodet. Sjukdomen är vanligast hos äldre och kvinnor, och orsakas oftast av en godartad tumör i en bisköldkörtel (80–85% av fallen) eller mer diffus förstoring av flera bisköldkörtlar.

Bisköldkörtlarnas fysiologiska uppgift är att upprätthålla normala kalciumnivåer i blodet genom att utsöndra PTH. Detta hormon höjer kalciumnivåerna genom att öka konverteringen av D-vitamin till aktiv form, vilket i sin tur höjer upptaget av kalcium från tarmen, minskar utsöndringen av kalcium till urinen och påverkar benomsättningen.

Sjukdomen kan orsaka benskörhet och frakturer, njursten och muskelsvaghet, men också kognitiva besvär, nedstämdhet och hjärtkärl-sjukdom. Tidigare upptäcktes sjukdomen oftast i avancerade stadier med uttalade symptom och följdtillstånd. De senaste 50 åren har utveckling gått mot att diagnosen ställs vid avsevärt mildare sjukdom, ofta utan några specifika symptom eller tecken till följdtillstånd.

Den enda botande behandlingen är att operera bort den eller de sjuka bisköldkörtlarna. Medicinsk behandling (cinacalcet) kan ges för att lindra symptom vid hög kalciumnivå, men påverkar inte utvecklingen av benskörhet, frakturer, njursten eller hjärtkärl-sjukdom.

De flesta undersökningarna av behandlingsresultat vid kirurgi för pHPT är gjorda på patienter med avsevärt mer avancerad sjukdom än vad de flesta patienter har idag. Därför kan vi inte med säkerhet säga att dagens patienter har lika stor nytta av operation. Syftet med denna avhandling är att undersöka hur risken för förtida död, frakturer, benskörhet och hjärtkärl-sjukdom påverkas av operation, samt om vi kan förutsäga vilka patienter som har mest nytta av operation.

I den första delstudien undersöktes dödligheten hos patienter som opererats för pHPT jämfört med kontrollpersoner av samma kön, ålder och bostadsort. Patienterna hade inte ökad dödlighet jämfört med kontrollpersonerna, men bland patienterna hade de med högre kalciumnivå i blodet ökad dödlighet.

I den andra delstudien undersöktes risken för frakturer före och efter operation för patienter med pHPT, jämfört med kontrollpersoner av samma kön, ålder och bostads-

ort. Frakturrisken var ökad upp till fyra år före operation, men minskade efter operation till samma nivå som för kontrollpersonerna.

I den tredje delstudien undersöktes faktorer för att förutsäga risken för frakturer och sannolikheten för att bentätheten förbättras efter operation för pHPT. Förhöjd mängd kalcium i urin visade sig kunna förutsäga både minskad risk för frakturer efter operation och ökad bentäthet.

I den fjärde delstudien undersöktes risken för hjärtkärl-sjukdom före och efter operation för patienter med pHPT, jämfört med kontrollpersoner av samma kön, ålder och bostadsort. Risken för TIA var förhöjd före operation, liksom risken för att utveckla hjärtsvikt eller mitralisstenos, och dessa risker minskade efter operation. Risken att diagnosticeras med pulsåderbråck på aorta var förhöjd hos patienterna, med det påverkades inte av operation. Bland patienterna hade de med högre kalciumnivå i blodet ökad risk för akut hjärtinfarkt, kranskärlssjukdom och hjärtsvikt efter operation.

Sammanfattningsvis har nutida patienter med pHPT nytta av kirurgisk behandling i form av minskad risk för frakturer och hjärt-kärlsjukdom. Efter operation är risken för förtida död inte ökad. Bland patienter är risken för hjärtkärl-sjukdom och förtida död störst bland dem med högst kalciumnivå i blodet. Förhöjd mängd kalcium i urinen förutsäger både minskad frakturrisk och förbättrad bentäthet, och ska därför inte förbises vid beslut om kirurgisk behandling.

List of papers

Paper I

Nilsson M, Ivarsson K, Thier M, Nordenström E, Bergenfelz A, Almquist M. Mortality after surgery for primary hyperparathyroidism: results from a nationwide cohort. *The British journal of surgery* 2021;108(7): 858-863.

Paper II

Nilsson M, Ståhl E, Åkesson KE, Thier M, Nordenström E, Almquist M, Bergenfelz A. Reduced fracture incidence in patients having surgery for primary hyperparathyroidism. *Clinical endocrinology* 2022;97(3): 276-283.

Paper III

Nilsson M, Åkesson KE, Thier M, Nordenström E, Almquist M, Bergenfelz A. 24-hour urine calcium predicts reduced fracture incidence and improved BMD after surgery for primary hyperparathyroidism. *Submitted.*

Paper IV

Nilsson M, Smith JG, Thier M, Nordenström E, Almquist M, Bergenfelz A. Cardiovascular morbidity in patients undergoing surgery for primary hyperparathyroidism. *Manuscript.*

Author's contribution to the papers

Paper I

Planning the project, filing applications for ethical review and data collection from SQRTPA and cross-linking with Statistics Sweden and National Board of Welfare. Data validation and statistical analysis. Drafting of the manuscript and revision.

Paper II

Planning the project, filing applications for ethical review and data collection from SQRTPA and cross-linking with Statistics Sweden and National Board of Welfare. Data validation and statistical analysis. Drafting of the manuscript and revision.

Paper III

Planning the project, filing applications for ethical review and cross-linking with Statistics Sweden and National Board of Welfare. Data validation and statistical analysis. Drafting of the manuscript and revision.

Paper IV

Planning the project, filing applications for ethical review and data collection from SQRTPA and cross-linking with Statistics Sweden, National Board of Welfare, SwedeHeart and RiksStroke. Data validation and statistical analysis. Drafting of the manuscript and revision.

Thesis at a glance

Paper	Aim	Method	Results	Conclusion
I	Evalutate mortality in patients after surgery for pHPT.	National cohort of pHPT patients with matched controls were cross-linked with the Cause of Death Register.	The mortality was not increased but related to total serum calcium, the mortality rate 30% higher if calcium is above 2.82 mmol/L.	Contemporary patients do not have increased mortality following surgery for pHPT, but mortality among patients is related to the level of hypercal–caemia.
II	Evaluate fracture risk in patients having surgery for pHPT.	National cohort of pHPT patients with matched controls were cross-linked with the National Patient Register.	Fracture incidence was increased up to 4 years before surgery, normalizing postoperatively. Fracture incidence was not related to disease-specific factors.	Contemporary patients with pHPT have an increased risk of fratures, which is reversed by surgery.
III	Evaluate predictors for fracture risk and BMD recovery in patients having surgery for pHPT.	Local cohort of pHPT patients with matched controls were with the National Patient Register. Detailed preoperative bio-chemistry and BMD, repeated at 1-year follow-up.	24-hour urine calcium predicted reduced fractures and BMD recovery following surgery.	The level of 24-hour urine calcium should not be neglected in counselling on surgical treatment.
IV	Evaluate cardio-vascular morbidity in patients having surgery for pHPT.	National cohort of pHPT patients with matched controls were cross-linked with the National Patient Register, SwedeHeart and RiksStroke.	TIA, heart failure and mitral valve stenosis were increased preoperatively, and decreased following surgery. Total serum calcium was associated with AMI, coronary artery disease and heart failure.	Contemporary patients with pHPT suffer increased cardiovascular morbidity, which is reduced by surgery. Higher total serum calcium is suggestive of higher cardiovas-cular risk in spite of surgery.

Abbreviations

ALP	alkaline phosphatase
AMI	acute myocardial infarction
BMD	bone mineral density
CCS	Charlson's comorbidity score
CDK	chronic kidney disease
$CI_{95\%}$	95% confidence interval
CTX	C-terminal cross-linking telopeptides of type I collagen
CV	coefficient of variance
CVD	cardiovascular disease
CVI	cerebrovascular insult, stroke
DXA	dual energy x-ray absorptiometry
GFR	glomerular filtration rate
HR	hazard ratio, effect measure in Cox regression
IQR	interquartile range
IRR	incidence rate ratio
LSC	least significant change
LVH	left ventricular hypertrophy
LVM	left ventricular mass
OR	odds ratio, effect measure in logistic regression
P1NP	N-terminal pro-peptides of type 1 procollagen
pHPT	primary hyperparathyroidism
PTH	parathyroid hormone
RCT	randomized controlled trial

SD	standard deviation
sHPT	secondary hyperparathyroidism
TIA	transient ischemic attack

Introduction

Primary hyperparathyroidism, pHPT, is a common endocrine disorder characterized by inappropriately elevated parathyroid hormone, PTH, in relation to serum calcium levels.

pHPT has an estimated incidence of between 16 and 120 per 100 000 person-years in Western industrialized countries.[1-3] In Swedish general population surveys, the prevalence has been estimated to 0.21–0.36%.[4] In UK and US population- and insurance claims-based studies, prevalence was 0.23–0.90% in women, and 0.09–0.41% in men, with a female to male ratio of 2.5.[3, 5] Incidence and prevalence is also markedly higher among the elderly, with prevalence reported to be as high as 2–5% among postmenopausal women.[6, 7]

The only curative treatment of pHPT is parathyroid surgery with extirpation of the glands secreting PTH excessively, a procedure called parathyroidectomy. In 2022, 14.7 patients per 100 000 inhabitants had parathyroid surgery for pHPT in Sweden.[8]

Symptomatic hypercalcaemia can be managed with calcimimetic agents, such as cinacalcet, but they have proven no effect on long-term end-organ complications such as mortality, osteoporosis, fractures, nephrolithiasis or cardiovascular disease, CVD. Oral bisphosphonates and other anti-resorptive agents, such as denosumab, can be used to reduce the impact of pHPT on bone mineral density, BMD, in conservatively managed patients.[9]

It is controversial whether patients with mild or asymptomatic pHPT should be offered parathyroidectomy, as the general quality of evidence is low for surgical treatment. There are only a few, relatively small, randomized controlled trials evaluating the effect of parathyroidectomy on pHPT disease complications. Current international guidelines[10] are largely based on observational studies, that often were conducted in patients with considerably more advanced disease than contemporary patients.

Historical perspective

The parathyroid glands are the most recently discovered organs of the human body. First described in an Indian Rhinoceros by Sir Richard Owen in 1852,[11] and

subsequently in man by the great German pathologist Rudolf Virchow in 1863,[12] they were initially thought to be part of the thyroid gland, and their physiological role was unknown. Ivar Sandström, then a medical student in Uppsala, was the first to describe them as separate glands in man, dog, cat, rabbit, ox, and horse in 1880.[13]

The thyroid gland became an early target for surgical procedures after the introduction of ether anaesthesia in 1846,[14] and aseptic surgery in 1865.[15] Previously, surgery had generally been restricted to radical measures either to relieve excruciating pain (urinary tract stone surgery), or to remove immediate threats to life (amputation of limbs, drainage of abscesses). Speed and effectiveness had been the highest virtues for a surgeon, and a typical procedure lasted only a few minutes.

Theodor Billroth, Theodor Kocher and William Halsted, among several others, developed thyroid surgery during the late 19th century. The thyroid gland was considered not to be a vital organ, and thus it was quite unexpected when serious complications after total thyroidectomy, such as severe seizures, tetany, were observed. Halsted found that that the meticulous dissection by Kocher was less prone to result in tetany, compared to Billroth's surgical technique. In subsequent publications, he demonstrated that tetany would be relieved by injections of parathyroid extract, that transplantation of parathyroid glands reduced the risk of tetany, as did staged surgery (lobectomy rather than total thyroidectomy) and ligation of the thyroid arteries distal to the parathyroid.[16]

Meanwhile, the French physiologist Eugène Gley had shown in 1892 by experimental surgery in rabbits, that concomitant removal of the thyroid and the external parathyroid glands produced lethal tetany in 90% of cases. Subsequently, the Austrian histologist Alfred Kohn demonstrated in 1895–1896 that cats and rabbits have four parathyroid glands, one pair external to the thyroid gland and one pair located intrathyroidal. The Italian pathologists Giulio Vassale and Francesco Generali confirmed in 1896 that removal of all four parathyroid glands in cats and dogs produced lethal tetany.[17]

In 1891, one of Virchow's pupils, the pathologist Friedrich Daniel von Recklinghausen, was the first to systematically describe a debilitating skeletal disorder, *osteitis fibrosa cystica*, which is the most extreme variant of skeletal disease in primary hyperparathyroidism. He described the case of a 40-year old mason, in clinical course and *post mortem*. In one-and-a-half year, the patient was hospitalized twice for traumatic fractures (first a probable left hip fracture after a 3-m fall, and then a clavicle fracture after minor trauma). During the second hospitalization, he had a spontaneous fracture of his right femur while in bed. The skeletal pain and deformities increased, and the patient turned cachectic. In the autopsy, von Recklinghausen described multiple skeletal deformities, fractures, fibrosis, hematogenous pigment, cysts, and conglomerates of giant cells. He also described what most probably was a very enlarged left inferior parathyroid gland (the size of the thyroid), but he did not make any connection with the

skeletal disease, which he deemed as vascular in origin. In a similar autopsy case in 1904, Max Askanazy also described advanced *osteitis fibrosa cystica* together with a tumorous left-sided parathyroid, measuring 4.5 x 2 x 2 cm.[17]

The physiology of the parathyroid glands remained elusive. However, the Austrian pathologist Jacob Erdheim conducted a series of experiments on rats where he removed all parathyroid glands. In the animals that survived the following tetany, he observed altered enamel and dentin of the incisor teeth, which turned fragile and deformed. He also did a series of autopsies on patients with fatal tetany after thyroidectomy, without finding any remnant of parathyroid tissue. In a separate study on patients with *osteomalacia* (an acquired skeletal disease characterized by impaired skeletal mineralization due to dietary deficiency of Vitamin D, calcium or phosphorus, or malabsorption), Erdheim found enlarged parathyroid glands. From this, he concluded that the parathyroid glands must have a role in the calcium metabolism, and that parathyroid enlargement in skeletal disease was probably compensatory.[17]

All were not convinced that this applied to *osteitis fibrosa cystica*. Friedrich Schlagenhaufer, another Austrian pathologist, reported in 1915 about two autopsy cases of parathyroid tumour and *osteomalacia*, and one of them also with *osteitis fibrosa cystica*, suggesting removal of the parathyroid tumour as treatment of the skeletal disease. In a compilation of 17 previously publicized cases of *osteitis fibrosa cystica*, Siegfried Hoffheinz, found that in 12 cases, there was a single enlarged tumorous parathyroid gland, whereas in the remaining five cases there were 2–4 enlarged glands.[17]

In 1925, the Austrian surgical resident Felix Mandl admitted a 38-year old man with long-standing *osteitis fibrosa cystica*, which previously had been treated with parathyroid extract injections Having tried transplanting parathyroid glands from an accident victim without result, Mandl performed a surgical neck exploration, finding a 2.5 x 1.5 x 1.2 cm parathyroid tumour which was removed. Postoperatively, the patient improved dramatically with reduced pain, improved walking, increased density at skeletal x-ray examination and reduced urine calcium. Mandl's publication radically changed the perception of parathyroid pathophysiology, with *osteitis fibrosa cystica* as a disease complication rather than the cause of parathyroid enlargement, and the potential for surgical treatment.[17, 18]

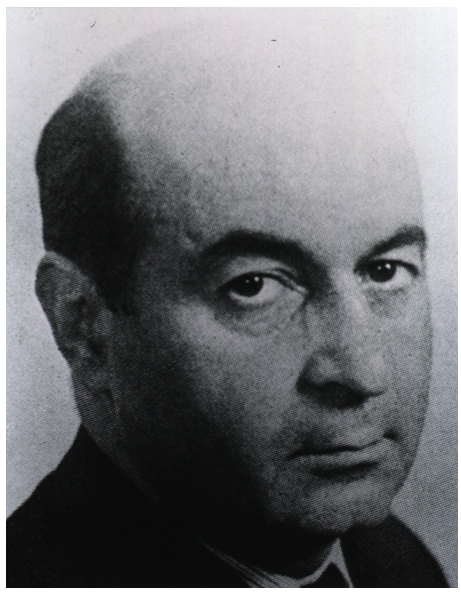

Figure 1 & 2. Ivar Sandström (1852–1889) and Felix Mandl (1892–1957).

Anatomy and embryology

The parathyroid glands are usually oval, bean shaped or spherical and typically reside on the dorsal aspect of the thyroid gland. They are yellow-brown-reddish in colour, and a normal parathyroid gland measures about 6 x 4 mm. The mean weight is approximately 30 mg, varying depending on total body weight and composition.[19] The number of glands is variable, as their precise anatomical location. The superior parathyroid gland originates from the fourth pharyngeal pouch, whereas the inferior gland originates from the third pharyngeal pouch together with the thymus.

In a Swedish autopsy study of 503 deceased individuals, 84% had four parathyroid glands, which were located symmetrically in 80%. Of the deceased, 13% had at least one supranumerous gland, in most cases located in the thymus. The superior parathyroid gland is typically located in the area craniodorsal to the intersection between *arteria thyroidea inferior* and *nervus laryngeus recurrens*, whereas the most common position of the inferior parathyroid gland is in the region caudal to the artery-nerve intersection between the inferior thyroid pole and thymus. The inferior parathyroid gland is generally more ventral in relation to the superior gland, but can be located anywhere along its migration path from the pharynx.[20]

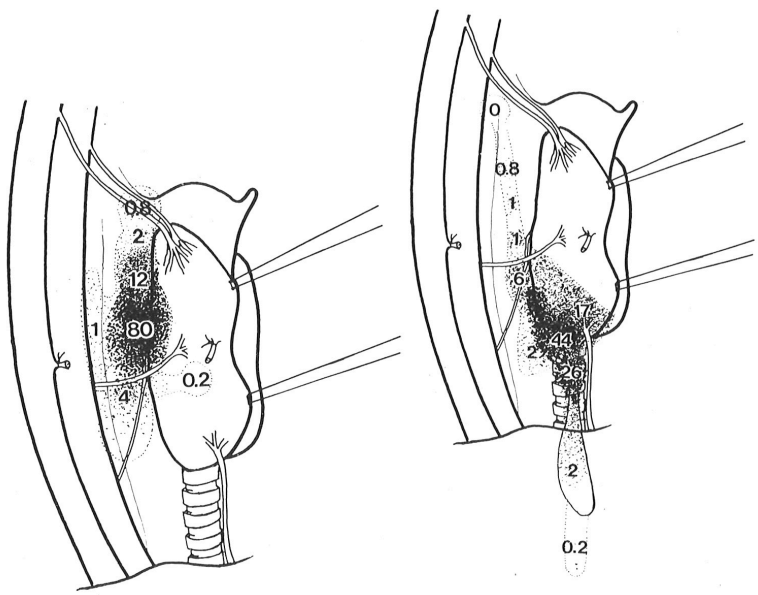

Figure 3. Locations of the superior and inferior parathyroid glands.
The more common locations are indicated by the darker shading. The numbers represent the percentages of glands found at the different locations.
From Åkerström G et al (1984), Surgical anatomy of human parathyroid glands. Surgery. 95(1):14-21. Reproduced with permission from Elsevier.

Physiology

The parathyroid glands maintain the calcium homeostasis. Serum calcium is closely kept within the range 2.15–2.50 mmol/L in healthy adult subjects (ionized calcium 1.15–1.33 mmol/L).[21] About 50% of the extracellular calcium is free, or ionized; the remaining is either protein-bound (40%) or complexed with anions (bicarbonate, phosphate, lactate and citrate).[22] Symptoms of hypocalcaemia include paraesthesia, muscle spasms and tetany, whereas hypercalcaemia is characterized by muscle weakness, reduced gastrointestinal motility and cognitive impairment.[23]

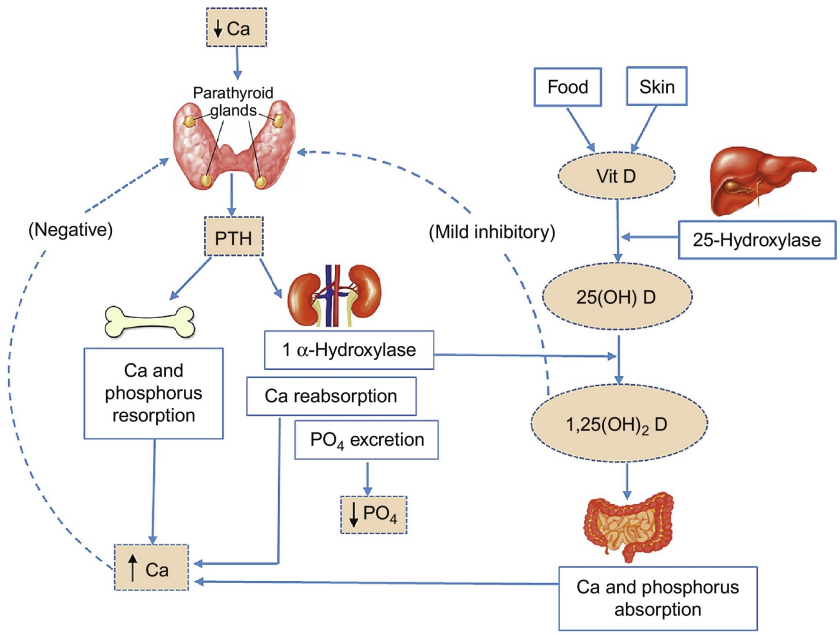

Figure 4. Schematic of calcium homeostatis.
Solid line represents stimulatory interaction, *dashed line* indicates negative feedback.
From Song, L. (2017). Chapter One - Calcium and Bone Metabolism Indices. Advances in Clinical Chemistry. G. S. Makowski, Elsevier. 82: 1-46. Reproduced with permission from Elsevier.

The G-protein coupled calcium-sensing receptor, CaSR senses the level of extracellular calcium. This receptor is found on the cell surface of parathyroid cells, renal tubuli cells, thyroid C-cells, Vitamin D-producing cells, osteoblasts, osteoclasts and calcium-absorbing cells of the intestinal mucosa.[23]

When extracellular ionized calcium decreases below the set-point of the CaSR, the parathyroid cells secrete the peptide hormone PTH 1–84, the active metabolite of pre-pro-PTH 1–115. PTH binds to the PTH receptor, PTH1R, which raises intracellular cyclic

AMP and activate phospholipase C. In renal tubuli cells, this increases renal calcium resorption, renal excretion of phosphate and the conversion of 25-OH Vitamin D to the active form 1,25-$(OH)_2$ Vitamin D through 1α-hydroxylase which increases intestinal absorption of calcium. Prolonged increase in the levels of PTH induces activation of osteoclasts, resulting in bone resorption.[22, 24]

On the contrary, when extracellular calcium exceeds the set-point of CaSR, intracellular calcium is increased which results in degradation of PTH, reduced transcription of pre-pro-PTH, and inhibited PTH secretion and proliferation of the parathyroid cells. 1,25$(OH)_2$-Vitamin D and derangement in the magnesium homeostasis also influence PTH secretion.[22, 23]

Pathobiology

Sporadic pHPT is caused by either a monoclonal expansion, in 80–85% of cases a single adenoma or very rarely parathyroid carcinoma, or in remaining cases a polyclonal expansion with multiple adenomas or hyperplasia, which can be both nodular and diffuse.[25, 26] The most frequently involved genes in sporadic adenomas pHPT are *MEN1* (12–35% of cases) and *CCDN1* (20–40% of cases). *MEN1* code for menin, which regulate transcription and cell proliferation, and *CCDN1* code for cyklin D1, a regulator of the cell cycle progression.[27]

The set-point of CaSR is elevated, which results in excessive secretion of PTH, causing elevated serum calcium by increased bone resorption, increased conversion of 25-OH Vitamin D into 1,25-$(OH)_2$ Vitamin D, and increased absorption of calcium from the gut. The excretion of calcium in urine is also typically elevated as an effect of increased extracellular calcium.[27]

Heterozygotic germline mutations in the *CASR*, coding CaSR, lead to familial hypocalciuric hypercalcaemia, FHH, type 1, characterized by elevated PTH and serum calcium, a differential diagnosis to PHPT. In contrast to pHPT, patients with FHH have very low urinary excretion of calcium. Homozygotic, or heterozygous compound mutations in the *CASR*, cause neonatal severe hyperparathyroidism, which is lethal. FHH type 2 and 3 are caused by mutations in *GNA11* and *AP2S1*, respectively.[27]

There are several hereditary syndromes associated with pHPT. Multiple endocrine neoplasia 1, or MEN1, is caused by an inactivating mutation of tumour suppressor gene *MEN1*. There is a very high penetrance for pHPT (90%), and other associated tumours are pituitary, neuroendocrine tumours in pancreas and the intestine, adrenocortical tumours, facial angiofibromas, collagenomas and lipomas. MEN2A is caused by an activating mutation of the *RET* proto-oncogene, giving rise to pHPT in 30% of

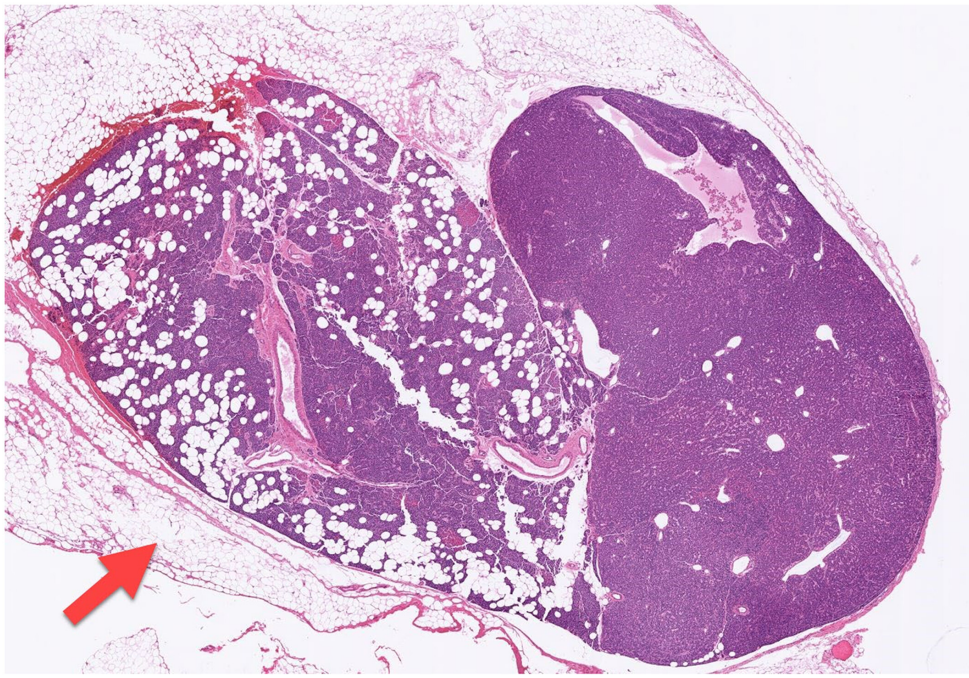

Figure 5. Parathyroid adenoma, chief cell type.
Note normal rim of parathyroid cellularity on left noted with red arrow.
From Perrier N et al (2022), Surgical Aspects of Primary Hyperparathyroidism. J Bone Miner Res, 37: 2373-2390. Reproduced with permission from Oxford University Press on behalf of ASBMR.

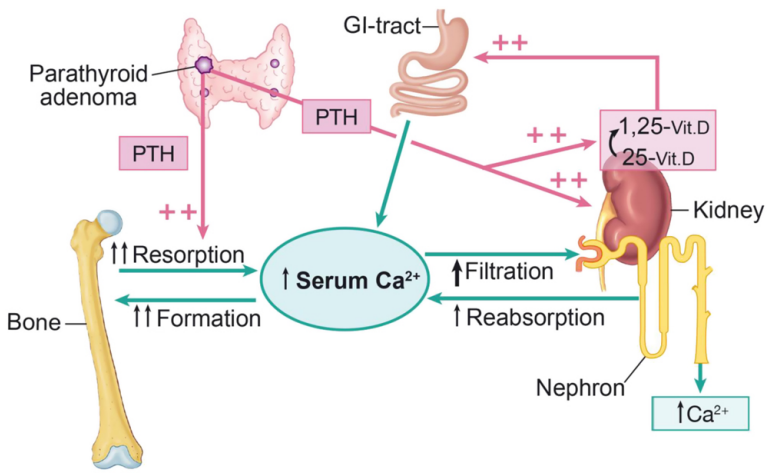

Figure 6. Overall calcium homeostasis in primary hyperparathyroidism.
Reproduced under the CC-BY licence from Bollerslev J et al (2019), MANAGEMENT OF ENDOCRINE DISEASE: Unmet therapeutic, educational and scientific needs in parathyroid disorders. Eur J Endocrinol, 181(3):P1-P19.

patients. Otherwise, MEN2A is characterized by medullary thyroid cancer and pheochromocytomas. MEN4 was recently described, caused by a mutation in the *CDKN1* gene, which codes for CDKI, another regulator of the cell cycle. MEN1, MEN2A and MEN4 all give rise to multiglandular hyperplasia. Hyperparathyroidism-Jaw tumour syndrome, HPT-JT, caused by an inactivating mutation of the tumour suppressor gene *CDC73*, give rise to parathyroid adenomas carcinomas (15%), ossifying jaw fibromas, renal cysts and nephroblastoma.[26, 28]

Previous exposure to neck irradiation and long-term use of oral lithium, typically administered for mental stabilizing in connection to affective disorders, are risk factors for pHPT.[27] sHPT is characterized by elevated PTH with normal or low serum calcium, typically in the context of chronic kidney disease, CDK, Vitamin D deficiency or liver disease. In advanced CDK, sHPT can progress into tertiary hyperparathyroidism, with autonomous PTH production irrespective of extracellular calcium levels.[29]

Disease presentation and surgical treatment

There has been a shift in the presentation of pHPT from the 1970's and onwards, most probably due to the increased availability of biochemical diagnostics since the arrival of automatized biochemical analytic equipment. Patients used to be diagnosed with severe, debilitating disease. Nowadays, patients are screened for hypercalcemia in the work-up for osteoporosis, nephrolithiasis, affective disorders and cognitive impairment. At diagnosis, most patients have milder disease, typically with modest hypercalcemia (serum total or ionized calcium <0.25 mmol/L above upper reference), and most often few or none of the overt disease complications. The majority is thus diagnosed with *mild* or *asymptomatic* pHPT.[30-34]

Traditionally, disease manifestations of pHPT have been divided into *classical* and *non-classical* complications. Symptomatic bone disease with bone pain, deformities, fractures, or brown tumour, nephrolithiasis and proximal myopathy are considered classical disease complications. S*ymptomatic disease* would also include hypercalcaemic crisis, and hypercalcaemia in conjunction with peptic ulcer disease and pancreatitis. Non-classical complications include CVD, neurobehavioral and neurocognitive symptoms.[35]

Patients with pHPT might further be categorized as having *hypercalcaemic*, *normohormonal* or *normocalcaemic* pHPT. Hypercalcaemic pHPT is defined as having increased total serum or ionized calcium with elevated PTH at two measurement instances. In normohormonal pHPT, total serum calcium is elevated and PTH inappropriately above normal. In normocalcaemic pHPT, serum calcium is above

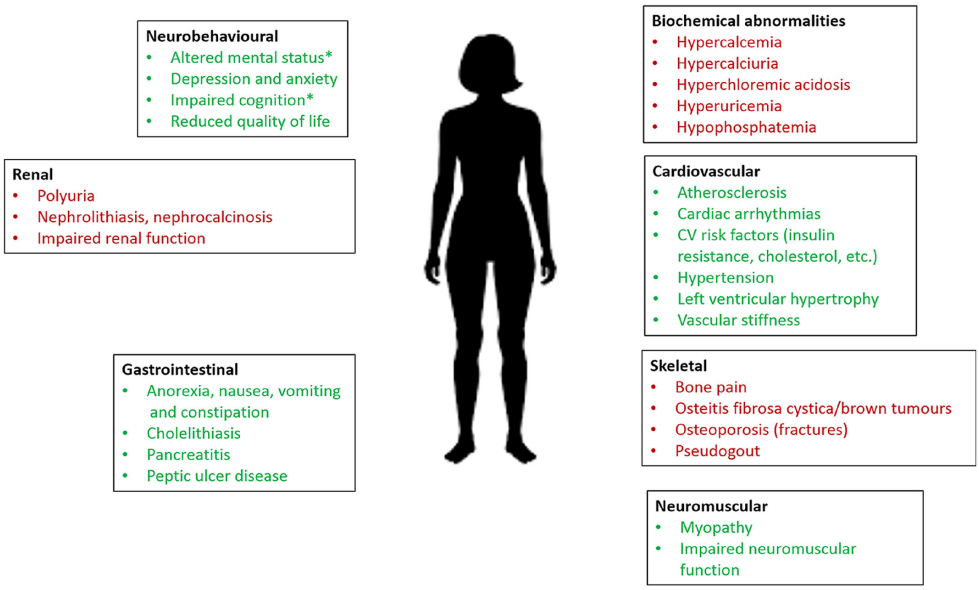

Figure 7. Symptoms and organ involvement in patients with PHPT.
Symptoms and complications depend on disease severity, as detailed in individual sections of the review. Color code: causal in red and association in green. Causality is implied from evidence by reversal with surgery or from mechanistic studies. *Moderate to severe hypercalcaemia may cause changes in mental status or cognitive function that are often reversible with correction of the hypercalcaemia.
Reproduced under the CC-BY from El-Hajj Fuleihan G et al (2022), Classical and Nonclassical Manifestations of Primary Hyperparathyroidism. J Bone Miner Res, 37: 2330-2350 (ASBMR).

normal and PTH elevated or again inappropriately above normal at two measurement instances, with exclusion of common causes of sHPT such as Vitamin D deficiency or renal insufficiency (glomerular filtration rate, GFR, <60 mL/min/1.73 m^2). With mild to moderate hypercalcemia, the diagnosis of FHH should also be excluded by 24 hour urine calcium excretion or urine calcium to creatinine clearance ratio. [36]

Indications for surgical treatment

Surgical and endocrinological practitioners unanimously agree that patients with overt symptomatic pHPT or classical complications should be recommended surgery. If the hypercalcemia is severe, preoperative correction is given, with calcimimetics, intravenous fluids, diuretics, and bisphosphonates.

International and national guidelines for treatment of pHPT have evolved over the last three decades in response to increasing number of patients diagnosed with pHPT, Table 1. According to current international guidelines, patients with asymptomatic or mild disease should be offered surgery if serum calcium is >0.25 mmol/L above the upper reference value, i.e. >2.75 mmol/L; BMD on DXA (dual energy x-ray absorptiometry) is consistent with osteoporosis, i.e. with a T-score <-2.5; there are radiologically documented vertebral fractures or nephrolithiasis; the kidney function is impaired; there is hypercalciuria; or the patient is <50 year old.[10]

Table 1. Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism: A Comparison of Current Recommendations with Previous Ones.

From Bilezikian, J. P. et al. (2022). Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. J Bone Miner Res 37(11): 2293-2314 (ASBMR). Reproduced with permission from Oxford University Press on behalf of ASBMR.

Parameter	1990	2002	2008	2013	2022
Serum Calcium (>upper limit of normal)	1–1.6 mg/dL (0.25–0.4 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: *Z*-score < −2.0 (site unspecified)	BMD by DXA: *T*-score < −2.5 at any site	BMD by DXA: *T*-score < −2.5 at any site Previous fragility fracture	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius b. Vertebral fracture by X-ray, CT, MRI, or VFA	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius* b.Vertebral fracture by X-ray, CT, MRI or VFA
Renal	a. eGFR reduced by >30% from expected. b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR reduced by >30% from expected b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR <60 cc/min b. 24-Hour urine for calcium not recommended	a. eGFR <60 cc/min b. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT	a. eGFR <60 cc/min** b. Complete 24-hour urine for calcium >250 mg/day in women (>6.25 mmol/day) or > 300 mg/day in men (>7.5 mmol/day) c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT
Age	<50 years	<50 years	<50 years	<50 years	<50 years

This table does not include the clearcut indication for surgery in anyone who has symptomatic PHPT (marked hypercalcemia, kidney stones, fractures). Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible and also in patients opting for surgery, in the absence of meeting any guidelines, as long as there are no medical contraindications. Patients need meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.

*Consistent with the position established by ISCD the use of *Z*-scores instead of *T*-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 years.[174] These individuals meet criteria for surgery by virtue of age.

**Special consideration might be justified in those whose eGFR is >60 cc/min but in whom there is only one kidney. In those situations, parathyroidectomy could be considered to be special indication for surgery.

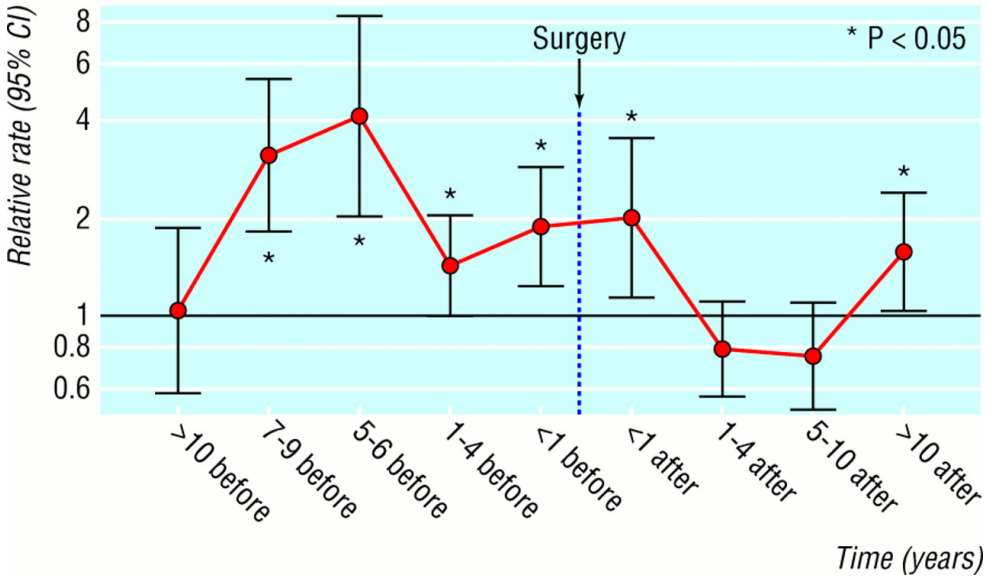

Figure 8. Relative rates and 95% confidence intervals for risk of fracture in cases compared with matched controls stratified by time before and after surgery. Note the log scale on the ordinate. From Vestergaard P et al (2000), Cohort study of risk of fracture before and after surgery for primary hyperparathyroidism. BMJ, 321(7261):598-602. Reproduced with permission from BMJ Publishing Group Limited.

Fracture incidence and the effect of surgery

Fracture incidence in pHPT has been evaluated in several observational studies of varying sizes, both in untreated disease and in relation to surgery. However, no investigation has demonstrated any association to disease-specific predictors.

Larsson et al found no difference in the incidence of hip fractures between patients with pHPT and the background population, although they used a large cohort, 1 924 patients, with a long follow-up.[37]

Khosla et al found a three-fold increased incidence of vertebral fractures, and a two-fold increase of radius, sternum, and pelvic fractures in a cohort of 407 patients with pHPT as compared to the general population. The increased fracture incidence was associated with age and sex in multivariable analysis.[38]

Vestergaard et al compared 674 patients with pHPT to 2 021 matched population controls before and after surgery, finding a fourfold increased fracture incidence 5–6 years before surgery, which normalized one year postoperatively, Figure 8.[39] In a subsequent study in a cohort of 1 934 surgically treated and 1 279 conservative

managed patients with pHPT, surgically treated patients had half the risk of hip and upper extremity fractures compared to conservatively managed. However, these patients had advanced disease (mean serum calcium in the surgery group 2.95 mmol/L, and mean adenoma weight 2.4 g), and surgically treated patients were 6 years younger than conservatively managed.[40]

In a large cohort of 452 surgically treated and 1 117 conservatively managed patients with pHPT, VanderWalde et al found a 10-year fracture-free survival of 73% among surgically treated patients and 59% among conservatively treated. There was no association between fracture risk and serum calcium or PTH, but between female sex and creatinine.[41] In a sub cohort of 533 patients with BMD measurements available, VanderWalde et al confirmed that BMD can reliably be used to predict fracture risk in pHPT patients. In addition, surgically treated patients had higher 10-year fracture-free survival than conservatively treated, regardless of BMD.[42]

Vignali et al compared vertebral fracture rate in 150 women with pHPT to 300 matched controls and found increased fracture rate among postmenopausal women with pHPT, regardless of whether they were classified as symptomatic or not. Lumbar spine BMD was the only variable that was linked to vertebral fracture rate.[43]

Orr et al evaluated the effect of bisphosphonate treatment in a cohort of 1 737 patients with pHPT and osteoporosis as medical treatment, or in addition to surgery, and found that surgery only, or surgery followed by bisphosphonate treatment, were both associated with lower fracture risk (HR 0.55 and 0.46, respectively) than conservative treatment, whereas surgery and surgery followed by bisphosphonate treatment increased BMD (+5.5% and +6.3%, respectively).[44]

In a large longitudinal cohort study of 210 206 subjects with pHPT, comparing surgical vs. conservative treatment in Medicare beneficiaries, Seib et al demonstrated a reduced fracture rate (HR 0.78) associated with parathyroidectomy and an absolute risk reduction of 5.1% over 10 years following surgery.[45]

Similarly, Axelsson et al recently published a large retrospective study on 16 374 subjects with pHPT, 10 controls matched each, on comorbidities and clinical outcomes in pHPT based on the Swedish National Patient Registry for the years 2006–2017, comparing surgical treatment to conservative or medical management and population controls. The fracture incidence was increased in pHPT (HR 1.39 for any fracture, HR 1.51 for hip fracture), but following surgery, fracture incidence was reduced (HR 0.83 and 0.78, respectively).[46]

Bone mineral density and the effect of surgery

Most studies on skeletal complications in pHPT and the effect of surgery are observational, although there are a few RCTs that report on BMD and fracture risk. The treatment effect is evaluated with bone densitometry using either DXA or, historically, single-photon absorptiometry, but there are also studies using bone histomorphometry, a histological method for evaluation of bone biopsies. Follow-up range from a few months to 15 years.

Leppla et al and Abugassa et al evaluated bone mineral content, BMC, in small pHPT cohorts, 37 and 7 patients respectively, using single- and dual-photon absorptiometry, finding decreased BMC which improved following surgery.[47, 48] Valdemarsson et al could not reproduce this in a cohort of 40 patients with predominantly mild pHPT, although bone turnover markers improved.[49]

In several papers, Christiansen and Steiniche et al investigated BMD and BMC change measured with DXA and bone histomorphometry in patients with pHPT, 24 and 19 patients respectively, finding normalized bone remodelling and increased BMD in cancellous bone at 6 months after surgery. After 3 years, BMC increased in both cancellous and cortical bone, and bone turnover was markedly decreased. In cortical bone, the relative cortical width increased, and porosity decreased.[50, 51]

Thorsen et al found BMD to increase significantly in lumbar spine, femoral neck, Ward's triangle and trochanter following surgery in a cohort of 12 postmenopausal women.[52] Suzuki et al followed biochemistry and BMD using DXA for more than two years after surgery, finding rapid normalization in biochemistry, but only incomplete improvement in BMD in lumbar spine among 24 symptomatic patients,[53] whereas Tanaka et al found rapid improvement of BMD over the first three months and a prolonged recovery phase for the rest of the one-year follow-up in a cohort 50 surgically treated patients.[53]

Silverberg et al followed 61 surgically and 52 conservatively treated patients with pHPT with DXA and reported improved BMD in lumbar spine (+12%) and femoral neck (+14%) over 10 years following surgery. Among conservatively treated patients, they initially reported unaltered BMD, but at long-term follow up of 57 patients 15 years after diagnosis BMD was markedly decreased in both the lumbar spine (-10%) and femoral neck (-35%). Among the 59 surgically treated patients, BMD improvement was sustained at all measured sites.[54-57]

In a cohort of 62 surgically treated patients, Lumachi et al found increased BMD in lumbar spine at follow-up (ranging up to 2 years after surgery) for men (+13%), pre- and postmenopausal women (+12%). In a subgroup analysis of women ≤60 years old, they found significantly larger improvement in premenopausal women.[58]

Nordenström et al analysed recovery of BMD in lumbar spine and hip and BMC in radius, finding bone recovery in total hip to be associated with 1,25-$(OH)_2$ Vitamin D and GFR, in a multivariable analysis adjusted for sex and age. 42% of the 126 patients had improved more than least significant change, LSC, ($\geq 1.96\sqrt{2} \cdot CV$, assuming a CV of 0.01) in distal radius, 54% in lumbar spine and 48% in total hip. In the lumbar spine, BMD recovery also correlated with baseline 24-hour urine calcium.[59]

Hagström et al evaluated BMD recovery and biochemistry in a cohort of 49 postmenopausal women found through calcium screening, compared to population controls. At the last follow-up 5 years after surgery, patients had improved in lumbar spine (+3%, +4% in women <67 years old) and did not deteriorate in femoral neck as their matched controls. There was an association between calcium and BMD in lumbar spine.[60]

In a cohort of 97 postmenopausal women with pHPT, Sitges-Serra et al similarly evaluated BMD in both in terms of absolute change in BMD and LSC at follow-up one year postoperatively and in relation to biochemistry, finding positive correlations with baseline PTH and 24-hour urine calcium in the femoral neck, as well as a negative correlation with creatinine. Adenoma weight and calcium was significantly higher among patients where BMD improved >LSC, but no significant impact on fracture rate.[61]

In a study conducted on 53 patients fulfilling the criteria for surgical treatment by NIH, Alonso et al found biochemical markers of bone turnover (N-terminal pro-peptides of type 1 procollagen, P1NP, and C-terminal cross-linking telopeptides of type I collagen, CTX) at baseline, correlated to BMD improvement at follow-up 6 months and one year after surgery.[62]

Dy et al investigated bone recovery with DXA up to three years after surgery in a large retrospective cohort at the Mayo clinic, consisting of 420 surgically treated patients with pHPT. In 38% of the patients, BMD increased with more than 5% at the most affected site (femoral neck, total hip or L1–L4). Lower age, worse preoperative BMD, higher levels of serum or 24-hour urine calcium, and PTH at baseline predicted improved BMD.[63]

In a Danish cohort of 236 surgically treated patients, Rolighed et al found increased BMD one year after surgery in hip and lumbar spine, similarly correlated to preoperative ionized serum calcium and PTH. ALP was associated with increased BMD in the lumbar spine, whereas higher age reduced the probability of BMD increase in the hip.[64]

Sharma et al found that male sex, age <55 years, DXA investigation >2.5 years after surgery, previous fracture and private health care insurance predicted BMD increase >5% in a multivariable analysis of a retrospective surgical cohort of 123 pHPT patients.

However, this cohort only included patients with available DXA, from a total consecutive single-centre series of 757 patients.[65]

Rajeev et al compared the effect of surgery in 92 patients to medical treatment with bisphosphonates in 30 patients unfit for surgery on bone turnover markers (P1NP, CTX, and bone-specific ALP) 6–12 months after surgery and BMD in spine and hip 1–2 years follow-up DEXA scan. They found that P1NP and CTX decreased in both groups, whereas bone-specific ALP and BMD only improved with surgery.[66]

In a series of 55 surgically treated patients, Koumakis et al found that hypercalcemia predicted increased BMD (>LSC) in lumbar spine, hip or radius, 74% versus 44% among patients with normocalcemic pHPT one year postoperatively. ALP over median also predicted improved BMD.[67]

In a post-hoc analysis of a randomized trial with 150 participants evaluating the effect of Vitamin D-supplementation on metabolic risk factors and bone recovery after surgery for pHPT, Nilsson et al found that BMD increase in the hip and distal radius was related to baseline 24-hour urine calcium and PTH at baseline.[68]

In a cohort 92 patients, Lee et al compared the effect of surgery on biochemistry and BMD in lumbar spine, femoral neck, total hip and radius in patients with typical pHPT to normocalcemic and normohormonal disease. Patients with normocalcemic disease did not improve at any site, whereas normohormonal patients improved in femoral neck, and patients with typical pHPT improved in lumbar spine, femoral neck, and total hip.[69]

Mendoza-Moreno et al found that low BMD preoperatively was associated with higher probability of BMD improvement (>LSC) following surgery in lumbar spine and femoral neck, and that low PTH preoperatively was also associated with improved BMD in femoral neck in a Spanish series of 108 postmenopausal women.[70]

Çalişkan et al evaluated BMD gain in a Turkish cohort of 91 pHPT patients with fairly advanced disease (39% of patients with asymptomatic disease had osteoporosis at any site), finding markedly higher BMD gain after surgery in both lumbar spine and femoral neck. Preoperative PTH was found to predict BMD gain.[71]

In an Indian cohort of 63 pHPT patients with even more advanced disease (preoperative serum calcium 12.1 mg/dL), Pal et al found that lower BMD at baseline predicted higher BMD gain in lumbar spine, total hip, and forearm. Preoperative PTH predicted BMD gain in lumbar spine and femoral neck, and body mass gain predicted BMD gain at all investigated sites.[72]

Randomized controlled trials and meta-analyses

Horiuchi et al randomized 22 elderly female patients with pHPT between parathyroidectomy and etidronate therapy, finding a 20% increase in lumbar spine BMD in the surgical group, vs. a 10% increase for patients treated with etidronate.[73]

Almqvist et al randomized 50 patients with mild pHPT between surgery and observation for a year before surgery, finding significant BMD recovery in lumbar spine in both groups, but in the femoral neck and trochanter only among those randomized to surgery without observation. The BMD increase was correlated to preoperative serum calcium, CTX and osteocalcin.[74]

Rao et al randomized 53 patients with mild pHPT between surgery and observation, finding improved BMD femoral neck and total hip among surgically treated compared with observation, whereas there was no significant difference in lumbar spine or forearm.[75]

Ambrogini et al randomized 50 asymptomatic patients with pHPT between surgery and observation, finding significantly increased BMD in lumbar spine, total hip, femoral neck and trochanter associated with surgery.[76]

In the Scandinavian Study on Primary Hyperparathyroidism, SIPH, Bollerslev et al randomized 191 patients with mild pHPT (of which 24 withdrew) between surgery and observation, finding significantly improved BMD in lumbar spine at 5 years after randomization among those having surgery compared with observation.[77] At 10-year follow-up, patients having surgery had significantly better BMD in lumbar spine, femoral neck and distal radius than those conservatively managed, but the rates of radiography-assessed vertebral fractures and reported peripheral fractures were not reduced.[78, 79]

In a meta-analysis on fracture risk including observational studies, Ejlsmark-Svensson et al found a two-fold increase in fracture risk among patients with pHPT, compared to controls.[80]

Pappachan et al conducted a recently published Cochrane meta-analysis on the effect of parathyroidectomy on morbidity in pHPT, finding no effect on BMD or fractures. For BMD, the underlying sample was only 366 patients, and except for the study by Horiuchi, only included patients with mild or asymptomatic disease. [81]

Cardiovascular morbidity and the effect of surgery

There both observational studies and RCTs evaluating cardiovascular risk factors, physiological indices and CVD events. With a few exceptions, most studies are relatively small. A number of biochemical markers have been evaluated, including disease-specific predictors such as serum calcium, PTH and adenoma weight.

Valdemarsson et al investigated biochemical risk factors of cardiovascular and metabolic disease in a cohort of 117 surgically treated pHPT patients, finding disturbed glucose metabolism and that triglycerides were lowered after surgery for pHPT in men. Uric acid was increased preoperatively and lowered postoperatively.[82] Westerdahl et al found elevated serum uric acid to be an independent risk factor for arteriosclerotic disease among 130 patients with surgically treated pHPT.[83]

Kosch et al showed reduced flow-mediated vasodilation as an effect of endothelial dysfunction in 20 patients with pHPT compared to controls, improving after surgery. However, there was no evidence of arterial stiffness (isobaric carotid distensibility coefficient, carotid intima-media thickness or aortic pulse-wave velocity).[84-86]

Nilsson et al investigated endothelium-dependent and independent vasodilation by occlusion plethysmography and infusion of methacholine and nitroprusside in 25 patients with pHPT compared to controls, showing impaired vasodilation that improved after surgery. In a subsequent study, calcium was infused systemically and locally in the arm of 12 healthy volunteers, finding disturbed endothelial vasodilation similar to what has been described in pHPT. Further, Nilsson et al investigated cardiac function after parathyroidectomy in 30 pHPT patients finding improved regulation of blood pressure, left ventricular diastolic function, and reduced cardiac irritability.[87-89]

In the two-year evaluation of the randomized SIPH-study, Bollerslev et al found no effect on biochemical markers of glucose metabolism, triglycerides, cholesterols, or markers of endothelial function (vWF and VCAM).[90] When echocardiographic measures at two-years follow-up were evaluated in the first 49 surgical patients, Persson et al found only minor improvement.[91]

In a large cohort of 845 patient operated for pHPT in Gothenburg, Hedbäck et al found that CVD was related to serum calcium, adenoma weight, *osteitis fibrosa cystica*, creatinine and inversely to GFR. Hypertensive patients with pHPT had 50% higher mortality than normotensive.[92]

Nuzzo et al found increased intima-media thickness in the carotids in a series of 20 patients with pHPT, compared to controls.[93] In a similar study on 27 pHPT patients with healthy controls by Lumachi et al, intima-media thickness did not differ at baseline, but in patients it correlated negatively with PTH. There was a slight reduction in intima-media thickness at follow-up among patients with pHPT (-10.4%, ns).[94]

Baykan et al found that flow-mediated vasodilation was reduced in series of 21 patients with pHPT, compared to controls.[95] In a cohort of 40 pHPT patients, Ekmekci et al also found impaired flow-mediated dilation compared to controls, which improved after surgery.[96]

In a retrospective cohort of 368 patients undergoing surgery for pHPT, Heyliger et al showed that blood pressure decreases after surgery in subjects with concomitant hypertension.[97] Rydberg et al found increased 24-hour blood pressure among patients with hyperension following surgery, whereas 24-hour blood pressure decreased among patients without hypertension in a prospective study of 49 surgically treated pHPT patients.[98]

Farahnak et al compared 51 patients with mild pHPT without cardiovascular complications to healthy controls, finding peak systolic myocardial velocities that decreased following surgery.[99] In a somewhat restricted group, Ring et al found that pHPT patients had similar arterial function as healthy controls, but increased systolic blood pressure and pulse-wave velocity at baseline that improved after surgery.[100] Subsequently, Farahnak et al investigated cardiovascular biochemical risk markers in the same cohort, finding 25-OH Vitamin D deficiency that improved following surgery.[101]

Schillaci et al found signs of increased arterial stiffness (aortic and carotid-radial pulse wave velocity) in a series of 17 patients with pHPT that improved after surgery, also after adjustment for blood pressure change. The change in pulse wave velocity correlated with change in PTH.[102]

Broulik et al investigated change in blood pressure after surgery in 1 020 pHPT patients, finding reduced blood pressure in patients with concomitant pHPT and hypertension, also when restricted to patients on antihypertensive agents only. Uric acid also improved. PTH was significantly higher preoperatively among patients with pHPT and hypertension than without hypertension. The prevalence of hypertension was 69.8%, and pHPT was advanced (mean serum calcium 3.01 ± 0.1 mmol/L).[103]

Rosa et al compared blood pressure and arterial stiffness in 44 pHPT patients with and without hypertension to patients with hypertension and healthy controls respectively, finding preoperatively increased pulse-wave velocity in pHPT patients regardless of hypertension. Pulse-wave velocity was reduced after surgery, as was systolic blood pressure and pulse pressure.[104]

In a series of 30 pHPT patients, Luigi et al showed that patients with asymptomatic pHPT frequently fulfilled the criteria for metabolic syndrome (38%), were hypertensive (81%), and had pathological nocturnal “non-dipping” ambulatory blood pressure registration (57% compared with 35% among hypertensive controls). Systolic blood pressure correlated with PTH. Left ventricular mass, LVM, and carotid intima-media thickness were increased in patients with pHPT compared to normal subjects. Systolic blood pressure and nocturnal ambulatory registrations improved, mean number of anti-hypertensive agents decreased and fewer patients fulfilled the criteria for metabolic syndrome following surgery.[105]

Walker et al found that carotid stiffness and carotid intima-media-thickness improved significantly (28% and 3%) at two years after curative surgery in 44 patients with mild pHPT and abnormal findings at baseline. Mean isovolumic relaxation time (a measure of diastolic dysfunction) normalized in subjects that had abnormal readings at baseline (-13%).[106]

Agarwal et al investigated 56 symptomatic Indian patients with pHPT with controls, finding left ventricular hypertrophy, LVH, among both hypertensive and normotensive pHPT patients, with poorer diastolic function than controls. LVM was correlated to PTH. Measures of LVM, systolic, and diastolic dysfunction were improved at 6 months postoperatively in hypertensive and normotensive patients. Nitrate-mediated vasodilation improved, but not flow-mediated vasodilation. 28% of patients had myocardial, septal or valvular calcification.[107]

Tuna et al compared 53 patients with mild pHPT, both surgically treated and with conservative management, to healthy controls. Flow-mediated vasodilation was impaired and carotid intima-media thickness was increased in patients with mild pHPT, even after exclusion of patients with hypertension. Both measures improved at follow-up 6–12 months after surgery.[108]

In a cohort of 48 patients with pHPT, Cansu et al investigated arterial stiffness and biochemical risk factors for CVD and impaired glucose tolerance, comparing patients with hypercalcaemic pHPT having surgery to conservatively managed patients with normocalcaemic pHPT and healthy controls. Carotid intima-media thickness and aortic pulse-wave velocity were increased in hypercalcaemic patients and improved following surgery. HOMA-IR, a measure of insulin resistance, and CD40 ligand, a biochemical risk marker of atherothrombosis, did not differ over groups and did not change after surgery.[109]

Dural et al compared several measures of arterial stiffness in 21 patients with pHPT before and after parathyroidectomy compared with controls from a living donor nephrectomy database. They found increased central systolic pressure and arterial augmentation index in pHPT, but coronary artery calcification was equal. There was no alteration at group level at follow-up after 6 months.[110]

In a cohort of 45 hypercalcemic pHPT patients, Karwacka et al reported improved systolic and cardiac function after 6 months in normotensive and improved overall cardiac function, lower blood pressure, and reduced LVH in hypertensive patients operated on for pHPT.[111]

Vestergaard et al investigated CVD events before and after surgery for pHPT, compared with population controls, in their previously published cohort of 674 patients operated 1979–1997. The incidence of AMI was increased (IRR 1.9) up to 10 years before surgery, and normalized after one year postoperatively, Figure 9. The

incidence of hypertension, heart failure, cardiac arrythmias, CVI, pancreatitis, and diabetes mellitus were also increased preoperatively. Arrythmias, pancreatitis and diabetes mellitus decreased significantly. There was no association between serum ionized calcium or adenoma weight and preoperative comorbidities.[112]

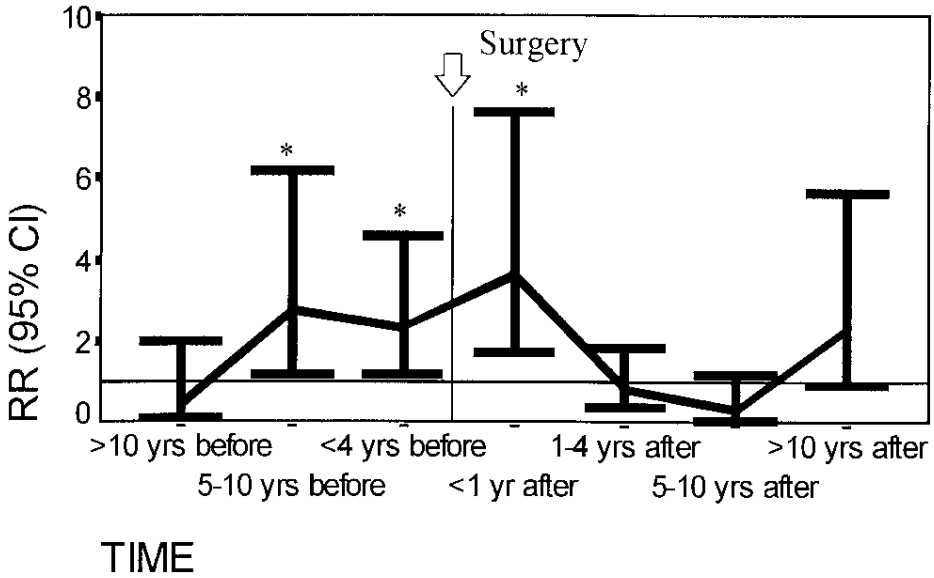

Figure 9. Relative risk (RR) of acute myocardial infarction in patients compared to normal controls before and after surgery for pHPT. [RR and 95% confidence intervals (CI)]. *p <0.05.
From Vestergaard P et al (2003), Cardiovascular events before and after surgery for primary hyperparathyroidism. World J Surg, 27(2):216-22. Reproduced with permission from John Wiley and Sons.

Kalla et al found increased prevalence of hypertension (OR 1.3) among patients with pHPT diagnosis in a registry study in the National Inpatient Sample database (37 922 admissions with pHPT, vs. 33 056 529 without).[113]

Graff-Baker et al investigated antihypertensive treatment in a large retrospective cohort of 2 117 patients with pHPT in Southern California Kaiser Permanente, showing that parathyroidectomy predicted taking fewer antihypertensive agents at one year postoperatively.[114]

In the investigation on comorbidities and effect of surgery in pHPT previously described, Axelsson et al found increased risk of CVD events (HR 1.45), fatal CVD (HR 1.73) and overall mortality (HR 1.72). Following parathyroidectomy, CVD events and overall mortality was reduced (HR 0.84 and 0.59, respectively).[46]

Seib et al conducted a similar investigation on CVD events among Medicare beneficiaries with pHPT using the same cohort as previously described, finding a moderate risk reduction among surgically treated compared with conservative management (an absolute risk reduction of 1.7%).[115] This was also confirmed by Grant et al in another analysis of CVD events in Medicare data of 108 869 patients with concomitant pHPT and CVD.[116]

Randomized controlled trials and meta-analyses

In a separate paper on cardiovascular effects in the same randomized trial of up-front vs. delayed surgery in mild pHPT as reported above, Almqvist et al showed increased LVM index in pHPT patients, correlated to PTH and a transient effect on systolic and diastolic function by surgery that normalize within two years.[117]

Ejlsmark-Svensson et al randomized 79 pHPT patients investigating the effect of surgery on cardiovascular risk factors in mild (ionized calcium <1.45 mmol/L) and moderate pHPT (≥1.45 to 1.60 mmol/L) between surgery upfront or delayed three months. Total cholesterol increased at follow-up among controls. Aortic pulse-wave velocity and augmentation index were not affected by surgery, but ambulatory blood pressure improved among controls. When analysis was restricted to subjects with moderate disease only, pulse-wave velocity improved in the surgical group.[118]

McMahon et al conducted a meta-analysis on the effect of surgery on LVM in patients with pHPT, finding LVM to decrease significantly (12.5%). Decrease in LVM was predicted by higher baseline PTH but not calcium.[119] However, in the Cochrane meta-analysis on the effect of parathyroidectomy on morbidity in pHPT, Pappachan et al found no effect on left ventricular ejection fraction. [81]

Mortality in pHPT

In a retrospective series from Helsinki until the end of 1980, including 334 patients having surgery for pHPT in the years 1956–1979, Ronni-Sivula found a mortality of 10.2%, compared to 6.3% in age and sex-matched controls. The pHPT patients, which had advanced disease (mean total serum calcium 3.08 mmol/L, mean adenoma weight 2 g) died mainly from cardiovascular disease, but also uraemia.[120]

Palmér et al investigated mortality among subjects with untreated hypercalcaemia (judged as pHPT after exclusion of other causes) compared to controls in a health screening program in Gävle, Sweden, finding impaired overall survival in hypercalcaemic subject aged <70 years, and that survival was related to serum calcium.[121] In a subsequent paper, survival among 441 patients operated in Uppsala between 1956 and 1979 was found to be lower in the first 5–8 years, compared to the general population. Age, hypertension and diabetes mellitus increased the risk of death,

however not preoperative serum calcium after exclusion of patients with hypercalcaemic crisis.[122] In a 25-year follow-up on the original Gävle cohort, Lundgren et al found increased cardiovascular mortality, but decreasing hypercalcemia among surviving subjects.[123]

In a series of publications, Hedbäck et al investigated long-term survival and mortality in a similar cohort of 896 patients having surgery in Gothenburg in the years 1953–1982, compared with the general population. They found increased mortality among patients having surgery for pHPT, overall, from cardiovascular and malignant disease.[25] Further, preoperative serum calcium, adenoma weight, age, year of surgery and time since surgery was found to influences survival.[124-126] Subsequently, the increased mortality rate after surgery for pHPT, overall and from CVD, was confirmed in a nation-wide registry study based on the National Patient Registry.[127]

On the contrary, when Söreide et al investigated a cohort of 1 052 patients operated in the years 1980–1984 at the Mayo Clinic in Rochester, Minnesota, overall survival was not decreased. Survival was better in patients with a history of nephrolithiasis or osteoporosis, and in the absence of muscle weakness.[128] Similarly, in a study by Wermers et al investigating the overall survival in patients with pHPT identified through the Rochester medical records linkage system, patients' overall survival was better than the survival of the background population. Similar to findings by Hedbäck et al, peak serum calcium was associated with mortality.[124, 129]

In a nation-wide Danish cohort of 3 213 patients with a diagnosis of pHPT between 1980 and 1999, Vestergaard compared morbidity before and after first diagnosis, and mortality between surgically and conservatively treated patients. Patients selected for surgery had lower rate of fractures and peptic ulcer disease postoperatively and had lower overall mortality. Nephrolithiasis in the history was associated with reduced mortality, probably by increasing the chance of being selected for surgery.[130] In the investigation on CVD, Vestergaard et al found that mortality was increased for patients operated 1979–1990 (SMR 1.32), but not in the period 1991–1997.[39, 112]

Nilsson et al investigated mortality in 11 882 pHPT patients with solitary adenoma at pathology according to the Swedish Cancer Registry in the years 1958–1997, finding increased overall, cardiovascular, tumour, urogenital, and endocrine mortality one year or more after surgery. For the last period, 1985–1997, there was no excess overall mortality among patients with pHPT, completing a downward trend through the defined time periods (1958–1964, 1965–1974, 1975–1984).[131]

In similar fashion, investigating pHPT patients having surgery 1964–1999 with parathyroid hyperplasia, identified through the National Patient Registry and the Swedish Cancer Registry, Nilsson et al found that excess mortality was reduced over time. In a subsequent study by Norenstedt et al, studying one-year mortality after

surgery for parathyroid solitary adenoma in 14 635 patients operated in the years 1961–2004, there was a similar decrease in perioperative mortality.[132, 133]

Bergenfelz et al investigated relative survival of 323 patients having surgery for sporadic pHPT in Lund in the years 1989–2003, finding reduced relative survival of pHPT patients after surgery. Diabetes mellitus and elevated serum uric acid in combination with pre-existing CVD was associated with higher mortality.[134]

In a population-based screening cohort in Tayside, Scotland in the years 1997–2006, Yu et al conducted the PEARS study of mild hyperparathyroidism finding that the 1,683 patients suffered an almost three-fold increase in overall and cardiovascular mortality (SMR 2.62 and 2.68, respectively). Patients with mild pHPT also had a significantly higher risk of CVD including cerebrovascular disease, renal impairment and fractures.[135] In a restricted propensity score-adjusted survival analysis, removing patients with pre-existing renal impairment, nephrolithiasis and osteoporotic fractures, Yu et al found largely unchanged outcome measure.[136]

In an Australia longitudinal cohort of 561 patients with pHPT diagnosed in 1961–2011. Both surgically treated and conservatively managed patients had increased overall mortality, compared to the general population. Total serum calcium >3.00 mmol/L did not influence survival. Nephrolithiasis was again associated with reduced mortality.[137]

In the recently published Swedish observational study by Axelsson et al, mortality was increased in patients with pHPT compared to controls (HR 1.72, HR1.27 after adjustment for age, sex and Charlson's comorbidity score, CCS), and parathyroidectomy was associated with reduced mortality (HR 0.59, HR 0.64 after adjustment for CCS).[46]

Aims of the thesis

As the indication for surgery in mild or asymptomatic pHPT is unclear, the main aim of the thesis is to investigate the disease complications of pHPT in a modern context, and to establish whether surgical treatment is beneficial. Secondly, to better select patients for surgery, preferably using disease markers available at preoperative surgical evaluation.

Paper I

What is the mortality rate after surgery for pHPT compared to controls? What are the causes of death and do they differ from those of the controls? Can mortality after surgery for pHPT be predicted by serum calcium, adenoma weight or multiglandular disease?

Paper II

Is the fracture incidence increased in patients, which subsequently are operated for pHPT, compared to controls, and is the fracture incidence reduced after surgery? Can fracture incidence be predicted by serum calcium, adenoma weight or multiglandular disease?

Paper III

Which biochemical markers can predict increased fracture incidence in patients with pHPT, or reduced fracture incidence after surgery? How does BMD correlate with preoperative fracture incidence, and to what extent can improved BMD predict reduced fracture incidence after surgery? Which biochemical markers can predict improved BMD in the individual pHPT patient after surgery?

Paper IV

Is the incidence of CVD increased in patients, which subsequently are operated for pHPT, compared to controls, and is the incidence of CVD reduced after surgery? Is the incidence of heart failure or cardiac diseases related to calcification increased, and is the incidence reduced after surgery? Is their global vascular risk in terms of arteriosclerotic disease increased, and how is this affected by surgery? Can CVD incidence be predicted by serum calcium, adenoma weight or multiglandular disease?

Material and Methods

Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA)

The primary data source for Paper I, II and IV is SQRTPA, which is the national Swedish quality register for endocrine surgery. Pilot registration in SQRTPA began in 2003–2004, and the register has been in full operation since 2005. At the end of the series used for this thesis (2003–2013), SQRTPA claimed a coverage of 97%, defined as the proportion of parathyroidectomy procedures in Sweden carried out at the participating departments of Surgery and Otolaryngology. The primary aim of Swedish quality registers is to increase the quality of care, and secondly, to support clinical research. So far, there are 51 publications using data from SQRTPA.

Baseline registration in SQRTPA is done at the time of surgery. Preoperative patient characteristics, indication for surgery including serum calcium, and investigations prior to surgery are collected, as well as information detailing the surgical procedure. At postoperative discharge from hospital, serum calcium and information on perioperative complications is registered. At follow-up 4–6 weeks and 6 months postoperatively, serum calcium and information on histological examination and postoperative complications is collected. Participating in quality registration is voluntary. Information is given in conjunction with the preoperative outpatient visit, allowing for opt-out.

Registered data is validated through a yearly audit at 4–6 participating departments by a validator appointed by the SQRTPA board. Both external validity, i.e. that registration is complete and unselected, and internal validity, i.e. that registered information is correct, is assessed through comparison of patient records and SQRTPA.

The patient cohort from SQRTPA, hereafter referred to as the *national cohort*, consisted of 6 092 individuals with at least one registered parathyroid procedure, parathyroidectomy or parathyroid exploration, for sporadic pHPT, registered with a date of surgery up until 2013. Patients with hereditary disease, parathyroid carcinoma on histology or lithium treatment were not included. If a patient had more than one procedure in the register, only the last registered procedure was included in the cohort. Patients were divided in three groups by year of surgery (2003–2007, 2008–2010 and 2011–2013).

Lund cohort

Between 1989 and 2013, data on a consecutive series of pHPT patients having surgery at the Department of Surgery in Lund was collected prospectively. This is the primary data source for Paper III.

Preoperative characteristics, including symptomatology, medications, biochemical data, BMD, localization investigations, procedure details, histology, complications, and extensive follow-up data on biochemistry and BMD have been registered. Biochemical analyses and investigation methods have been introduced, changed or abandoned during the long time-series. Patients were informed about ongoing research in conjunction with the preoperative outpatient visit, allowing for opt-out.

The Lund cohort, hereafter referred to as the *local cohort,* consisted of 832 patients operated for sporadic non-malignant pHPT at the Department of Surgery. Patients with hereditary disease or lithium treatment were not included. As the Department of Surgery has participated in SQRTPA since its start, there was an overlap of 383 patients between the cohorts (after exclusions). Patients were divided in three groups by year of surgery (1989–1996, 1997–2004 and 2005–2013).

Biochemistry

All biochemical analyses for the local cohort were performed at the Department of Clinical Chemistry, Skåne University Hospital, Lund.

Total serum calcium, reference range 2.20–2.60 mmol/L until 2009, since 2010 adjusted to 2.15–2.50, was measured using a routine laboratory analyser on Hitachi 917, with a coefficient of variation, CV, of 2.0% at serum calcium 2.40 mmol/L. Creatinine and albumin were also measured by routine laboratory analyser.

24-hour urine calcium was measured after a two-step process of complex formation with 5-nitro-5'-metyl-BAPTA, followed by EDTA. Ionized calcium and calcium complexes were measured bichromatically at 376 and 340 nm, with a CV of 1.2% at 1.8 mmol and 1.0% at 2.6 mmol, reference range 2.5–7.5 mmol.

Plasma PTH was initially measured using an N-terminal PTH assay (Incstar). This was replaced in 2000 by an assay for intact PTH (Hitachi modular -E), reference range 1.6–6.9 pmol/L, with a CV of 5.9% at 100 pmol/L. A correction algorithm has been adapted by the Department of Clinical Chemistry, $PTH_{new} = 1.4 \cdot PTH_{old} - 0.2$, which has been applied for this cohort.

25-OH Vitamin D was measured using high pressure liquid chromatography, HPLC. The equipment was changed during the study period to Nichols Advantage (Nichols Institute Diagnostics), reference range 25–125 nmol/L with a CV of 15% at 50 nmol/L. The previous equipment produced result in µg/L, which was corrected using an algorithm, 25-OH Vitamin $D_{new} = 2.5 \cdot$ 25-OH Vitamin D_{old}.

1,25-$(OH)_2$ Vitamin D was measured using a radioimmunoassay (Incstar) with a CV of 10% in the range 50–60 nmol/L.

Kidney function, or glomerular filtration rate, GFR, was quantified using iohexol clearance. A relative GFR of >80 ml/min/1.73 m^2 in subjects <51 years old, or >60 ml/min/1.73 m^2 in subjects ≥51 years old, is considered normal.

Osteocalcin was measured using a one-step immunometric assay, electrochemiluminescence immunoassay based on a ruthenium derivate, reference range 10–43 g/L in adults, with a CV of 3% at 19 g/L.

Alkaline phosphatase, ALP, was bichromatically measured at 450 and 480 nm at alkaline pH, reference range 0.60–1.8 µkat/L, with a CV of 6.9% at 0.57 µkat/L.

Phosphate was measured bichromatically at 340 and 700 nm by the difference in absorbance. Reference range 0.8–1.5 mmol/L, with a CV of 5.8% at 0.7 mmol/L.

Bone mineral density

Bone mineral density, BMD, measured using dual energy x-ray absorptiometry, DXA is the standard method to evaluate fracture risk and to diagnose osteoporosis and osteopenia. Previously, other measures were used, such as bone mineral content, BMC, measured using single-photon absorptiometry.

Technically, the DXA scanner uses X-ray beams of two different wavelengths, which have different absorption and attenuation properties in tissue. The soft tissues absorptions can then be subtracted out and the BMD calculated from each beam's attenuation in bone at the measured sites, which typically include femoral neck, lumbar spine and distal radius.

BMD is expressed in grams per square centimeter, g/cm^2, and as standard deviations from the mean of a population of young healthy female individuals, T-score, using the NHANES III cohort for reference. A Z-score can also be calculated, which is the BMD relative to a reference population of the same gender and age. Z-score is used for premenopausal women and men aged <50 years. According to the recommendations by International Osteoporosis Foundation and the International Society of Clinical Densitometry, osteoporosis is defined by a T-score <-2.5 SD at the femoral neck, but

in practice other sites are used as well. A T-score between -1 and -2.5 SD is defined as osteopenia.[138, 139]

The fracture risk can be calculated from the BMD using nomograms of the reference population. The most commonly used is the Sheffield Fracture Risk Assessment Tool, FRAX, which report the 10-year hip fracture and major osteoporotic fracture risk, given age, weight, height, smoking, alcohol over-consumption, fracture history, heredity, glucocorticoid medication, rheumatoid arthritis, and femoral neck BMD.[140]

BMD has been measured preoperatively and at 1-year follow-up in patients operated for pHPT in Lund since 1994. Until 2011, all investigations were performed at the Department of Clinical Physiology, Skåne University Hospital, Lund. From this point, patients were referred to nearest local clinic performing DXA investigations (Malmö, Ängelholm, Hässleholm).

In Lund, Lunar Expert-XL (1994–2004), GE Lunar Prodigy (2004–2014), GE Lunar iDXA (2014–) equipment has been used (Lunar Corp, GE Healthcare). Measurement precision for the studied sites (lumbar spine, L2–L4, femoral neck and distal third of radius), has been determined at three instances (2010, 2013 and 2021), yielding CVs ranging 0.012–0.019 for lumbar spine, 0.019–0.025 for femoral neck and 0.019 for distal radius. In Malmö, Ängelholm and Hässleholm, GE equipment has also been used.

Pathology

Adenoma weight was defined as the weight in grams of the excised formaldehyde-fixed parathyroid gland with a primary histological diagnosis of parathyroid adenoma.

Multiglandular disease was defined as more than one excised gland and the primary histological diagnosis not being adenoma.

Data management and validation

After data retrieval, the datasets were scrutinized for irregularities in key variables such as date of surgery, biochemical analyses and BMD. In a number of cases, patients were registered with different dates of surgery in the local and national cohorts, respectively. Dates of surgery dates were then corrected from patient records. If biochemical analyses or BMD diverged radically from the physiological spectrum, patient records were checked, or, if this was not possible, the suspected faulty value was dropped.

Statistics Sweden (Statistiska Centralbyrån, SCB)

The national and local cohort datasets were handed to Statistics Sweden, which de-identified the datasets (removed personal identification number, PIN, and date of birth) and provided three controls from the *Total Population Register* for each patient operated for pHPT. The controls were matched for sex, age, municipality and were to be alive at the date of surgery in order to avoid immortal time bias. The controls were assigned the same day of surgery as their respective index patient. Each subject was assigned a unique identifier and patient-control sets were conserved.

Further, Statistics Sweden provided socioeconomic data by cross-linking the datasets with the *Total Population Register*, the *Income and Taxation Register* and the *Longitudinal integrated database for health insurance and labour market studies*.

The National Board of Welfare

The National Board of Welfare holds the official Swedish statistics on health and social welfare. The de-identified datasets were crosslinked with the *Swedish Cause of Death Register*, the *National Patient Register*, and the *Swedish Prescribed Drug Register*.

The *Swedish Cause of Death Register* includes all deaths in Sweden since 1961, with detailed information on date and cause of death with related circumstances such as substance abuse, diabetes mellitus, recent surgery, and accidental or inflicted injury. The general validity and data quality is considered to be good, although the frequency of autopsies has fallen dramatically in Sweden over the last decades.[141]

The *National Patient Register* has collected information on inpatient care since 1964, with nationwide coverage since 1987. The predecessors of the regional health care provider Region Skåne, Malmöhus läns landsting, the Municipality of Malmö, and Kristianstad läns landsting are covered since 1970. The *National Patient Register* contains dates of admission and discharge, diagnoses, and procedure codes. The validity and data quality of inpatient care are generally high.[142] Since 2001, the register also contains information on specialized outpatient care, not including primary care.

The *Swedish Prescribed Drug Register* is a more recently instated register collecting data on all pharmacy expedited prescriptions, in operation since mid-2005. The validity and data quality is very high, as information on every expedited prescription is automatically transferred to the register. However, if the patient is administered medications at a day-care facility (e.g. intravenous bisphosphonates, monoclonal antibody therapy, chemotherapy), or is a resident of a nursing home, provided medication from a central dispensary, data on such medications will be missing.[143]

SwedeHeart and RiksStroke

To enable a sub-cohort analysis of aetiological factors for CVD events, the de-identified datasets were also crosslinked with the national Swedish quality registers of ischemic heart disease, *SwedeHeart*, and of cerebrovascular disease, *RiksStroke*.

SwedeHeart was created in 2009 through a merge of several pre-existing quality registers in cardiology and thoracic surgery. Observation, medical and surgical interventions for acute coronary syndrome, ACS, have been registered with high coverage of patients in cardiology care since the mid 1990's. Subsequently, registration has encompassed secondary prevention, and interventions for valvular disease. However, patients observed and treated outside coronary or intensive care units are not included, resulting in a total coverage for AMI of about 55%.[144] Patients not included were generally older, more often female, had more comorbidities and were less likely to receive invasive coronary artery procedures.

RiksStroke collects data on observation, interventions and outcomes for cerebrovascular insult, CVI, since 1994. It includes ischemic CVI, haemorrhagic CVI and (lately) transitory ischemic attack, TIA. The total coverage for first-time stroke was 86% in 2022.[145]

Exclusions

Patients with an invalid or reused personal identification number, PIN, were excluded, as they could not be crosslinked with the *Total Population Register*.

The exposure of interest was successful surgery for pHPT. Thus, patients registered with negative exploration or biochemical evidence of persisting disease, defined as hypercalcaemia (ionized serum calcium >1.33 mmol/L or total serum calcium >2.50 mmol/L with albumin within the reference range) at the six-month follow-up; reoperation either by subsequent registration in either dataset or by a registered procedure code (Op6 0850-53/0882/0898 or KKÅ BBA10/20/30/40/50/99) in the *National Patient Register*; or missing follow-up were excluded together with their respective controls.

In the local cohort, patients with recurrent disease, defined as hypercalcemia at the one- or five-year follow-up were also excluded, together with their respective controls.

Controls were excluded if they had a registered parathyroid procedure code (Op6 0850-53/0882/0898 or KKÅ BBA10/20/30/40/50/99) in the *National Patient Register*.

Charlson's comorbidity score

To adjust for comorbidity in the statistical analyses, a longitudinal Charlson's comorbidity score, CCS, was calculated based on incident inpatient discharge diagnoses from the *National Patient Register* up until the day of surgery according to the algorithm of Quan.[146]

CCS is presented in points, where diagnoses of chronic disease are weighted according to Table 2, and the total score predicts mortality within one year.[147, 148] For statistical analysis, CCS was categorized as having 0, 1–2 or >2 points. For Paper IV, CCS was calculated omitting CVD event diagnoses.

Table 2. Weighted index of comorbidity.

Points	Comorbidity
1	AMI, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild hepatic disease, and diabetes mellitus
2	diabetes mellitus with end-organ damage, hemi- or paraplegia, cancer, moderate to severe kidney disease
3	moderate to severe hepatic disease
6	metastatic cancer, AIDS

Outcomes

Mortality and Causes of Death

In Paper I, the main outcome was *overall mortality*, retrieved from the *Swedish Cause of Death Register*. Causes of death were tabulated by the chapters of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, ICD-10.

Fractures, osteoporosis and bone mineral density

In Paper II & III the main outcomes were *any fracture*, which included all fractures with the exceptions of skull and digits, and *fragility fracture* (in Paper III denoted *major osteoporotic fracture*), which included vertebral, proximal humerus, distal upper extremity, pelvic or hip fracture. Secondary outcomes were *multiple fractures anytime*, defined as several fracture discharge diagnoses at either the same or separate occasions, and *osteoporosis*.

Fracture diagnoses were retrieved from the *National Patient Register* and grouped according to anatomical site, Table 3. Multiple events per subject were allowed, but new fracture diagnoses were not included, i.e. censored, up until six months.

Osteoporosis was defined by incident discharge diagnoses (ICD-9 7330–1, ICD-10 M80–2) in the *National Patient Register* or more than one expedited prescription of bisphosphonates as registered in the *Swedish Prescribed Drug Register*. In Paper III, patients with a BMD T-core <-2.5 in femoral neck, lumbar spine or the distal third of radius were also defined as having *osteoporosis*.

Exposure to other bone density affecting medications such as oestrogens and systemic glucocorticoids were also investigated using the *Swedish Prescribed Drug Register*. More than one expedited prescription was required to be deemed as exposed, and at least six months observation time to exclude exposure.

In Paper III, the main BMD outcome was *absolute BMD change*, Δ 1-year post-operatively. For practical reasons, a relative change of BMD of at least 2.77%, which equals least significant change, LSC, ($\geq 1.96\sqrt{2} \cdot CV$), assuming a CV of 1%, was considered to be *significantly improved BMD*.

Table 3. ICD-8/9/10 codes defining anatomical fracture site.

Fracture site	ICD-8	ICD-9	ICD-10
Vertebral	80500/10/21/31/90/91, 80600/10/21/22/31/32/90/91/92	8050–5, 8060–5	S12, S220–1, S320, M485
Rib	80700/10/90	8070–1	S223–4
Proximal humerus	81200/10/90	8120–1	S422
Distal radius	81300/10/42/52/90/92	8134–5	S525–6
Upper extremity including shoulder	810–1, 81221/31/42/ 52/91/92, 81321/31/ 63/73/91/93	810–1, 8122–5	S420–1, S423–9, S520–4, S527–9
Hand	814–7	814–7	S62
Pelvic	80542/52/92, 80643/ 53/93, 808	8056–7, 8066–7, 808	S321–8
Hip	820	820	S720–2
Lower extremity	821–4	821–4	S723–9, S82
Foot	825–6	825–6	S92
Other	80564/74/94, 80664/ 74/94, 80721/31/42/ 52/91/92, 809, 818–9, 827–8	8072–3 8075–6, 809, 818–9, 827–8	S222, S225–9, T02, T08, T10, T12, T142

Cardiovascular morbidity

In Paper IV, the main outcomes were *acute myocardial infarction, AMI, and cerebrovascular insult, CVI*. Secondary outcomes were *coronary artery disease, heart failure, aortic valve stenosis, mitral valve stenosis, ischemic CVI, haemorrhagic CVI, transient ischemic attack, TIA, carotid artery stenosis, peripheral artery disease,* and *aortic aneurysm*.

Cardiovascular disease diagnoses and procedure codes were retrieved from the *National Patient Register* and the *Swedish Cause of Death Register*, and outcomes were defined according to Table 4. Multiple events per subject were allowed for *AMI, CVI, ischemic CVI, haemorrhagic CVI* and *TIA,* but new diagnoses were censored up until three months, except for *TIA*.

In a subcohort analysis of subjects registered in *SwedeHeart* or *RiksStroke*, *AMI* was defined as registration in *SwedeHeart* not assessed as *"No infarct"* and to which the matched discharge diagnoses were not I20/24/25, R07/740/943A or Z034 in the absence of I21 (or corresponding ICD-9 codes). *CVI* was defined by the registered diagnosis in *RiksStroke.*

Table 4. ICD-9/10 and procedure codes defining cardiovascular events and chronic diseases.

CVD outcomes	ICD-9	ICD-10	KKÅ; Op6
Acute myocardial infarction	410	I21	
Coronary artery disease	410, 412†, 414†	I21, I22†–23†, I25†	FN; 3065, 3066, 3068, 3080, 3092, 3105, 3127, 3158
Heart failure	428A	I501, I111	
Aortic valve stenosis	424B	I350, I352	
Mitral valve stenosis	394A, 394C	I050, I052, I342	
Cerebrovascular insult, CVI	433, 434	I63	
Ischemic CVI	430–432	I60–62	
Haemorrhagic CVI	430–4, 436	I60–64	
Transient ischemic attack	435	G45	
Carotid artery stenosis	433	I65	PAE10–25, PAF10–21, PAF40, PAP10–21, PAQ10–21; 8831, 8833, 8863
Peripheral artery disease	440B/C/X, 443X, 444C/W/X, 557A/B/X	I70.1–2, I70.9, I73, I74.2–9, K55.0–1, K55.9, N28.0	PBE/F/H/P/Q, PCE/F/H/P/Q, PDE/F/H/P/Q, PEE/F/H/P/Q, PFE/F/H/P/Q, PGW; 8802, 8864, 8884–7, 8815–8, 8825–6, 0963–5, 8836–7, 8861–2, 8865–8, 0967
Aortic aneurysm	441	I71	

†) if cause of death

Ethical considerations and review

Register-based research by cross-linking to official registers with high validity and data quality provides a unique possibility to study real-world outcomes for populations, less selected than in an RCT. There are however ethical implications that mandate consideration.

The ethical framework that regulate research on humans is codified in the *World Medical Association Declaration of Helsinki – Ethical principles for medical research involving human subjects*, which evolved after World War II as a reaction to the abuse against human subjects committed in Nazi Germany. The latest revision was adopted in 2013.

> 4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research.
>
> […]
>
> 6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
>
> […]
>
> 9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. […][149]

Paragraph 6 provides support for the use of register data in medical research, as they provide a powerful way to evaluate the effectiveness and safety of intervention. However, paragraph 4 & 9 emphasizes the need to always protect the patient's autonomy and privacy.

The privacy of the individual is further protected by the *European Convention on Human Rights*, which is part of Swedish constitutional law since 1994.

> Article 8 – Right to respect for private and family life
>
> 1. Everyone has the right to respect for his private and family life, his home and his correspondence.[150]

By crosslinking with Statistics Sweden, the National Board of Welfare and external quality registers, access is provided to sensitive personal data, which could be detrimental to the individual (e.g. information on prescriptions, diagnoses, involuntary commitment). However, as data is de-identified, and the datasets are large, it is virtually impossible to identify the individual patient.

The collection and investigation of the local cohort was reviewed and approved by the Regional Ethical Review Board at Lund University, diary number H4890/2004. Further, the data retrieval from SQRTPA and crosslinking with Statistics Sweden, the National Board of Welfare, *SwedeHeart* and *RiksStroke* was reviewed and approved, diary number 2016/26.

Statistical methods

All four studies in this dissertation are large-scale, observational studies using big datasets. The aim of the statistical analysis is to identify associations between exposure, successful parathyroidectomy for pHPT, and outcomes.

All variables were assessed for normality, visually either by histogram or by plotting quantiles against quantiles of the normal distribution. Measures of central tendency (arithmetic mean and median) and distribution (standard deviation, interquartile range) were compared between groups with Student's t-test or Wilcoxon's rank-sum test, as appropriate.

When the distributions of more than two groups were compared, the Kruskal-Wallis test and Cuzick's non-parametric test for trend were used. When proportions were compared, χ^2-test was used, except if any expected number was less than five and the Fisher's exact test was used instead.

Linear regression was used to adapt univariable and multivariable models for continuous outcomes, which were logarithmically transformed, if skewed. Logistic regression was used for categorical outcomes, conditional logistic regression to allow for patient-control sets when patients and controls were compared. Logistic regression is usually reported as an odds ratio, OR, with 95% confidence intervals, $CI_{95\%}$.

For all statistical analyses, the significance level used was 95%, and tests were two-sided. STATA 13.1 was used for Paper I, STATA 16.1 for Paper II–IV (StataCorp LLC).

Survival analysis

Methods used to investigate survival include standardized mortality ratio, Kaplan-Meier graphs, log-rank test and Cox regression.

A prerequisite for Cox-regression is the proportional hazards assumption, meaning that the ratio between the risks of the groups tested needs to be roughly proportional. This can be assessed visually in the Kaplan-Meier graph, by plotting the logarithmic cumulative hazards function to the logarithmic survival time, or by testing the proportional hazards assumption formally using Schoenfeld residuals.[151] The result of Cox regression is usually presented as a hazard ratio, HR, with $CI_{95\%}$.

Multiple imputation (MICE)

To reduce the bias in the multivariable analyses introduced by missing data, missing covariates can be imputed using various imputation techniques. One of them is multiple imputation by chained equations, MICE.

An important prerequisite for imputation of missing data is that data must be missing at random, MAR, i.e. that the missingness is not systematic or related to the missing values. This must be thoroughly evaluated, e.g. by tabulating or regressing missingness.

In MICE, an *m* number of datasets are created by regressing the missing data points given the available data in the variables, with a slight perturbance. All variables in the analysis model must be included. The higher the fraction of missing information, the higher the number of imputed datasets is needed. When analysing the data, each dataset is analysed separately, and then the results are pooled together combined using Rubin's rules.[152-154]

Poisson regression

Poisson regression is the standard regression model for incidence rates, i.e. events per time unit. The Poisson distribution is valid for occurrences of events, if they occur independently and at random. This can hold true for a variety of situations, e.g. radioactive decay, bacteria cultures in a petri dish or incident diagnoses in a community or exposed group.

In reality, disease occurrence in an individual is often neither independent, nor random. If the subject recently had a CVD event, a new event is more likely; if the subject had a fragility fracture due to osteoporosis, the risk of a new fracture is higher. The most common, and easiest, way to handle this is to only count first-time events, this however means censoring of a significant proportion of disease events. An alternative is to fit a mixed-effects model, allowing for the clustering of events in each subject. Variables changing over time also mandates consideration. Typically, age is handled by splitting follow-up time in shorter time periods, termed a Lexis expansion or diagram.[155] The result of Poisson regression is usually presented as an incidence rate ratio, IRR, with $CI_{95\%}$.

Paper I – Mortality

Date of entry was the date of surgery or the corresponding date of the controls, exit was death, emigration, and 10 years after surgery or 31st of December 2015, whichever came first.

Standardized mortality ratio, SMR was calculated separately for men and women using excerpts from the official population statistics from Statistics Sweden, dividing the observed overall mortality rate with the expected mortality rate in 5-year age-bands for each year 2003–2015.[156]

Survival analysis was employed using visual assessment with Kaplan-Meier graphs, log rank test to test whether groups differ in survival, and univariable and multivariable Cox regression to test for associations with survival.

Patient-control status, sex, age, Charlson's comorbidity score, socioeconomic factors (marital status, educational level, and disposable income), period of surgery, total serum calcium at baseline, adenoma weight and multiglandular disease were evaluated in univariable analyses. Calcium and adenoma weight were evaluated both continuously and in tertiles (divided in three equally sized groups).

A multivariable model for patient-control status was adapted, adjusted for sex, age >65 years, Charlson's comorbidity score, marital status, educational level, disposable income, and period of surgery. For patients, separate multivariable models were adapted for total serum calcium, adenoma weight and multiglandular disease, adjusted for the same covariates as patient-control status.

A series of subgroup analyses were performed by sex, marital status, disposable income, and excluding controls without hospitalizations prior to the day of surgery.

MICE was employed to impute missing data. Patterns of missingness were scrutinized using tabulation and logistic regression to assess whether it was plausible to judge variables as MAR.

Total serum calcium at baseline and six months postoperatively were included as linear predictors, adenoma histology using a logistic regression. Adenoma weight had to be logarithmically transformed due to skewness and was then imputed conditional on adenoma histology. Marital status and educational level were imputed using an ordered logistic regression. Age, sex, disposable income, year of surgery, Charlson's comorbidity score and the survival outcome (the Nelson-Aalen estimator for time to death together with the censoring indicator) were included as complete variables. 20 imputed datasets were created, using 30 iterations. Convergence was assessed visually.

Multivariable analyses were repeated on imputed data in each dataset and pooled according to Rubin's rules.

Paper II – Fractures

The fracture incidence rate for patients and controls were tabulated by anatomical site. For preoperative incidence, time of entry was 10 years preoperatively. Postoperatively, time of entry was the day of surgery and exit was death, emigration, and 10 years after surgery or 31st of December 2015, whichever came first.

The association between patient-control status and fracture incidence was investigated by anatomical site and for *any fracture* and *fragility fracture* using mixed-effects Poisson regression models (two-level, random intercept) pre- and postoperatively. Mixed-effects Poisson regression was also used to evaluate the relation between *any fracture* and *fragility fracture* and age >50 years, sex, marital status, educational level, disposable income, CCS and for patients also in relation to total serum calcium at baseline, osteoporosis preoperatively, multiglandular disease, adenoma histology and adenoma weight. Calcium and adenoma weight were evaluated both continuously and in tertiles.

The incidence rates of *any fracture* and *fragility fracture* were investigated in separate time periods, 10–7, 6–5, 4–1 and <1 year before surgery, <1, 1-4 and 5–10 years after surgery. The effect of parathyroidectomy was evaluated formally by the interaction variable *patient status x postoperative time period.*

Multivariable mixed-effects Poisson regression models of *any fracture* and *fragility fracture* were adapted for patients vs. controls, adjusted for sex, age (Lexis expansion in 10-year bands), CCS and marital status. Educational level, disposable income and period of surgery was not included, as they did not strengthen the model according to sequential likelihood ratio testing.

Multiple fractures anytime and *osteoporosis* were analysed using logistic regression, conditional on patient-control sets, univariably and in multivariable regression adjusted for sex, age >50 years, CCS and marital status.

Sensitivity analyses were performed excluding subjects with >1 expedited prescription of bisphosphonates, oestrogens or systemic glucocorticoids pre- or postoperatively.

Paper III – Bone recovery and reduced fractures

The fracture incidence rates for patients and controls were tabulated by anatomical site. For preoperative incidence, time of entry was 10 years preoperatively. Postoperatively, time of entry was the day of surgery and exit was death, emigration, and 10 years after surgery or 31st of December 2015, whichever came first.

Among patients, the incidence rates of *any fracture* and *major osteoporotic fracture* were evaluated using mixed-effects Poisson regression models (two-level, random intercept) in relation to total serum calcium, 24-hour urine calcium, PTH, osteocalcin,

25-OH Vitamin D, creatinine, iohexol clearance, BMD of femoral neck, lumbar spine and distal radius, osteoporosis, multiglandular disease, adenoma histology and adenoma weight. Numerical predictors were analysed both as continuous variables and in tertiles.

Total serum calcium, 24-hour urine calcium, PTH, osteocalcin, 25-OH Vitamin D, multiglandular disease and adenoma weight were similarly evaluated as predictors for *absolute change in BMD* and *significantly improved BMD,* using linear and logistic regression, respectively.

Multivariable models were adapted adjusted for sex, age (Lexis expansion in 10-year bands in Poisson regression, and age >50 years in linear and logistic regression) and period of surgery.

Sensitivity analyses were performed excluding subjects with >1 expedited prescription of bisphosphonates, oestrogens or systemic glucocorticoids pre- or postoperatively. In analyses with preoperative osteoporosis as predictor, subjects exposed to bisphosphonates were not excluded as this was part of the definition.

Post-hoc, sex-specific hypercalciuria according to the current international guidelines on evaluation and treatment of pHPT (>250 mg/d in women, >300 mg/d in men) preoperatively and 1 year postoperatively, was evaluated in relation to *any fracture* and *major osteoporotic fracture, absolute change in BMD* and *significantly improved BMD* using mixed-effects Poisson regression, linear regression and logistic regression, respectively. Further, total serum calcium, PTH, 25-OH Vitamin D, osteocalcin, creatinine, iohexol clearance, and bisphosphonate treatment were also evaluated as predictors to logarithmically transformed 24-hour urine calcium using linear regression.

Paper IV – Cardiovascular morbidity

The CVD incidence rates for patients and controls were tabulated by outcome event. For preoperative incidence, time of entry was 10 years preoperatively. Postoperatively, time of entry was the day of surgery and exit was death, emigration, and 10 years after surgery or 31st of December 2015, whichever came first.

The association between patient-control status and the incidence rates of *AMI*, *CVI*, *ischemic CVI*, *haemorrhagic CVI,* and *TIA* was investigated using mixed-effects Poisson regression models (two-level, random intercept) pre- and postoperatively. For *heart failure*, *aortic valve stenosis*, *mitral valve stenosis*, *carotid artery stenosis*, *peripheral artery disease*, and *aortic aneurysm*, incidence rates among patients and controls were evaluated with standard Poisson regression including first events only, as these were considered chronic diagnoses.

The incidence rates of CVD outcomes were investigated in separate time periods, 10–7, 6–5, 4–1 and <1 year before surgery, <1, 1-4 and 5–10 years after surgery. The effect of parathyroidectomy was evaluated formally by the interaction variable *patient status x postoperative time period.*

Among patients, the cardiovascular outcomes were also evaluated in relation to total serum calcium, multiglandular disease, and adenoma weight. Calcium and adenoma weight were evaluated, both continuously and in tertiles.

Multivariable mixed-effects Poisson regression models of CVD outcomes were adapted for patients vs. controls, adjusted for sex, age (Lexis expansion in 10-year bands), CCS and marital status, and similarly for calcium, multiglandular disease and adenoma weight. A subgroup analysis of *AMI* and *CVI* was performed on subjects aged 65 years or older.

Results

Paper I – Mortality

After exclusions, the national cohort consisted of 5 009 patients and 14 983 controls, Figure 10. Time at risk was 29 419 person-years for patients and 87 493 person-years for controls. The median follow-up was 5.7 years, IQR 3.8–7.9, equally among patients and controls.

27.8% of the subjects had missing covariates in any of the multivariable models. Total serum calcium at six months had the largest fraction of missing information, 0.241.

Patients and controls were well matched, although CCS was higher among patients, Table 5. Preoperative serum calcium, clinical presentation, perioperative characteristics and histopathological findings are summarized in Table 6.

SMR was not increased for any group except female controls and causes of death did not differ substantially between patients and controls, Table 7 and 8.

In univariable Cox regression, the overall mortality of patients operated for pHPT was not increased compared with controls. Age, CCS, disposable income, marital status, and educational level were associated with mortality in patients and controls, Table 9. There were no interactions that needed to be included in the multiple imputation or multivariable regression model. In a multivariable model adjusted for age, sex, CCS, marital status, educational level, disposable income and period of surgery, patients had better survival than controls, HR 0.83, $CI_{95\%}$ 0.75–0.92.

In univariable regression, total serum calcium at baseline was associated with mortality among patients, HR 2.20, $CI_{95\%}$ 1.53–3.16. There was a trend towards an association between adenoma weight and mortality. In multivariable analysis on the original dataset, there was no association between any of the predictors and mortality. When imputed data was analysed, total serum calcium remained associated with mortality, HR 1.79, $CI_{95\%}$ 1.19–2.70. Tables 10 & 11, Figure 11.

In the pre-specified subgroup analyses, the association of total serum calcium and mortality was stronger in patients with disposable income in the lowest quartile, HR 2.04, $CI_{95\%}$ 1.11–3.78, uniglandular disease, HR 2.02, $CI_{95\%}$ 1.23–3.31, or adenoma on histology HR 1.67, $CI_{95\%}$ 1.07–2.63 (original dataset).

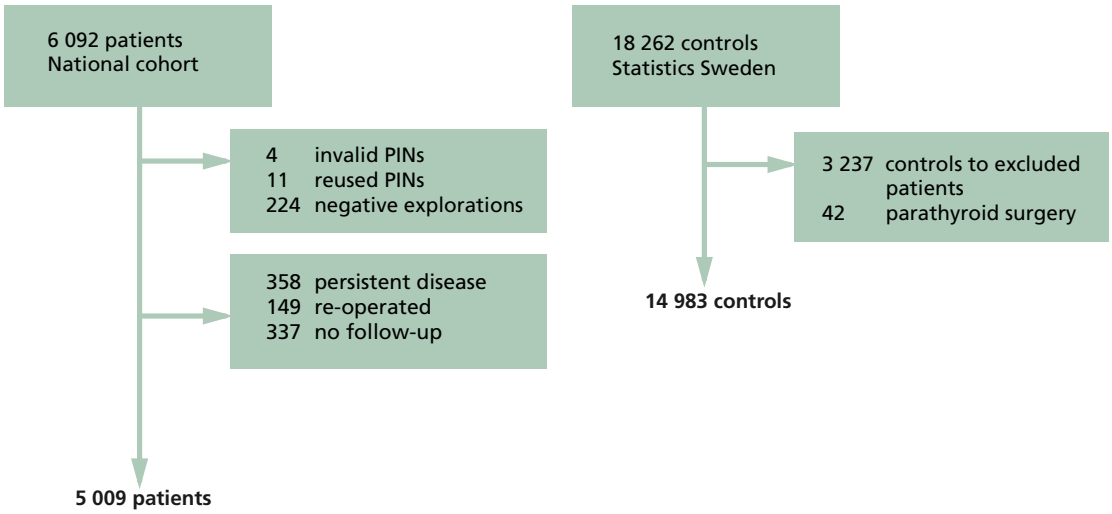

Figure 10. Patient flow-chart of the national cohort from SQRTPA, with controls and exclusions

Table 5. Demography and comorbidity, national cohort.

Characteristic	Patients	Distribution	Controls	Distribution	*p*†
Age, years	5 009	61.7 ± 13.7	14 983	61.7 ± 13.7	0.903
Male sex, *n*	5 009	1 129 (22.5)	14 983	3 380 (22.6)	0.977
Unmarried, *n*	4 982	2 346 (47.1)	14 851	7 053 (47.5)	0.623
Charlson's score, p	5 009	0 (0–1)	14 983	0 (0–0)	<0.001
Disposable income, SEK	5 009	167 845 (121 327–241 683)	14 981	166 782 (119 899–243 049)	0.250
Elementary school only, *n*	4 955	1 324 (26.7)	14 738	4 304 (29.2)	0.003
Year of surgery	5 009		14 983		0.999
2003–2007		1 428 (28.5)		4 272 (28.5)	
2008–2010		1 756 (35.1)		5 249 (35.0)	
2011–2013		1 825 (36.4)		5 462 (36.5)	

Distribution in mean ± SD, median (IQR), *n* (%). †) *t*-test for normal distributed variables (age); Wilcoxon rank-sum test for skewed variables (Charlson's score, disposable income); χ^2-test for nominal variables (sex, unmarried, elementary school only, year of surgery).

Table 6. Clinical presentation, perioperative characteristics and histopathology, patients.

Characteristic	*N*	Distribution
Total serum calcium, mmol/L	4 958	2.78 ± 0.199
Ionized calcium, mmol/L	4 955	1.46 ± 0.104
Cognitive symptoms	148†	148 (3.0)
Fatigue	501†	501 (10.0)
Urinary stone	126†	126 (2.5)
Skeletal disease	229†	229 (4.6)
Unilateral or focused exploration	5 009	2 399 (47.9)
Operation time, minutes	3 876	70 (45–103)
Multiglandular disease	4 101	394 (9.61)
Adenoma on histologic examination	4 970	4 359 (87.7)
Adenoma weight, g	3 702	0.58 (0.3–1.15)

Distribution in mean ± SD, median (IQR), *n* (%). †) Only registered with positive finding.

Table 7. Standardized mortality ratio, separately for women (♀) and men (♂).

	♀ Patients	♀ Controls	♂ Patients	♂ Controls
Deceased	365	1 199	137	427
Expected	372.3	1 080.8	132.8	400.0
SMR ($CI_{95\%}$)	0.98 (0.88–1.09)	1.11 (1.05–1.17)	1.03 (0.87–1.22)	1.07 (0.97–1.17)

Table 8. Causes of death.

Disease group ICD-10	Patients	Controls
Cardiovascular I00–I99	196	571
Tumour C00–D48	162	502
Respiratory J00–J99	23	97
Endocrine E00–E90	13	42
Urogenital N00–N99	9	19
Gastrointestinal K00–K93	1	6
Psychiatric F00–F99	21	94
Neurologic G00–G99	20	84
Trauma, violence V01–Y99	24	65
Infectious A00–B99	11	39
Miscellaneous	23	109
Total	503	1 628

Table 9. Univariable Cox regression of mortality, patients and controls.

Variable	Available cases		Complete cases†	
	HR ($CI_{95\%}$)	*p*	HR ($CI_{95\%}$)	*p*
Patient	0.92 (0.83–1.01)	0.084	0.94 (0.85–1.05)	0.282
Age, years	1.11 (1.11–1.12)	<0.001	1.12 (1.11–1.12)	<0.001
<65 years	1.00 (ref)		1.00 (ref)	
>65 years	7.52 (4.52–12.5)	<0.001	7.34 (6.53–8.25)	<0.001
Sex				
female	1.00 (ref)		1.00 (ref)	
male	1.26 (1.14–1.38)	<0.001	1.26 (1.14–1.40)	<0.001
Charlson's score, p	1.59 (1.56–1.63)	<0.001	1.58 (1.54–1.61)	<0.001
0	1.00 (ref)		1.00 (ref)	
1–2	3.91 (3.55–4.30)	<0.001	3.82 (3.46–4.22)	<0.001
>2	9.60 (8.56–10.8)	<0.001	8.96 (7.93–10.13)	<0.001
Disposable income, SEK				
q1 (–36,079–)	5.07 (4.29–5.99)	<0.001	4.97 (4.17–5.93)	<0.001
q2 (120,261–)	4.27 (3.60–5.06)	<0.001	4.48 (3.75–5.35)	<0.001
q3 (167,058–)	1.48 (1.22–1.80)	<0.001	1.55 (1.27–1.90)	<0.001
q4 (242,669–)	1.00 (ref)		1.00 (ref)	
Civil status				
married	1.00 (ref)			
unmarried	1.77 (1.62–1.93)	<0.001	1.76 (1.61–1.93)	<0.001
Educational level				
elementary school	3.67 (3.23–4.18)	<0.001	3.65 (3.20–4.17)	<0.001
upper secondary school	1.66 (1.45–1.90)	<0.001	1.68 (1.46–1.93)	<0.001
higher education	1.00 (ref)		1.00 (ref)	
Year of surgery				
2003–	1.00 (ref)		1.00 (ref)	
2008–	0.84 (0.76–0.93)	0.001	0.87 (0.78–0.96)	0.008
2011–	0.75 (0.65–0.86)	<0.001	0.74 (0.64–0.86)	<0.001

†) *N* = 4 929 patients and 14 613 controls

Table 10. Univariable Cox regression of mortality in patients, before and after imputation.

Variable	Available cases		Complete cases		Imputed data	
	HR ($CI_{95\%}$)	*p*	HR ($CI_{95\%}$)	*p*	HR ($CI_{95\%}$)	*p*
Total serum calcium, mmol/L continuous	2.20 (1.53–3.16)	<0.001	2.30 (1.35–3.91)	0.002	2.20 (1.53–3.17)	<0.001
2.17–	1.00 (ref)		1.00 (ref)		1.00 (ref)	
2.69–	1.00 (0.79–1.26)	0.967	0.90 (0.65–1.24)	0.508	0.98 (0.78–1.24)	0.889
2.82–	1.40 (1.13–1.75)	0.002	1.30 (0.97–1.75)	0.079	1.46 (1.17–1.82)	0.001
Adenoma weight, g continuous	1.00 (0.96–1.04)	0.977	1.00 (0.96–1.05)	0.987	1.01 (0.97–1.04)	0.781
0.05–	1.00 (ref)		1.00 (ref)		1.00 (ref)	
0.38–	1.21 (0.93–1.57)	0.160	1.06 (0.79–1.43)	0.680	1.18 (0.94–1.49)	0.157
0.89–	1.26 (0.97–1.63)	0.078	1.10 (0.82–1.48)	0.518	1.23 (0.98–1.53)	0.069
Multiglandular disease	1.16 (0.85–1.57)	0.344	collinearity		collinearity	

Complete cases denote patients (*N* = 3 126) that are complete in all variables of the multivariable model.

Table 11. Main exposures of risk stratification multivariable Cox regression models.

Variable	Available cases		Imputed data	
	HR ($CI_{95\%}$)	*p*	HR ($CI_{95\%}$)	*p*
Total serum calcium, mmol/L				
continuous	1.49 (0.97–2.30)	0.072	1.79 (1.19–2.70)	0.005
2.17–	1.00 (ref)		1.00 (ref)	
2.69–	1.04 (0.82–1.32)	0.731	1.02 (0.81–1.29)	0.853
2.82–	1.20 (0.96–1.51)	0.108	1.30 (1.04–1.62)	0.022
Adenoma weight, g				
continuous	1.00 (0.95–1.05)	0.970	1.01 (0.97–1.06)	0.531
0.05–	1.00 (ref)		1.00 (ref)	
0.38–	1.04 (0.79–1.36)	0.785	1.11 (0.88–1.41)	0.366
0.89–	1.01 (0.77–1.32)	0.930	1.07 (0.85–1.35)	0.567
Multiglandular disease	1.18 (0.86–1.62)	0.310	not selected	

Each model adjusted for age >65 years, sex, CCS (0, 1–2, >2 points), marital status, educational level, disposable income in quartiles and period of surgery.

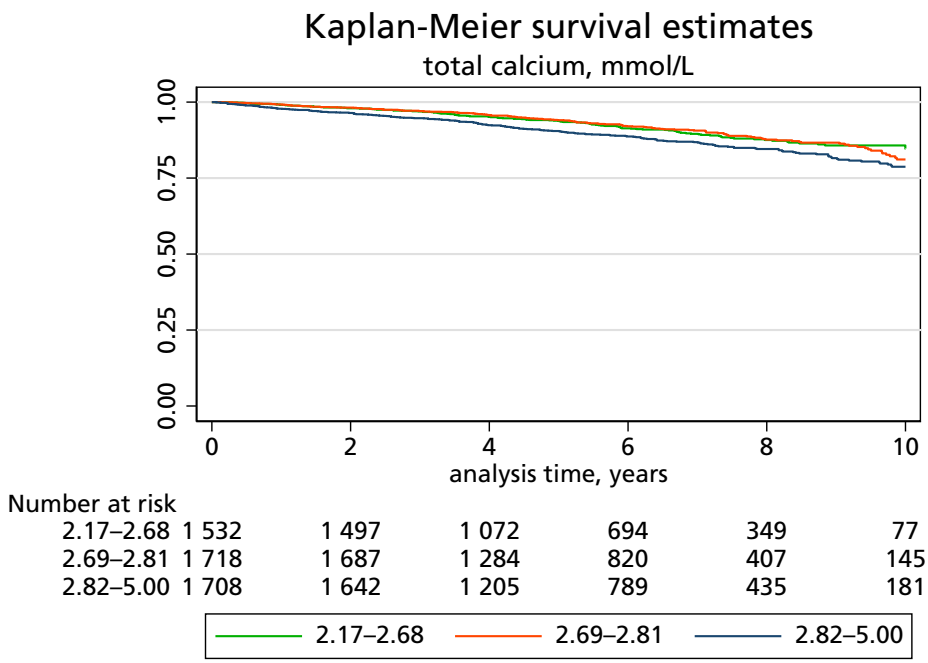

Figure 11. Kaplan-Meier graph of overall survival related to preoperative total serum calcium. Log-rank test *p* <0.001.

Paper II – Fractures

Exclusions, demographic and socioeconomic details on the national cohort of patients having had surgery for pHPT with population controls are reported under *Paper I – Mortality*.

Preoperatively, time at risk was 49 522 and 148 319 person-years for patients and controls. Postoperatively, time at risk was 29 322 and 86 423 person-years respectively. The median follow-up time was 15.7 years, IQR 13.7–17.9, equally for patients and controls. Temporal trends in patient characteristics were examined, finding a decrease in total serum calcium over time, presented in Table 12. Details on exposure to bisphosphonates, oestrogens and systemic glucocorticoids are given in Table 13.

The tabulated fracture incidence by anatomical site is presented in Table 14. Upper extremity fractures, except for proximal humerus, were increased among patients with pHPT preoperatively, and distal upper extremity fractures were significantly reduced after surgery. Rib fractures were increased postoperatively. The incidence rates in patients of both *any fracture* and *fragility fracture* were increased preoperatively, most pronounced one year prior to surgery, and were significantly reduced after surgery, Figure 12.

The results of univariable mixed-effects Poisson regressions of *any fracture* and *fragility fracture* in relation to patient-control status, comorbidity and socioeconomics are presented in Tables 15 & 17.

In univariable mixed-effects Poisson regressions of *any fracture* and *fragility fracture* among patients, there was no association between disease-specific factors, i.e. total serum calcium, adenoma weight and multiglandular disease, Tables 16 & 18.

Multivariable mixed-effects Poisson regression were adapted for *any fracture* and *fragility fracture* for patients vs. controls, Tables 19 & 20. Effect measures were virtually unchanged.

In conditional logistic regression, *osteoporosis* was more prevalent among patients than controls preoperatively, OR 2.77, $CI_{95\%}$ 2.42–3.16, postoperatively, OR 1.93, $CI_{95\%}$ 1.69–2.20, or for the complete follow-up, OR 2.43, $CI_{95\%}$ 2.19–2.69. This did not change substantially in multivariable regression. *Multiple fractures anytime* was not increased among patients in any interval.

In pre-specified sensitivity analyses, excluding subjects with exposure to bone affecting medication (n = 8 597), incidence rates of *any fracture*, *fragility fracture* and *multiple fractures anytime* were unchanged.

Table 12. Temporal trends in patient characteristics, *n* (%), mean ± SD or median (IQR), national cohort.

Characteristic	2003–2007	2008–2010	2011–2013	*p*†
Male sex	313 (21.9)	427 (24.3)	389 (21.3)	0.080
Age, years	61.9 ± 13.9	70.0 ± 13.4	61.3 ± 13.8	0.377
Total serum calcium, mmol/L	2.79 ± 0.208	2.78 ± 0.183	2.77 ± 0.205	0.001
Adenoma weight, g	0.56 (0.30–1.10)	0.59 (0.32–1.15)	0.59 (0.30–1.19)	0.841

†) χ^2 test for proportion, Kruskal-Wallis test for age, calcium and adenoma weight.

Table 13. Exposure to bone density affecting medications among patients and controls, national cohort.

Medication class	Patients	*n* (%)	Controls	*n* (%)
Bisphosphonates				
Preoperatively	4 564	435 (9.5)	13 639	553 (4.1)
Postoperatively	5 000	309 (6.2)	14 940	548 (3.7)
Systemic glucocorticoids				
Preoperatively	4 564	636 (13.9)	13 639	1 392 (10.2)
Postoperatively	5 000	514 (10.3)	14 940	1 258 (8.4)
Oestrogens				
Preoperatively	4 564	1 146 (25.1)	13 639	2 915 (21.4)
Postoperatively	5 000	434 (8.7)	14 940	1 085 (7.3)

>1 expedited prescription required for exposure.

Table 14. Incidence rate ratios (IRR) of fractures, patients vs. controls, national cohort.

Fracture site	Preoperatively		IRR ($CI_{95\%}$)	Postoperatively		IRR ($CI_{95\%}$)	*p*†
	Patients	Controls		Patients	Controls		
Vertebral	43	113	1.1 (0.8–1.6)	60	194	0.9 (0.7–1.2)	0.379
Rib	15	64	0.7 (0.4–1.2)	33	56	1.7 (1.1–2.7)*	0.014
Proximal humerus	34	72	1.4 (0.9–2.2)	32	90	1.1 (0.7–1.6)	0.312
Distal upper extremity	76	123	1.9 (1.4–2.5)*	41	113	1.1 (0.7–1.5)	0.021
Upper extremity incl. shoulder	47	87	1.6 (1.1–2.3)*	34	97	1.0 (0.7–1.5)	0.117
Hand	7	28	0.7 (0.3–1.8)	3	14	0.6 (0.1–2.3)	0.831
Pelvic	19	61	0.9 (0.5–1.6)	31	80	1.1 (0.7–1.8)	0.544
Hip	95	228	1.2 (1.0–1.6)	123	370	1.0 (0.8–1.2)	0.141
Lower extremity	93	267	1.0 (0.8–1.3)	59	205	0.9 (0.6–1.1)	0.258
Foot	11	14	2.4 (1.0–5.6)	4	19	0.6 (0.2–1.9)	0.052
Other	142	356	1.2 (1.0–1.5)	92	303	0.9 (0.7–1.1)	0.062
Any fracture	408	995	1.2 (1.1–1.4)*	400	1 160	1.0 (0.9–1.1)	0.010
Fragility fracture‡	255	575	1.3 (1.1–1.5)*	278	818	1.0 (0.9–1.2)	0.005

†) Mixed-effects Poisson regression of the interaction *patient-control status x postoperative time-period*. ‡) Fractures of vertebrae, proximal humerus, distal upper extremity, pelvis or hip. *) p <0.05.

Table 15. Univariable mixed-effects Poisson regression of *any fracture*, patients and controls, national cohort.

Variable	Preoperatively		Postoperatively	
	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Patient	1.27 (1.11–1.46)	0.001	0.99 (0.86–1.14)	0.859
Sex				
male	1.00 (ref)		1.00 (ref)	
female	1.48 (1.26–1.75)	<0.001	1.63 (1.38–1.92)	<0.001
Age, years				
continuous	1.06 (1.05–1.06)	<0.001	1.09 (1.08–1.10)	<0.001
<50 years	1.00 (ref)		1.00 (ref)	
>50 years	3.76 (2.95–4.78)	<0.001	7.22 (5.37–9.70)	<0.001
Charlson's score, p				
continuous	1.40 (1.35–1.46)	<0.001	1.44 (1.38–1.51)	<0.001
0	1.00 (ref)		1.00 (ref)	
1–2	2.39 (2.08–2.75)	<0.001	2.51 (2.18–2.89)	<0.001
>2	4.81 (3.97–5.83)	<0.001	4.93 (3.99–6.10)	<0.001
Disposable income (SEK)				
q1 (–36,079–)	2.53 (2.09–3.06)	<0.001	3.53 (2.89–4.32)	<0.001
q2 (120,261–)	2.39 (1.97–2.89)	<0.001	3.20 (2.61–3.93)	<0.001
q3 (167,058–)	1.40 (1.14–1.73)	0.001	1.43 (1.15–1.79)	0.002
q4 (242,669–)	1.00 (ref)		1.00 (ref)	
Civil status				
married	1.00 (ref)		1.00 (ref)	
unmarried	1.70 (1.49–1.93)	<0.001	1.74 (1.53–1.97)	<0.001
Educational level				
elementary school	2.01 (1.71–2.37)	<0.001	2.60 (2.19–3.08)	<0.001
upper secondary school	1.15 (0.97–1.35)	0.101	1.46 (1.23–1.73)	<0.001
higher education	1.00 (ref)		1.00 (ref)	

Table 16. Univariable mixed-effects Poisson regression of *any fracture* in relation to disease-specific factors, patients only, national cohort.

Variable	Preoperatively		Postoperatively	
	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Total serum calcium, mmol/L				
continuous	0.96 (0.55–1.70)	0.897	0.80 (0.42–1.55)	0.508
Δ 6 months			0.92 (0.46–1.85)	0.818
2.17–	1.00 (ref)		1.00 (ref)	
2.69–	0.78 (0.58–1.03)	0.080	0.71 (0.52–0.97)	0.032
2.82–	1.06 (0.81–1.39)	0.681	0.95 (0.71–1.28)	0.756
Osteoporosis preoperatively	3.44 (2.59–4.56)	<0.001	2.59 (1.83–3.67)	<0.001
Multiglandular disease	1.38 (0.93–2.03)	0.108	0.84 (0.52–1.37)	0.482
Adenoma on histology	0.84 (0.60–1.16)	0.281	1.35 (0.90–2.03)	0.150
Adenoma weight, g				
continuous	1.02 (0.98–1.06)	0.313	0.96 (0.88–1.03)	0.251
0.05–	1.00 (ref)		1.00 (ref)	
0.38–	1.11 (0.80–1.54)	0.522	1.13 (0.79–1.62)	0.498
0.89–	1.18 (0.85–1.63)	0.319	1.10 (0.77–1.58)	0.601

Table 17. Univariable mixed-effects Poisson regression of *fragility fracture*, patients and controls, national cohort.

Variable	Preoperatively		Postoperatively	
	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Patient	1.39 (1.16–1.65)	<0.001	0.99 (0.84–1.17)	0.913
Sex				
male	1.00 (ref)		1.00 (ref)	
female	2.26 (1.78–2.86)	<0.001	1.78 (1.46–2.16)	<0.001
Age, years				
continuous	1.09 (1.08–1.10)	<0.001	1.12 (1.11–1.12)	<0.001
<50 years	1.00 (ref)		1.00 (ref)	
>50 years	6.71 (4.52–9.97)	<0.001	16.01 (9.76–26.27)	<0.001
Charlson's score, p				
continuous	1.51 (1.44–1.59)	<0.001	1.47 (1.40–1.55)	<0.001
0	1.00 (ref)		1.00 (ref)	
1–2	2.86 (2.39–3.42)	<0.001	2.73 (2.33–3.20)	<0.001
>2	5.28 (5.80–9.14)	<0.001	5.49 (4.34–6.96)	<0.001
Disposable income (SEK)				
q1 (–36,079–)	3.34 (2.580–4.33)	<0.001	4.35 (3.40–5.55)	<0.001
q2 (120,261–)	3.08 (2.38–4.00)	<0.001	3.89 (3.04–4.99)	<0.001
q3 (167,058–)	1.54 (1.16–2.05)	0.003	1.47 (1.11–1.93)	0.006
q4 (242,669–)	1.00 (ref)		1.00 (ref)	
Civil status				
married	1.00 (ref)		1.00 (ref)	
unmarried	1.82 (1.55–2.15)	<0.001	1.74 (1.50–2.01)	<0.001
Educational level				
elementary school	2.39 (1.93–2.95)	<0.001	3.14 (2.57–3.84)	<0.001
upper secondary school	1.10 (0.88–1.36)	0.415	1.58 (1.29–1.94)	<0.001
higher education	1.00 (ref)		1.00 (ref)	

Table 18. Univariable mixed-effects Poisson regression of *fragility fracture* in relation to disease-specific factors, patients only, national cohort.

Variable	Preoperatively		Postoperatively	
	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Total serum calcium, mmol/L				
continuous	0.86 (0.42–1.77)	0.689	0.62 (0.28–1.37)	0.238
Δ 6 months			1.03 (0.45–2.36)	0.939
2.17–	1.00 (ref)		1.00 (ref)	
2.69–	0.69 (0.48–0.98)	0.038	0.70 (0.49–1.01)	0.057
2.82–	0.95 (0.68–1.33)	0.784	0.95 (0.68–1.34)	0.784
Osteoporosis preoperatively	4.53 (3.24–6.32)	<0.001	2.56 (1.71–3.82)	<0.001
Multiglandular disease	1.53 (0.96–2.46)	0.075	1.13 (0.67–1.90)	0.641
Adenoma on histology	0.77 (0.51–1.14)	0.192	1.07 (0.69–1.66)	0.776
Adenoma weight, g				
continuous	1.02 (0.96–1.07)	0.586	0.97 (0.90–1.06)	0.515
0.05–	1.00 (ref)		1.00 (ref)	
0.38–	1.23 (0.81–1.85)	0.331	1.19 (0.78–1.80)	0.426
0.89–	1.08 (0.71–1.65)	0.725	1.11 (0.73–1.70)	0.630

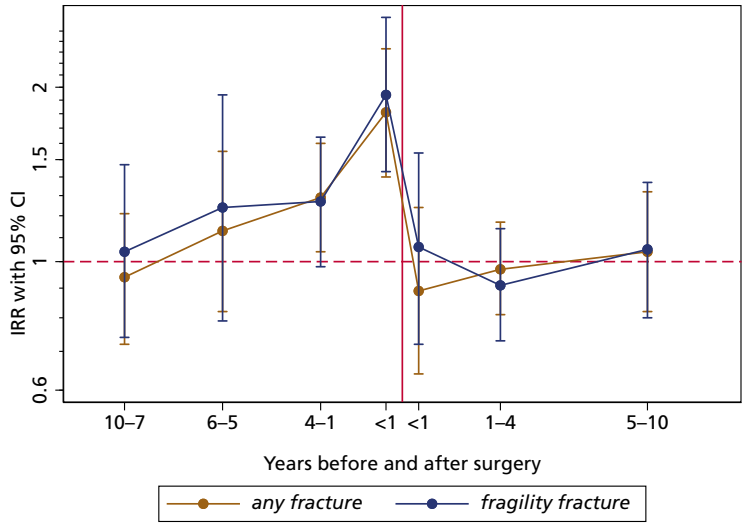

Figure 12. Fracture incidence rate for patients vs controls, national cohort.

Table 19. Multivariable mixed-effects Poisson regression of *any fracture*, patients and controls, national cohort.

Variable	Preoperatively IRR ($CI_{95\%}$)	*p*	Postoperatively IRR ($CI_{95\%}$)	*p*
Patient	1.24 (1.08–1.42)	0.002	0.93 (0.81–1.06)	0.269
Sex				
male	1.00 (ref)		1.00 (ref)	
female	1.33 (1.13–1.56)	0.001	1.39 (1.18–1.64)	<0.001
Age, years				
0	0.42 (0.05–3.38)	0.416	0.00 (0.00–)	0.999
10	0.61 (0.31–1.18)	0.144	1.89 (0.55–6.44)	0.312
20	0.25 (0.12–0.48)	<0.001	0.17 (0.04–0.70)	0.014
30	0.31 (0.21–0.46)	<0.001	0.12 (0.04–0.38)	<0.001
40	0.41 (0.32–0.52)	<0.001	0.40 (0.26–0.60)	<0.001
50	0.71 (0.60–0.84)	<0.001	0.67 (0.52–0.85)	0.001
60	1.00 (ref)		1.00 (ref)	
70	1.79 (1.54–2.09)	<0.001	2.42 (2.05–2.85)	<0.001
80	4.19 (3.38–5.21)	<0.001	5.77 (4.87–6.84)	<0.001
90	11.33 (4.54–28.24)	<0.001	11.88 (8.93–15.81)	<0.001
100			0.00 (0.00–)	0.999
Charlson's score, p				
0	1.00 (ref)		1.00 (ref)	
1–2	1.59 (1.38–1.84)	<0.001	1.58 (1.38–1.81)	<0.001
>2	2.61 (2.13–3.19)	<0.001	2.59 (2.12–3.17)	<0.001
Civil status				
married	1.00 (ref)		1.00 (ref)	
unmarried	1.40 (1.23–1.59)	<0.001	1.38 (1.22–1.56)	<0.001

Table 20. Multivariable mixed-effects Poisson regression of *fragility fracture*, patients and controls, national cohort.

Variable	Preoperatively		Postoperatively	
	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Patient	1.36 (1.14–1.62)	0.001	0.92 (0.79–1.08)	0.306
Sex				
male	1.00 (ref)		1.00 (ref)	
female	2.04 (1.60–2.59)	<0.001	1.51 (1.25–1.83)	<0.001
Age, years				
0	0.00 (0.00–)	0.997	0.00 (0.00–)	1.000
10	0.36 (0.11–1.16)	0.088	2.34 (0.54–10.19)	0.259
20	0.10 (0.02–0.41)	0.001	0.00 (0.00–)	0.997
30	0.17 (0.09–0.33)	<0.001	0.15 (0.04–0.60)	0.007
40	0.22 (0.14–0.33)	<0.001	0.18 (0.09–0.39)	<0.001
50	0.48 (0.38–0.61)	<0.001	0.49 (0.35–0.70)	<0.001
60	1.00 (ref)		1.00 (ref)	
70	2.12 (1.76–2.57)	<0.001	2.94 (2.39–3.60)	<0.001
80	5.47 (4.26–7.04)	<0.001	8.21 (6.69–10.07)	<0.001
90	12.89 (4.30–38.58)	<0.001	15.91 (11.53–21.96)	<0.001
100			0.00 (0.00–)	1.000
Charlson's score, p				
0	1.00 (ref)		1.00 (ref)	
1–2	1.68 (1.40–2.02)	<0.001	1.61 (1.38–1.88)	<0.001
>2	3.35 (2.65–4.23)	<0.001	2.64 (2.12–3.29)	<0.001
Civil status				
married	1.00 (ref)		1.00 (ref)	
unmarried	1.32 (1.12–1.56)	0.001	1.29 (1.12–1.49)	<0.001

Paper III – Bone recovery and reduced fractures

After exclusions, the local cohort consisted of 709 patients and 2 112 controls, Figure 13. Preoperatively, time at risk was 6 984 person-years for patients and 20 931 person-years for controls; postoperatively, time at risk was 4 519 person-years for patients and 13 440 for patients. The median follow-up was 16.2 years, IQR 13.7–20.0.

Demography and exposure to bone density affecting medications are summarized in Table 21. Among patients, fewer used bisphosphonates postoperatively. The exposure to oestrogens and systemic glucocorticoids also decreased, among both patients and controls. Clinical characteristics, including biochemistry and BMD measurements preoperatively and absolute change at 1 year postoperatively (Δ 1 year) are summarized in Table 22. Patients operated in later periods had significantly lower total serum calcium and higher PTH than previously, Table 23.

Among patients, upper extremity fractures, pelvic fractures, *any fracture* and *major osteoporotic fracture* were increased preoperatively, and normalized following surgery, Table 24.

Univariable mixed-effects Poisson regressions of *any fracture* and *major osteoporotic fracture* among patients are presented in Figure 14, Tables 25 & 26. 24-hour urine calcium was strongly associated with reduced postoperative fracture incidence, whereas 25-OH Vitamin D, GFR, estimated by iohexol clearance, and BMD were associated with fracture incidence both pre- and postoperatively. Serum creatinine and total serum calcium in the highest tertile at baseline were associated with increased fracture incidence postoperatively.

Multivariable mixed-effects Poisson regression models adjusted for sex, age and period of surgery were adapted for *any fracture* and *major osteoporotic fracture* among patients, Table 27. 24-hour urine calcium was associated with increased preoperative incidence of *any fracture*. Preoperative BMD in distal radius remained associated with lower fracture incidence preoperatively, and similarly BMD in femoral neck postoperatively.

At follow-up 1 year postoperatively, BMD was significantly improved (≥2.77%) at femoral neck in 42.5%, at lumbar spine in 51.7%, and at distal radius in 22.8% of patients.

Higher preoperative total serum calcium, PTH, osteocalcin and higher adenoma weight predicted higher *absolute change in femoral neck BMD* (Δ 1 year). Higher preoperative 24-hour urine calcium and PTH predicted higher *absolute change in lumbar spine BMD*. This did not change in multivariable models adjusted for sex, age >50 years and period of surgery. Regression analyses are summarized in Table 28. For all predictors except osteocalcin, a dose-response relationship could be confirmed using analysis by tertiles and Cuzick's nonparametric test for trend.

Similarly, total serum calcium and PTH were associated with *significantly improved BMD* at femoral neck, lumbar spine and distal radius. Higher 24-hour urine calcium at baseline was associated with *significantly improved BMD* at femoral neck and lumbar spine; osteocalcin with femoral neck and lumbar spine; adenoma weight with femoral neck and radius. Regression analyses, including multivariable models adjusted for sex, age >50 years and period of surgery, are summarized in Table 29.

In sensitivity analyses excluding subjects exposed to bone density affecting medications (193 patients and 412 controls preoperatively, 303 patients and 672 controls postoperatively), the incidences of *any fracture* and *major osteoporotic fracture*, and their associations to clinical factors, were diminished.

In post-hoc analysis, sex-specific preoperative hypercaliuria was associated with reduced incidence of *any fracture* postoperatively, IRR 0.27, $CI_{95\%}$ 0.08–0.88. PTH, creatinine and iohexol clearance correlated with 24-hour urine calcium pre- and postoperatively.

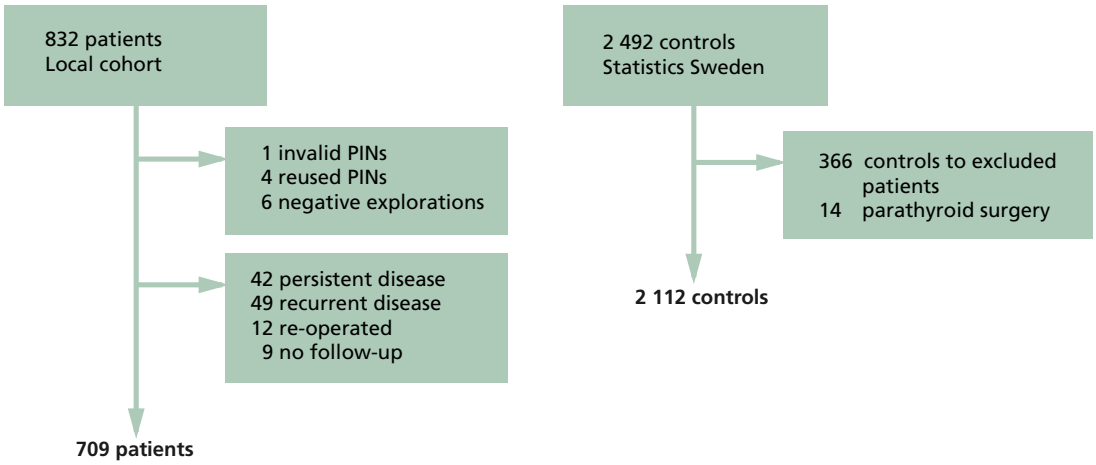

Figure 13. Patient flow-chart of the local Lund cohort, with controls and exclusions.

Table 21. Demography and prescriptions, local cohort.

Characteristic	Patients	Mean ± SD, *n* (%)	Controls	Mean ± SD, *n* (%)
Age, years	709	64.5 ± 13.3	2 112	64.4 ± 13.3
Male sex	709	160 (22.6)	2 112	477 (22.6)
Year of surgery	709		2 112	
1989–1996		140 (19.8)		416 (19.7)
1997–2004		126 (17.8)		374 (17.7)
2005–2013		443 (62.5)		1 322 (62.6)
Bisphosphonates				
Preoperatively	430	53 (12.3)	1 280	59 (4.6)
Postoperatively	636	34 (5.4)***	1 926	67 (3.5)
Systemic glucocorticoids				
Preoperatively	453	97 (21.4)	1 280	147 (11.5)
Postoperatively	636	74 (11.6)***	1 926	161 (8.4)**
Oestrogens				
Preoperatively	430	93 (21.6)	1 280	285 (22.3)
Postoperatively	636	67 (10.5)***	1 926	125 (6.5)***

>1 expedited prescription required for exposure. Postoperatively, only prescriptions expedited <10 years after surgery was included. *** denotes a p <0.001 comparing the proportions post- vs. preoperatively, ** similarly denotes p <0.01.

Table 22. Clinical characteristics, preoperative and Δ 1 year biochemistry and BMD, local cohort.

Characteristic	*N*	Distribution
Height, cm	655	166 ± 9.21
Weight, kg	657	75.3 ± 17.0
BMI, kg/m^2	655	27.2 ± 5.61
Osteoporosis preoperatively	709	356 (50.2)†
Multiglandular disease	658	71 (10.8)
Adenoma on histologic examination	661	601 (90.9)‡
Adenoma weight, g	623	0.65 (0.35–1.3)
Total serum calcium, mg/dL	702	11.0 ± 0.753
Albumin, g/dL	586	3.9 ± 0.35
24-hour urine calcium, mg/d	502	176 (112–253)
PTH, pg/mL	668	94 (71–130)
Alkaline phosphatase, U/L	651	102 (72.0–168)
Phosphate, mg/dL	645	2.5 ± 0.52
Osteocalcin, ng/mL	301	33 (23–46)
25-OH Vitamin D, ng/mL	563	20.3 ± 8.00
1,25-$(OH)_2$ Vitamin D, pg/mL	524	29.2 ± 11.6
Creatinine, mg/dL	673	0.79 (0.69–0.95)
Iohexol clearance, mL/min/1.73 m^2	294	76.9 ± 21.8
BMD femoral neck, g/cm^2	512	0.815 ± 0.139
BMD femoral neck, T-score SD	512	-1.60 ± 1.00
BMD L2–L4, g/cm^2	545	1.06 ± 0.211
BMD L2–L4, T-score SD	545	-0.988 ± 1.75
BMD distal radius, g/cm^2	421	0.594 ± 0.125
BMD distal radius, T-score SD	421	-3.29 ± 1.41
Change at 1 year postoperatively		
Δ Total serum calcium, mg/dL	643	-1.60 (-2.12– -1.20)
Δ 24-hour urine calcium, mg/d	413	-72.0 (-133– -25.6)
Δ PTH, pg/mL	597	-47 (-76– -26)
Δ Alkaline phosphatase, U/L	546	-18.0 (-42.0– -6.00)
Δ Osteocalcin, ng/mL	266	-16 (-25– -8)
Δ BMD femoral neck, g/cm^2	442	0.021 ± 0.038
Δ BMD femoral neck, %	442	2.65 ± 4.91
Δ BMD femoral neck, T-score SD	442	0.149 ± 0.271
Δ BMD L2–L4, g/cm^2	472	0.035 ± 0.071
Δ BMD L2–L4, %	472	3.62 ± 6.28
Δ BMD L2–L4, T-score SD	472	0.294 ± 0.595
Δ BMD distal radius, g/cm^2	360	0.002 ± 0.039
Δ BMD distal radius, %	360	6.78 ± 8.04
Δ BMD distal radius, T-score SD	360	0.020 ± 0.440

Distribution in mean ± SD, median (IQR), *n* (%). †) Among the controls, 63 had an osteoporosis diagnosis preoperatively (3.0%). ‡) Includes 18 patients with mixed picture of hyperplasia and adenoma on histology.

Table 23. Temporal trends in patient characteristics, *n* (%), mean ± SD or median (IQR), local cohort.

Characteristic	1989–1996	1997–2004	2005–2013	*p*†
Male sex, *n*	124 (22.3)	120 (24.0)	393 (22.3)	0.966
Age, years	64.1 ± 13.2	67.9 ± 13.5	63.6 ± 13.1	0.163
Total serum calcium, mg/dL	11.1 ± 0.831	11.2 ± 0.780	10.8 ± 0.693	<0.001
24-hour urine calcium, mg/d	186 (124–256)	180 (108–244)	168 (111–257)	0.186
PTH, pg/mL	78 (60–110)	100 (74–140)	94 (75–130)	<0.001
Adenoma weight, g	0.63 (0.34–1.32)	0.63 (0.35–1.09)	0.67 (0.35–1.38)	0.817

†) χ^2 test for proportion, Cuzick's nonparametric test for trend across ordered groups for age, total serum calcium, 24-hour urine calcium, PTH and adenoma weight.

Table 24. Incidence rate ratios (IRR) of fractures, patients vs. controls, local cohort.

Fracture site	Preoperatively		IRR ($CI_{95\%}$)	Postoperatively		IRR ($CI_{95\%}$)	*p*†
	Patients	Controls		Patients	Controls		
Vertebral	5	16	0.9 (0.3–2.7)	18	33	1.6 (0.9–3.0)	0.467
Rib	6	6	3.0 (0.8–11)	4	13	0.9 (0.2–3.0)	0.179
Proximal humerus	5	8	1.9 (0.5–6.5)	7	17	1.2 (0.4–3.1)	0.538
Distal upper extremity	11	15	2.2 (0.9–5.1)	7	17	1.2 (0.4–3.1)	0.332
Upper extremity incl. shoulder	14	17	2.5 (1.1–5.3)*	9	13	2.1 (0.8–5.3)	0.845
Hand	2	7	0.9 (0.1–4.5)	2	2	3.0 (0.2–41)	0.433
Pelvic	7	6	3.5 (1.0–13)*	7	19	1.1 (0.4–2.7)	0.107
Hip	17	47	1.1 (0.6–1.9)	36	93	1.2 (0.8–1.7)	0.935
Lower extremity	11	33	1.0 (0.5–2.0)	10	39	0.8 (0.3–1.6)	0.610
Foot	0	1	0 (0–116)	1	4	0.8 (0–7.6)	0.996
Other	25	50	1.5 (0.9–2.5)	19	52	1.1 (0.6–1.9)	0.438
Any fracture	73	147	1.5 (1.1–2.0)*	95	228	1.2 (1.0–1.6)	0.228
MOF‡	44	88	1.5 (1.0–2.2)*	74	168	1.3 (1.0–1.7)	0.290

†) Mixed-effects Poisson regression of the interaction *patient-control status x postoperative time-period*. For pelvic fracture, there was no convergence for the mixed-effects model, result of standard Poisson regression is reported. ‡) Major osteoporotic fracture, includes fractures of vertebrae, proximal humerus, distal upper extremity, pelvis or hip. *) p <0.05.

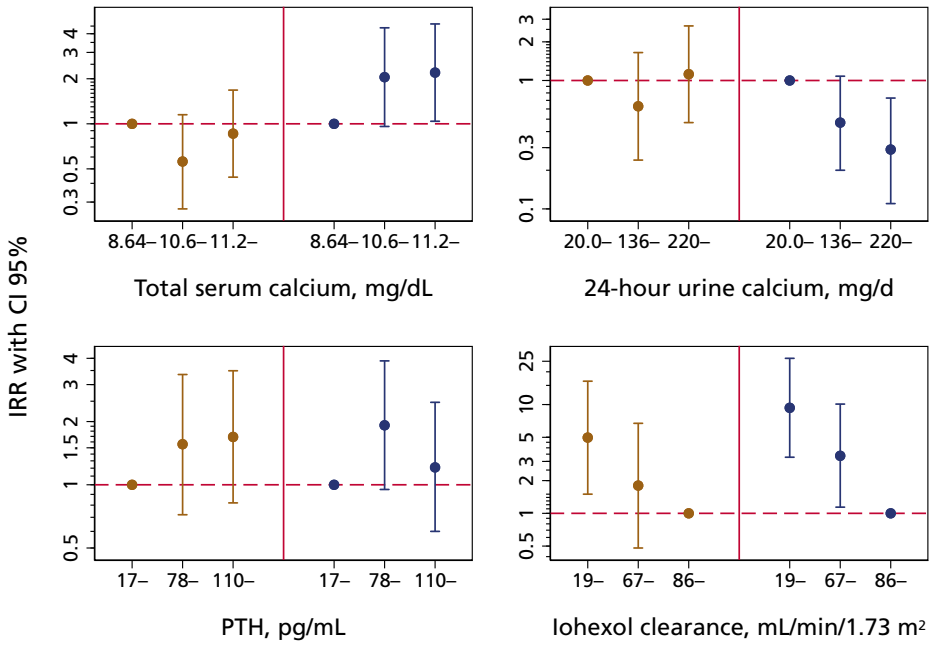

Figure 14. Incidence rate ratios (IRRs) of *any fracture* before and after surgery (brown | blue), univariable analyses by serum calcium, 24-hour urine calcium, PTH and iohexol clearance at baseline divided in tertiles. Patients only.

Table 25. Univariable mixed-effects Poisson regression of *any fracture*, patients.

Variable	Preoperatively		Postoperatively	
	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Total serum calcium, mg/dL	0.96 (0.66–1.41)	0.842	1.32 (0.92–1.90)	0.135
Δ 1 year			0.91 (0.64–1.31)	0.626
24-hour urine calcium, mg/d	1.00 (1.00–1.00)	0.328	0.99 (0.99–1.00)	0.006
Δ 1 year			1.00 (1.00–1.01)	0.071
PTH, pg/mL	1.00 (1.00–1.00)	0.577	1.00 (1.00–1.00)	0.971
Δ 1 year			1.00 (1.00–1.00)	0.983
Osteocalcin, ng/mL	1.00 (0.98–1.01)	0.602	1.00 (0.99–1.02)	0.536
Δ 1 year			1.00 (0.98–1.01)	0.861
25-OH Vitamin D, ng/mL	0.95 (0.91–1.00)	0.045	0.96 (0.93–1.00)	0.046
Δ 1 year			1.03 (0.99–1.07)	0.184
Creatinine, pg/mL	0.61 (0.20–1.86)	0.388	7.17 (3.03–17.0)	<0.001
Δ 1 year			8.03 (1.26–51.0)	0.027
Iohexol clearance, mL/min/1.73 m^2	0.97 (0.95–0.99)	0.007	0.96 (0.94–0.97)	<0.001
Δ 1 year			1.02 (0.97–1.08)	0.403
BMD femoral neck, g/cm^2	0.01 (0.00–0.20)	0.002	0.00 (0.00–0.01)	<0.001
Δ 1 year			1.09 (0.00–4 680)	0.984
improved (≥2.77%)			1.30 (0.66–2.56)	0.451
BMD L2–L4, g/cm^2	0.15 (0.03–0.80)	0.026	0.17 (0.04–0.76)	0.020
Δ 1 year			0.12 (0.00–5.41)	0.273
improved (≥2.77%)			0.85 (0.45–1.59)	0.605
BMD distal radius, g/cm^2	0.00 (0.00–0.06)	<0.001	0.01 (0.00–0.24)	0.005
Δ 1 year			0.03 (0.00–457)	0.462
improved (≥2.77%)			0.57 (0.18–1.88)	0.359
Osteoporosis preoperatively	1.68 (0.93–3.03)	0.084	1.48 (0.85–2.57)	0.169
Multiglandular disease	0.73 (0.25–2.08)	0.550	0.79 (0.28–2.28)	0.665
Adenoma on histology	0.80 (0.28–2.26)	0.674	0.77 (0.29–2.09)	0.610
Adenoma weight, g	1.02 (0.85–1.22)	0.835	0.95 (0.79–1.15)	0.628

Table 26. Univariable mixed-effects Poisson regression of *major osteoporotic fracture*, patients.

Variable	Preoperatively		Postoperatively	
	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Total serum calcium, mg/dL	0.58 (0.35–0.98)	0.042	1.35 (0.89–2.04)	0.162
Δ 1 year			0.87 (0.58–1.31)	0.507
24-hour urine calcium, mg/d	1.00 (0.99–1.00)	0.760	0.99 (0.99–1.00)	0.012
Δ 1 year			1.00 (1.00–1.01)	0.088
PTH, pg/mL	1.00 (1.00–1.00)	0.897	1.00 (1.00–1.00)	0.720
Δ 1 year			1.00 (1.00–1.00)	0.959
Osteocalcin, ng/mL	0.98 (0.96–1.01)	0.225	1.00 (0.99–1.02)	0.802
Δ 1 year			1.00 (0.98–1.02)	0.960
25-OH Vitamin D, ng/mL	0.94 (0.89–1.00)	0.057	0.96 (0.92–1.01)	0.086
Δ 1 year			1.02 (0.97–1.06)	0.507
Creatinine, pg/mL	0.32 (0.07–1.60)	0.166	5.24 (1.89–14.5)	0.001
Δ 1 year			5.90 (0.64–54.6)	0.118
Iohexol clearance, mL/min/1.73 m^2	0.97 (0.94–1.00)	0.030	0.95 (0.93–0.98)	<0.001
Δ 1 year			1.03 (0.97–1.09)	0.331
BMD femoral neck, g/cm^2	0.01 (0.00–0.34)	0.009	0.00 (0.00–0.00)	<0.001
Δ 1 year			1.08 (0.00–36 800)	0.989
improved (≥2.77%)			1.57 (0.69–3.58)	0.284
BMD L2–L4, g/cm^2	0.16 (0.02–1.22)	0.077	0.08 (0.01–0.49)	0.007
Δ 1 year			0.05 (0.00–4.05)	0.184
improved (≥2.77%)			0.77 (0.36–1.65)	0.507
BMD distal radius, g/cm^2	0.00 (0.00–0.10)	0.004	0.00 (0.00–0.09)	0.002
Δ 1 year			0.06 (0.00–14 300)	0.655
improved (≥2.77%)			0.41 (0.08–2.09)	0.286
Osteoporosis preoperatively	1.73 (0.85–3.50)	0.128	1.42 (0.75–2.70)	0.285
Multiglandular disease	0.43 (0.09–2.02)	0.287	0.60 (0.17–2.17)	0.438
Adenoma on histology	1.12 (0.29–4.33)	0.869	0.83 (0.26–2.67)	0.756
Adenoma weight, g	1.00 (0.80–1.24)	0.990	0.93 (0.75–1.16)	0.506

Table 27. Multivariable mixed-effects Poisson regression of fracture incidence, patients only.

Variable	N	*any fracture*				*major osteoporotic fracture*			
		Preoperatively		Postoperatively		Preoperatively		Postoperatively	
		IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*	IRR ($CI_{95\%}$)	*p*
Total serum calcium, mg/dL	702	0.92 (0.62–1.36)	0.661	1.09 (0.78–1.53)	0.598	0.53 (0.31–0.89)	0.017	1.09 (0.74–1.61)	0.673
Δ 1 year	643			1.01 (0.72–1.42)	0.955			0.97 (0.65–1.44)	0.878
24-hour urine calcium, mg/d	502	1.00 (1.00–1.01)	0.038	1.00 (0.99–1.00)	0.209	1.00 (1.00–1.01)	0.411	1.00 (0.99–1.00)	0.309
Δ 1 year	413			1.00 (1.00–1.00)	0.366			1.00 (1.00–1.00)	0.405
PTH, pg/mL	668	1.00 (1.00–1.00)	0.898	1.00 (1.00–1.00)	0.450	1.00 (0.99–1.00)	0.535	1.00 0.99–1.00)	0.339
Δ 1 year	597			1.00 (1.00–1.00)	0.620			1.00 (1.00–1.00)	0.634
Osteocalcin, ng/mL	301	0.99 (0.98–1.01)	0.503	1.00 (0.99–1.02)	0.587	0.98 (0.95–1.01)	0.149	1.00 (0.98–1.02)	0.983
Δ 1 year	266			1.00 (0.98–1.01)	0.623			1.00 (0.98–1.02)	0.888
25-OH Vitamin D, ng/mL	563	0.95 (0.91–1.00)	0.057	0.97 (0.93–1.00)	0.079	0.94 (0.88–1.01)	0.079	0.97 (0.93–1.02)	0.212
Δ 1 year	367			1.02 (0.99–1.06)	0.233			1.01 (0.97–1.05)	0.627
BMD femoral neck, g/cm^2	512	0.09 (0.00–2.32)	0.145	0.02 (0.00–0.33)	0.007	0.17 (0.00–9.78)	0.389	0.00 (0.00–0.11)	0.002
Δ 1 year, g/cm^2	442			9.35 (0.00–19 000)	0.565			11.0 (0.00–148 000)	0.622
improved (≥2.77%)				1.39 (0.74–2.61)	0.313			1.69 (0.78–3.69)	0.187
BMD L2–L4, g/cm^2	545	0.27 (0.05–1.54)	0.141	0.36 (0.09–1.53)	0.167	0.30 (0.04–2.43)	0.257	0.25 (0.04–1.40)	0.115
Δ 1 year, g/cm^2	472			0.04 (0.00–5.49)	0.196			0.01 (0.00–3.71)	0.124
improved (≥2.77%)				0.91 (0.50–1.65)	0.761			0.85 (0.41–1.73)	0.645
BMD distal radius, g/cm^2	421	0.00 (0.00–0.18)	0.006	0.04 (0.00–2.04)	0.111	0.00 (0.00–0.63)	0.035	(0.00–1.90)	0.087
Δ 1 year, g/cm^2	360			0.02 (0.00–773)	0.461			0.06 (0.00–39 400)	0.679
improved (≥2.77%)				0.58 (0.18–1.83)	0.351			0.41 (0.08–2.02)	0.271
Multiglandular disease	658	0.68 (0.24–1.93)	0.472	0.66 (0.25–1.76)	0.408	0.39 (0.09–1.81)	0.231	0.53 (0.16–1.72)	0.289
Adenoma weight, g	633	1.06 (0.89–1.27)	0.513	1.01 (0.85–1.20)	0.896	1.04 (0.84–1.29)	0.719	1.01 (0.83–1.23)	0.932

Each model adjusted for sex, age (in 10-year bands), and period of surgery (1989–1996, 1997–2004, 2005–2013).

Table 28. Linear regression of change in bone mineral denisty (Δ 1 year, absolute change), patients.

Site variable	*N*	Univariable regression β ($CI_{95\%}$)	*p*	r^2	Multivariable regression β ($CI_{95\%}$)	*p*	R^2
Δ BMD femoral neck							
Total serum calcium, mg/dL	440	0.01 (0.01–0.02)	<0.001	0.045	0.01 (0.01–0.02)	<0.001	0.057
24-hour urine calcium, mg/d	341	0.00 (0.00–0.00)	0.108	0.008	0.00 (0.00–0.00)	0.156	0.018
PTH, pg/mL	432	0.00 (0.00–0.00)	<0.001	0.034	0.00 (0.00–0.00)	<0.001	0.046
25-OH Vitamin D, ng/mL	364	0.00 (0.00–0.00)	0.717	<0.001	0.00 (0.00–0.00)	0.625	0.008
Osteocalcin, ng/mL	244	0.00 (0.00–0.00)	<0.001	0.073	0.00 (0.00–0.00)	<0.001	0.084
Multiglandular disease	437	0.00 (-0.01–0.01)	0.936	<0.001	0.00 (-0.01–0.01)	0.848	0.011
Adenoma weight, g	399	0.00 (0.00–0.01)	0.005	0.020	0.00 (0.00–0.01)	0.005	0.029
Δ BMD lumbar spine (L2–L4)							
Total serum calcium, mg/dL	470	0.01 (0.00–0.02)	0.103	0.006	0.01 (0.00–0.02)	0.113	0.009
24-hour urine calcium, mg/d	358	0.00 (0.00–0.00)	0.003	0.025	0.00 (0.00–0.00)	0.006	0.049
PTH, pg/mL	462	0.00 (0.00–0.00)	0.008	0.015	0.00 (0.00–0.00)	0.006	0.018
25-OH Vitamin D, ng/mL	394	0.00 (0.00–0.00)	0.232	0.004	0.00 (0.00–0.00)	0.244	0.004
Osteocalcin, ng/mL	259	0.00 (0.00–0.00)	0.188	0.007	0.00 (0.00–0.00)	0.239	0.010
Multiglandular disease	467	0.00 (-0.02–0.03)	0.819	<0.001	0.00 (-0.02–0.03)	0.805	0.003
Adenoma weight, g	426	0.00 (0.00–0.01)	0.119	0.006	0.00 (0.00–0.01)	0.122	0.007
Δ BMD distal radius							
Total serum calcium, mg/dL	358	0.00 (0.00–0.01)	0.525	0.001	0.00 (0.00–0.01)	0.471	0.004
24-hour urine calcium, mg/d	276	0.00 (0.00–0.00)	0.194	0.006	0.00 (0.00–0.00)	0.198	0.009
PTH, pg/mL	352	0.00 (0.00–0.00)	0.138	0.006	0.00 (0.00–0.00)	0.126	0.010
25-OH Vitamin D, ng/mL	289	0.00 (0.00–0.00)	0.915	<0.001	0.00 (0.00–0.00)	0.914	0.002
Osteocalcin, ng/mL	240	0.00 (0.00–0.00)	0.484	0.002	0.00 (0.00–0.00)	0.466	0.003
Multiglandular disease	355	0.00 (-0.02–0.01)	0.852	<0.001	0.00 (-0.02–0.01)	0.920	0.003
Adenoma weight, g	326	0.00 (0.00–0.00)	0.912	<0.001	0.00 (0.00–0.00)	0.969	0.012

Multivariable regressions for each predictor adjusted for sex, age >50 years, and period of surgery (1989–1996, 1997–2004, 2005–2013).

Table 29. Logistic regression of significantly improved bone mineral density (≥2.77%), patients.

Site variable	*N*	Univariable regression OR ($CI_{95\%}$)	*p*	Multivariable regression OR ($CI_{95\%}$)	*p*
Δ BMD femoral neck					
Total serum calcium, mg/dL	440	1.72 (1.27–2.34)	<0.001	1.77 (1.30–2.42)	<0.001
24-hour urine calcium, mg/d	341	1.00 (1.00–1.00)	0.029	1.00 (1.00–1.00)	0.093
PTH, pg/mL	432	1.01 (1.00–1.01)	0.001	1.01 (1.00–1.01)	<0.001
25-OH Vitamin D, ng/mL	364	0.97 (0.94–1.00)	0.028	0.97 (0.94–1.00)	0.027
Osteocalcin, ng/mL	244	1.01 (1.00–1.02)	0.030	1.01 (1.00–1.02)	0.026
Multiglandular disease	437	0.98 (0.50–1.92)	0.952	1.01 (0.51–1.99)	0.974
Adenoma weight, g	399	1.22 (1.06–1.42)	0.007	1.22 (1.05–1.41)	0.008
Δ BMD lumbar spine (L2–L4)					
Total serum calcium, mg/dL	470	1.36 (1.03–1.81)	0.031	1.38 (1.04–1.84)	0.026
24-hour urine calcium, mg/d	358	1.00 (1.00–1.00)	0.008	1.00 (1.00–1.00)	0.011
PTH, pg/mL	462	1.00 (1.00–1.01)	0.010	1.00 (1.00–1.01)	0.009
25-OH Vitamin D, ng/mL	394	0.99 (0.97–1.02)	0.431	0.99 (0.97–1.02)	0.466
Osteocalcin, ng/mL	259	1.01 (1.00–1.03)	0.017	1.01 (1.00–1.03)	0.016
Multiglandular disease	467	1.04 (0.54–1.99)	0.906	1.05 (0.54–2.01)	0.892
Adenoma weight, g	426	1.05 (0.94–1.18)	0.373	1.05 (0.94–1.18)	0.375
Δ BMD distal radius					
Total serum calcium, mg/dL	358	1.82 (1.26–2.64)	0.001	1.82 (1.25–2.64)	0.002
24-hour urine calcium, mg/d	276	1.00 (1.00–1.00)	0.546	1.00 (1.00–1.00)	0.509
PTH, pg/mL	352	1.00 (1.00–1.01)	0.009	1.00 (1.00–1.01)	0.008
25-OH Vitamin D, ng/mL	289	0.98 (0.95–1.02)	0.262	0.98 (0.94–1.01)	0.229
Osteocalcin, ng/mL	240	1.00 (1.00–1.01)	0.248	1.00 (1.00–1.01)	0.256
Multiglandular disease	355	1.07 (0.46–2.48)	0.870	1.05 (0.45–2.44)	0.909
Adenoma weight, g	326	1.15 (1.00–1.31)	0.049	1.14 (1.00–1.31)	0.050

Multivariable regressions for each predictor adjusted for sex, age >50 years, and period of surgery (1989–1996, 1997–2004, 2005–2013).

Paper IV – Cardiovascular morbidity

Exclusions were reported for the national cohort in Paper I, Figure 10. Preoperatively, time at risk was 49 935 person-years for patients and 149 341 person-years for controls; postoperatively, time at risk was 29 312 person-years for patients and 86 720 for controls. The median follow-up was 15.2 years, IQR 13.2–17.7.

Demography and socioeconomic details are reported in Table 5, perioperative characteristics are summarized in Table 6. Patients had in median 4 admissions (IQR 2–7) in the *National Patient Register* during the complete follow-up, controls in median 2 admissions (IQR 1–5).

The incidence rates pre- and postoperatively of CVD events and chronic cardiovascular dizease are summarized in Table 30, and Figures 15–20, which also present their associations with total serum calcium, adenoma weight and multiglandular disease.

Major CVD events such as *AMI* or *CVI* were not increased among patients pre- or postoperatively, but the incidence rates of *TIA* and *aortic aneurysm* were increased both pre- and postoperatively. However, the peak incidence of *TIA* was 1–4 years before surgery. *Heart failure* and *mitral valve stenosis* were increased preoperatively but normalized postoperatively. The incidence of *peripheral artery disease* was lower among patients than controls preoperatively.

Increasing total serum calcium was associated with increased incidence of *AMI*, *coronary artery disease* and *heart failure* postoperatively, and with *aortic aneurysm* preoperatively. Higher adenoma weight was associated with an increased incidence of *haemorrhagic CVI,* but lower incidence of *peripheral artery disease*. Multiglandular disease was associated with *mitral valve stenosis*, *aortic aneurysm* and *peripheral artery disease* preoperatively.

The subcohort registered in SwedeHeart and RiksStroke is described in Tables 31 & 32. There were no greater imbalances in relation to the complete national cohort or between patients and controls, although patients were slightly younger, less often unmarried, and had higher CCS, more admissions and higher educational level.

Patients registered in SwedeHeart were less likely to be present or former smokers, 47.1% compared to 52.0%, and fewer used moist snuff, 1.6% compared to 4.6%. Fewer patients previously had infarction, 22.7% compared to 26.8%, or cardiac surgery, 8.2% compared to 10.6%. The rate of hypertension was increased, 52.0% compared to 45.7%, but not the rates of previous CVI or diabetes mellitus.

Patients registered in RiksStroke did not differ significantly from registered controls.

Table 30. Cardiovascular events and chronic cardiovascular diseases, defined by ICD-9/10 codes given in Table 4.

Outcome	Preoperatively		IRR ($CI_{95\%}$)	Postoperatively		IRR ($CI_{95\%}$)	*p*‡
	Patients	Controls		Patients	Controls		
Acute myocardial infarction	156	433	1.08 (0.87–1.33)	194	554	1.04 (0.86–1.26)	0.900
Coronary artery disease†	191	490	1.17 (0.99–1.38)	225	641	1.04 (0.89–1.21)	0.421
Heart failure†	135	296	1.37 (1.11–1.67)*	269	722	1.10 (0.96–1.27)	0.255
Aortic valve stenosis†	20	57	1.05 (0.63–1.75)	30	110	0.81 (0.54–1.21)	0.088
Mitral valve stenosis†	14	13	3.22 (1.51–6.85)*	3	15	0.59 (0.17–2.05)	0.013
Cerebrovascular insult, CVI	166	457	1.11 (0.90–1.37)	239	648	1.07 (0.90–1.28)	0.623
Ischemic CVI	132	376	1.07 (0.85–1.34)	177	481	1.07 (0.87–1.31)	0.700
Haemorrhagic CVI	35	94	1.15 (0.75–1.78)	44	117	1.14 (0.78–1.68)	0.974
Transient ischemic attack	97	213	1.44 (1.08–1.91)*	113	235	1.38 (1.05–1.81)*	0.806
Carotid artery stenosis†	22	80	0.82 (0.51–1.32)	28	82	1.01 (0.66–1.56)	0.726
Peripheral artery disease†	76	327	0.70 (0.54–0.89)*	191	512	1.11 (0.94–1.31)	0.005
Aortic aneurysm†	52	92	1.69 (1.20–2.38)*	104	155	1.99 (1.55–2.55)*	0.429
Sub-group analyses of patients and controls with age ≥65 yy							
Acute myocardial infarction	104	347	0.91 (0.72–1.17)	151	436	1.03 (0.83–1.27)	0.262
Cerebrovascular insult	115	370	0.93 (0.73–1.20)	186	530	1.03 (0.84–1.25)	0.534

†) Standard Poisson regression for chronic diagnoses, only first-time event. ‡) Mixed-effects Poisson regression of interaction *patient status x postoperative time-period*. *) $p < 0.05$.

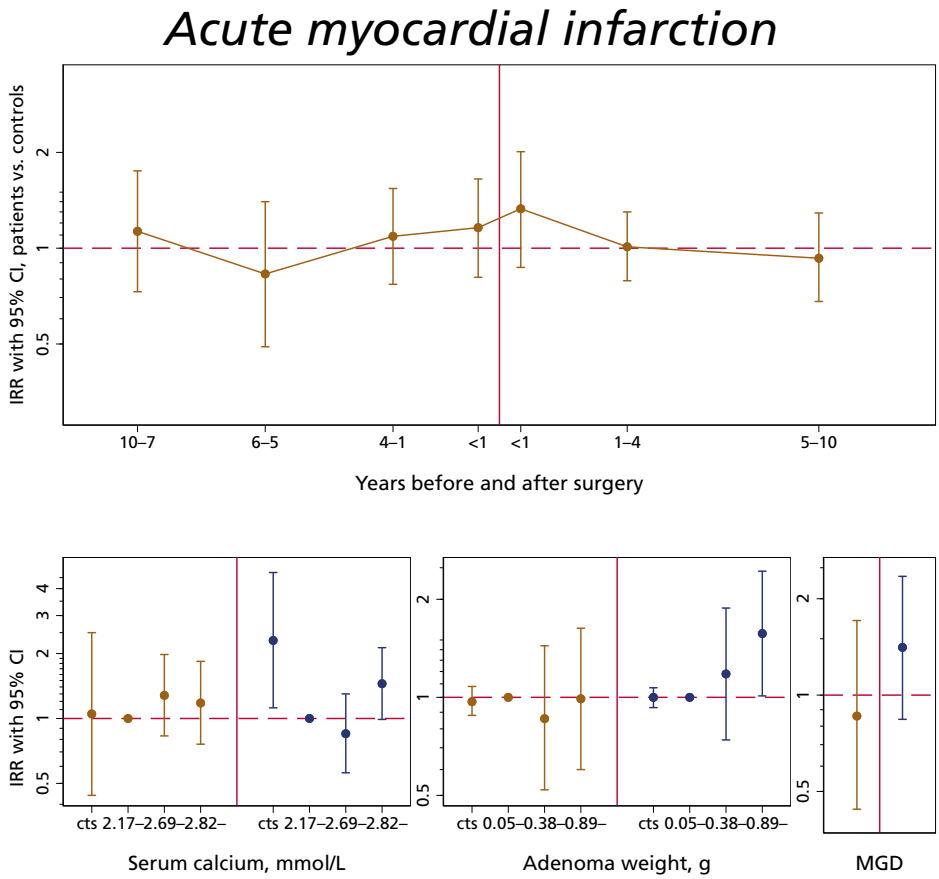

Figure 15. Incidence of *acute myocardial infarction* pre- and postoperatively, delimited by (|). In univariable regression of serum calcium at baseline, adenoma weight (analyses on continuous variable, cts, and in tertiles), and multiglandular disease (MGD), preoperative associations are given in brown and postoperative in blue.

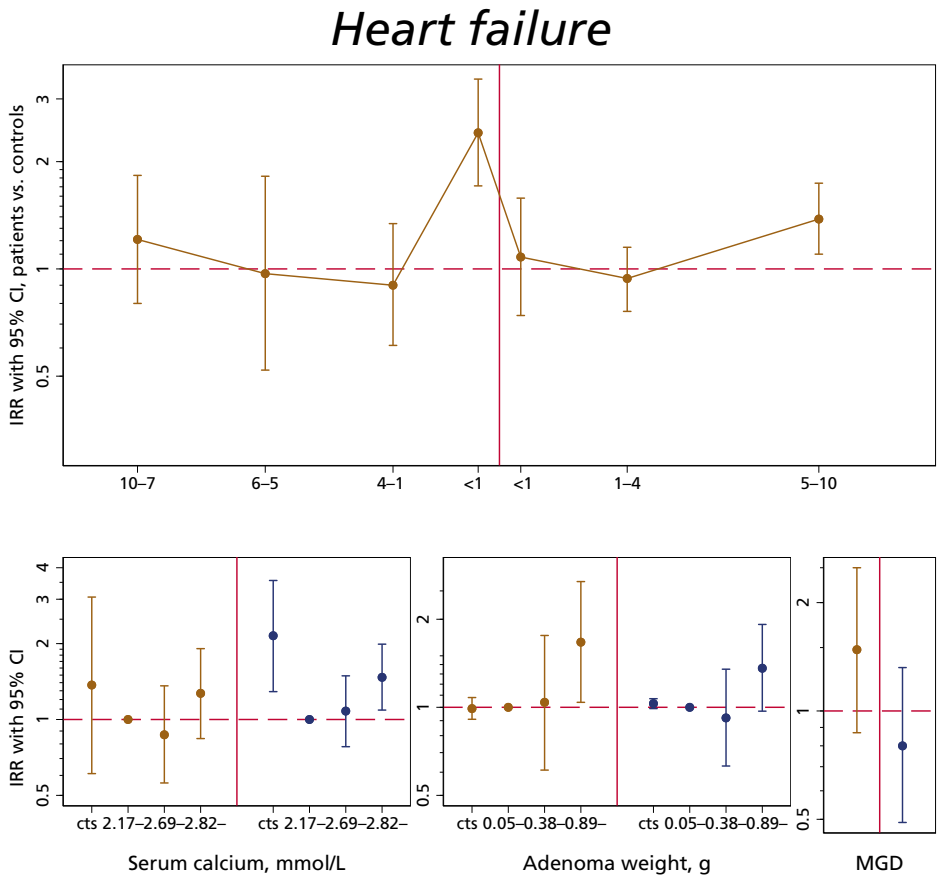

Figure 16. Incidence of *heart failure* pre- and postoperatively, delimited by (|).
In univariable regression of serum calcium at baseline, adenoma weight (analyses on continuous variable, cts, and in tertiles), and multiglandular disease (MGD), preoperative associations are given in brown and postoperative in blue.

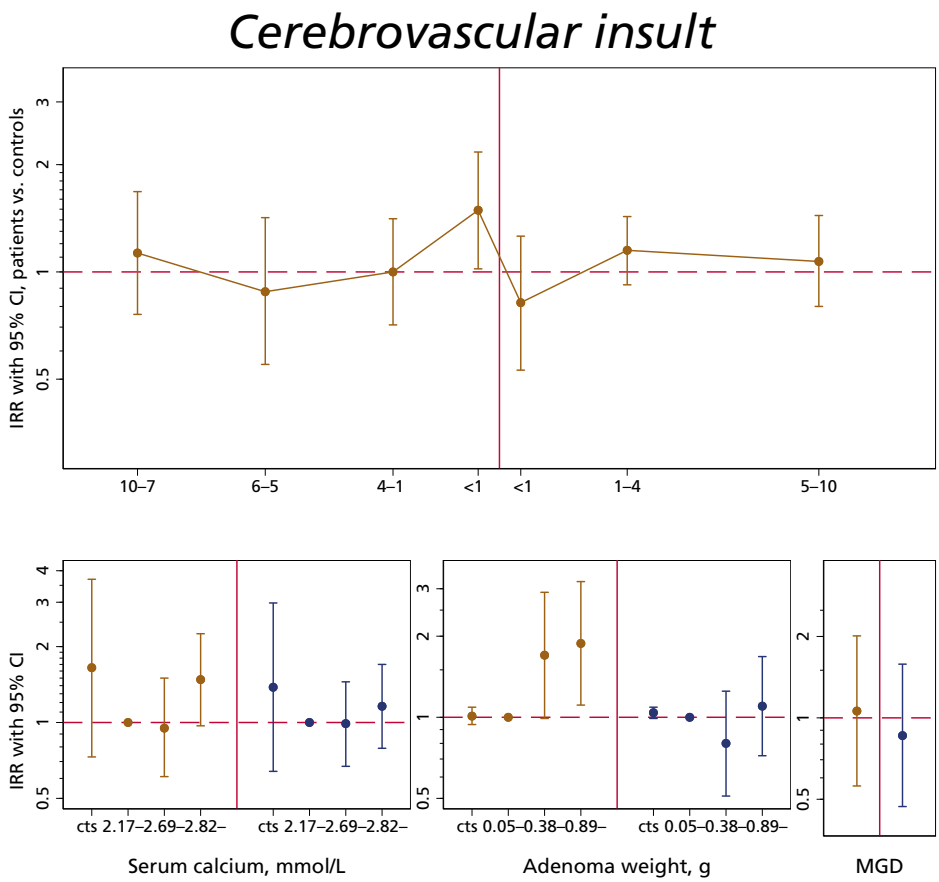

Figure 17. Incidence of *cerebrovascular insult* pre- and postoperatively, delimited by (|).
In univariable regression of serum calcium at baseline, adenoma weight (analyses on continuous variable, cts, and in tertiles), and multiglandular disease (MGD), preoperative associations are given in brown and postoperative in blue.

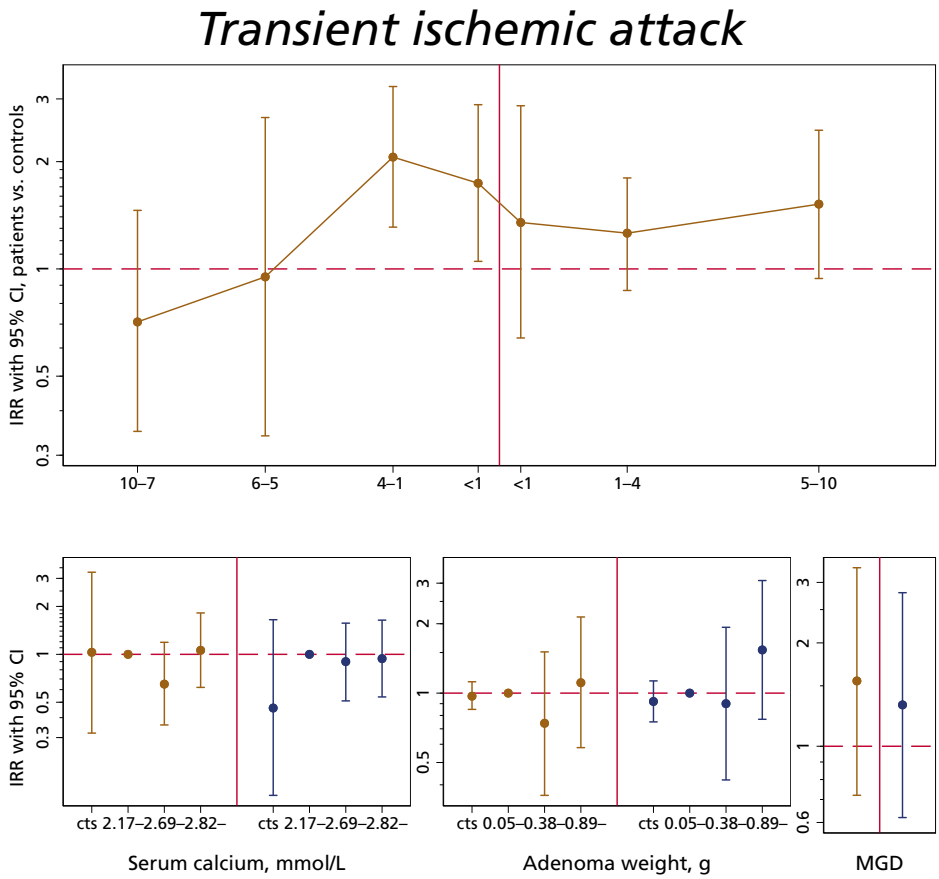

Figure 18. Incidence of *transient ischemic attack* pre- and postoperatively, delimited by (|). In univariable regression of serum calcium at baseline, adenoma weight (analyses on continuous variable, cts, and in tertiles), and multiglandular disease (MGD), preoperative associations are given in brown and postoperative in blue.

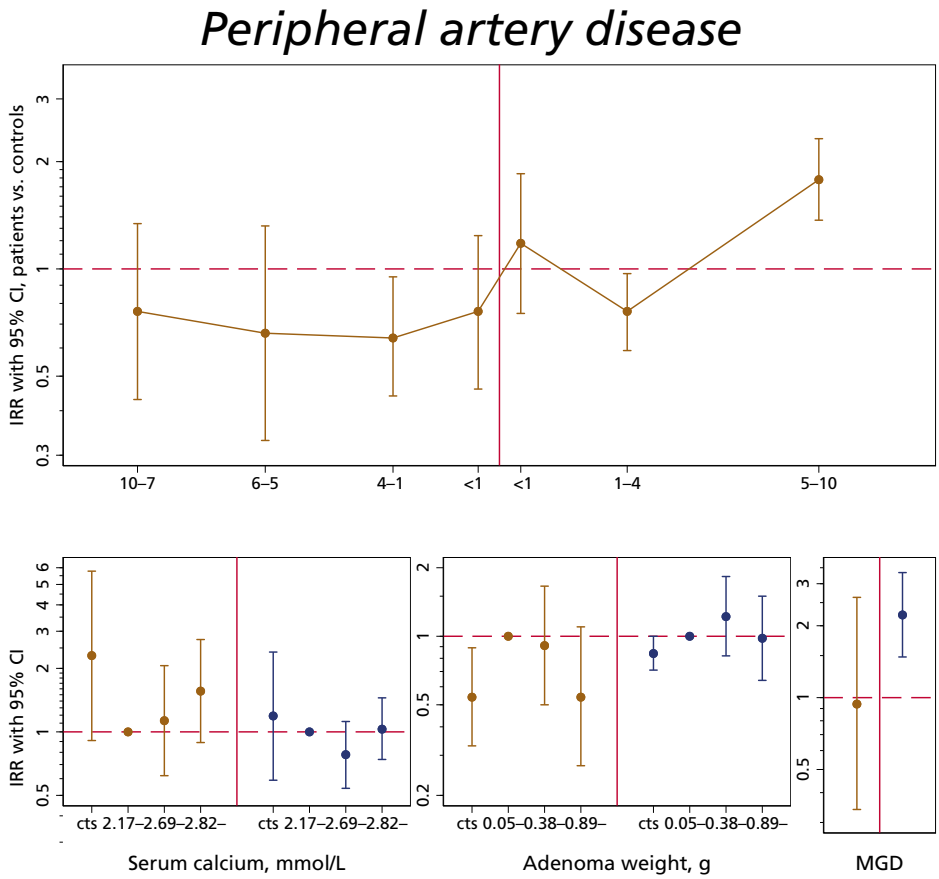

Figure 19. Incidence of *peripheral artery disease* pre- and postoperatively, delimited by (|). In univariable regression of serum calcium at baseline, adenoma weight (analyses on continuous variable, cts, and in tertiles), and multiglandular disease (MGD), preoperative associations are given in brown and postoperative in blue.

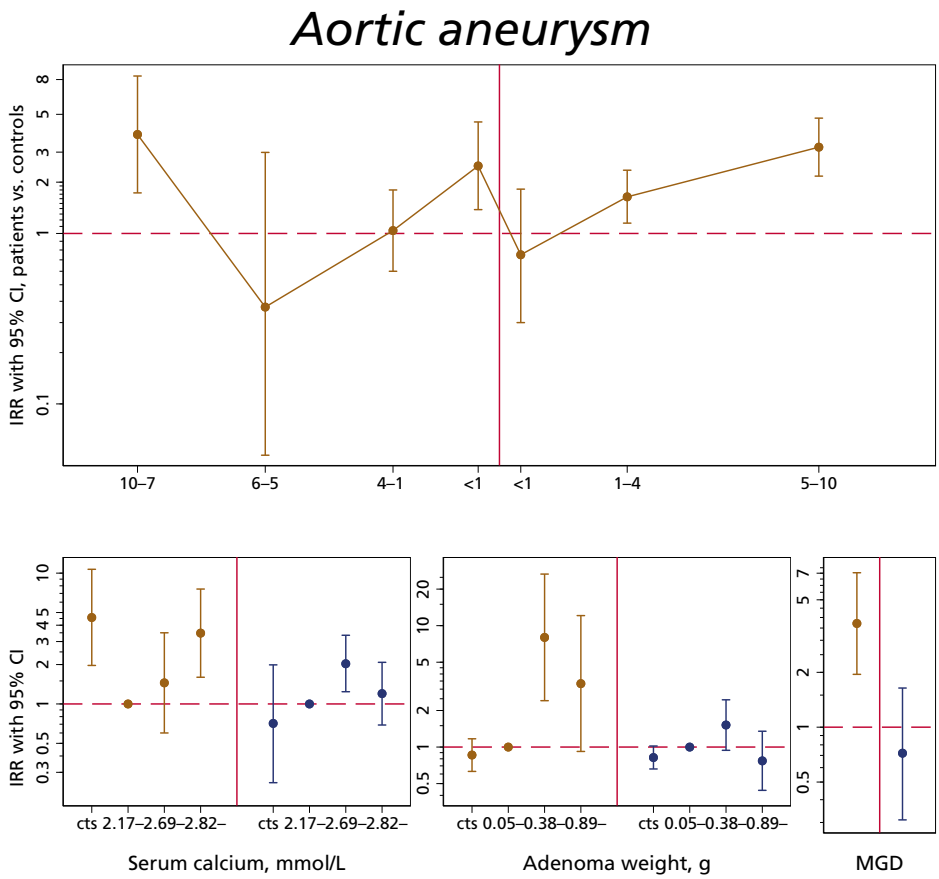

Figure 20. Incidence of *aortic aneurysm* pre- and postoperatively, delimited by (|).
In univariable regression of serum calcium at baseline, adenoma weight (analyses on continuous variable, cts, and in tertiles), and multiglandular disease (MGD), preoperative associations are given in brown and postoperative in blue.

Table 31. Demography and comorbidity in subcohort registered in SwedeHeart (652 patients and 1 536 controls) or RiksStroke (261 patients and 736 controls).

Characteristic	Patients	Distribution	Controls	Distribution	*p*†
Age, years	849	68.8 ± 10.2	2 113	70.1 ± 10.3	<0.001
Male sex, *n*	849	242 (28.5)	2 113	646 (30.6)	0.267
Unmarried, *n*	839	386 (46.0)	2 076	1 045 (50.3)	0.034
Charlson's score‡	849		2 113		<0.001
0 p		509 (60.0)		1 424 (67.4)	
1–2 p		281 (33.1)		554 (26.2)	
>2 p		59 (7.0)		135 (6.4)	
Admissions, *n*	849	8 (5–13)	2 113	6 (3–11)	<0.001
Disposable income, SEK	849	141 255 (113 168–193 390)	2 113	138 540 (110 868–188 685)	0.126
Elementary school only, *n*	840	301 (35.8)	2 080	893 (42.9)	0.002
Year of surgery	849		2 113		0.138
2003–2007		318 (37.5)		714 (33.8)	
2008–2010		296 (34.9)		802 (38.0)	
2011–2013		235 (27.7)		597 (28.3)	

Distribution in mean ± SD, median (IQR), *n* (%). †) *t*-test for normal distributed variables (age); Wilcoxon rank-sum test for skewed variables (admissions, disposable income); χ^2-test for nominal variables (sex, unmarried, Charlson's score, elementary school only, year of surgery), unless <5 expected in any cell, then Fisher's exact test was used. ‡) not including cardiovascular diagnoses.

Table 32. Perioperative characteristics for patients with outcomes registered in SwedeHeart or RiksStroke compared with the remaining cohort of patients with pHPT.

Characteristic	Subcohort		Remaining cohort		*p*†
	N	Distribution	*N*	Distribution	
Total serum calcium, mmol/L	842	2.78 ± 0.194	4 116	2.78 ± 0.200	0.705
Δ Total calcium, 6 months, mmol/L	582	-0.42 (-0.55– -0.32)	2 952	-0.41 (-0.53– -0.3)	0.058
Ionized serum calcium, mmol/L	841	1.46 ± 0.101	4 114	1.46 ± 0.104	0.745
Multiglandular disease	683	74 (10.8)	3 418	320 (9.4)	0.233
Adenoma on histology	839	728 (86.8)	4 131	3 631 (87.9)	0.365
Adenoma weight, g	600	0.614 (0.301–1.15)	3 102	0.57 (0.3–1.15)	0.530

Distribution in mean ± SD, median (IQR), *n* (%). †) t-test for normal distributed variables (calcium, ionized calcium); Wilcoxon rank-sum test for skewed variables (Δ total calcium, adenoma weight); χ2-test for nominal variables (multiglandular disease, adenoma on histology).

Discussion

Given the change in the disease severity towards *mild* or *asymptomatic* pHPT previously described, [30-34] and the increase in number of patients diagnosed, the indication for surgical treatment has been debated. The effects of surgical treatment previously described does not necessarily hold true in a contemporary context.

The most definitive outcome of any disease is mortality. In many of the Scandinavian studies from the 1980's and 1990's, including patients operated from the 1950's and onwards when patients diagnosed with and operated for pHPT had advanced disease with grave hypercalcemia, nephrolithiasis and severe, debilitating skeletal complications, mortality was increased even after surgery, suggesting unmitigated end-organ damage.[25, 120-127]

Subsequent observational studies from the late 1990's and onwards, present a mixed picture, which largely seems related to the disease severity in each cohort.[39, 112, 129-136] Several studies demonstrated decreasing mortality in patients operated in later time periods.[131-133] The SIPH study, a multicentre RCT on multiple outcomes in mild pHPT, showed no difference in survival.[79]

In Paper I, we found the mortality not to be increased among patients operated for pHPT compared with population controls. This is in line with the previously described decrease in mortality in later time periods.[131-133] The observed lower mortality among patients in the multivariable analysis correspond to the findings by Wermers et al and by Axelsson et al that parathyroidectomy reduce mortality.[46, 129] However, as these studies are observational series, they cannot fully account for the selection bias for treatment, i.e. patients with reduced expected survival not being offered or not opting for surgery.

An important difference from previous observational studies on mortality among patients operated for pHPT is that patients with biochemical evidence of persisting disease were excluded, which may in part explain the overall improved survival.

The use of CCS to adjust for comorbidity might not be ideal, but at least reasonable. As the management of many of the chronic diagnoses included in the score has shifted from inpatient to outpatient care, the validity could be questioned. However, in univariable Cox regression, CCS was strongly associated with increased mortality, equally in patients and controls.

We also confirmed that higher preoperative total serum calcium is associated with increased mortality among patients.[124, 129] This is also supported by experimental evidence on endothelial vasodilation and a previous cohort study on predictors of CVD morbidity,[89, 92] which dominate causes of death together with cancer diseases.

In Paper II, we found the fracture incidence to be increased in patients with pHPT up to four years before surgery, normalizing after surgery. This is directly comparable to the findings by Vestergaard et al and lately by Axelsson et al.[39, 40, 46]

There was no confirmed association with total serum calcium, adenoma weight or multiglandular disease. There might be a selection effect for earlier diagnosis and treatment in moderate to severe hypercalcemia, that interfere with longitudinal analysis on the effect of advanced disease.

Osteoporosis preoperatively was associated with increased fracture incidence both pre- and postoperatively, but this is difficult to interpret since being diagnosed with osteoporosis should prompt investigation to exclude pHPT. Osteoporosis and fractures are common with advanced age among the general population.

The distribution of fracture diagnoses can only be interpreted internal to study, as outpatient diagnoses are not included. Fractures types that generally not mandate inpatient care for surgery or rehabilitation are, most probably, underrepresented (e.g. radial fractures, vertebral compression fractures or costal fractures).

In Paper III, we found that 24-hour urine calcium predict both reduced fractures following surgery and improved BMD. The association between 24-hour urine calcium and BMD improvement has previously been demonstrated, but to our knowledge, not the association with reduced fracture incidence.[59, 61, 63, 68]

None of the proposed disease-specific predictors were associated with fracture incidence preoperatively. Impaired kidney function and BMD were associated with fracture incidence both pre- and postoperatively. Higher total serum calcium was, somewhat contradictory, associated with both increased fracture incidence and BMD recovery postoperatively.

Higher preoperative PTH, osteocalcin, and adenoma weight were associated with BMD recovery as previously described,[50, 63-65, 70-72, 74] but not with reduced fracture incidence as could be expected, given the observed association with BMD recovery.

Other factors previously linked to BMD recovery following surgery are lower BMD at baseline,[50, 55, 59, 65, 70, 72] premenopausal state in women,[58, 59] younger age,[63-65] increasing body weight postoperatively,[72] better kidney function,[51, 59] 1,25-$(OH)_2$ Vitamin D,[59] alkaline phosphatase,[50, 60, 64, 67] CTX,[50, 62, 66] and P1NP.[62, 66]

In Paper IV, we found increased incidence rates of *TIA* and *aortic aneurysm* among patients operated for pHPT, both pre- and postoperatively. *Heart failure* and *mitral valve stenosis* were both substantially increased preoperatively but normalized following surgery.

TIA is a strong risk factor for manifest cerebrovascular insult, CVI.[157] The incidence of *TIA* was increased two-fold 1–4 years preoperatively, and by 74% the last year before surgery. Postoperatively, the incidence decreased, but remained higher than that of controls. The incidence of *CVI* was increased the last year preoperatively only.

Overall, the incidences of major CVD events, i.e. *acute myocardial infarction, AMI,* or *CVI*, were not increased in patients compared to controls, in contrast to previously published cohort studies comparing patients to controls.[46, 112, 116] In observational studies, parathyroidectomy has previously been demonstrated to reduce the risk of major CVD events.[46, 115, 116] No RCT has been able to demonstrate any reduction of CVD morbidity following surgery.

However, we also found that higher total serum calcium is associated with increased incidence of *aortic aneurysm* preoperatively, and *AMI*, *coronary artery disease* and *heart failure* postoperatively, which is in line with previous findings by Hedbäck et al.[92]

Previous studies on patients with untreated pHPT have demonstrated increased prevalence of hypertension [103, 105, 113] and metabolic syndrome,[105] disturbed glucose metabolism,[82] increased physiologic measures of atherosclerosis,[93, 100, 102, 104-106, 108-110] disturbed endothelial vasodilation,[85, 95, 96, 107, 108] increased LVH,[105, 107, 117] cardiac diastolic dysfunction, and calcification of the myocardium and valves.[107] These findings provide a plausible pathophysiological framework for the observed increased incidence of *TIA*, *heart failure*, *mitral valve stenosis* and *aortic aneurysm.*

Following parathyroidectomy, previous studies have demonstrated improved measures of atherosclerosis,[100, 102, 104, 106, 108, 109, 118], improved endothelial vasodilation,[84, 96, 107, 108, 158] decreased LVM,[107, 111, 119] improved overall cardiac function,[99, 106, 107, 111, 158] and reduced cardiac irritability.[158] Decreased prevalence of metabolic syndrome and lowered triglycerides in males have also been reported.[82, 105] There is conflicting evidence on hypertension; while most studies have found improved blood pressure control and fewer medications needed,[97, 99, 100, 103-105, 111, 114, 158] two recent studies, including an RCT on cardiovascular risk factors, found no effect on blood pressure.[110, 118]

Our analyses may be biased in at least two respects. Patients having experienced a *TIA*, *CVI* or being diagnosed with chronic cardiac diseases might have a higher chance of being evaluated for hypercalcaemia and pHPT, i.e. a detection or work-up bias. Secondly, patients with evidence of severe atherosclerotic disease, such as having

symptomatic *peripheral artery disease* or a recent major CVD event, might to a lesser extent be offered or opt for parathyroidectomy, if pHPT is diagnosed, thereby posing a selection bias.

Possible explanations for the lack of association between pHPT and major CVD events in our cohort are that contemporary patients are diagnosed and operated with considerably milder disease than previously,[34] and that the general cardiovascular disease burden in the population is shifting with new treatment options.[159]

Large-scale observational studies provide a unique possibility to explore important clinical problems, both in terms of exposure analysis and investigation of treatment effects. RCTs provide the ideal method to evaluate interventions but may not be feasible if the disease is rare, the outcome far into the future or hard to measure biometrically. Population-bases or insurance claims-based registers can provide high quality data, provided that data collection is valid. Meta-analyses on large-scale observational studies from different settings in combination with available RCTs can be helpful in guiding clinicians and patients in treatment decisions, when evidence from RCTs alone do not provide enough advice.

A general problem in observational studies is that it is hard to rule out or completely account for biases, e.g. selection bias as discussed earlier. In the studies of this thesis, outcomes of a nation-wide patient cohort from a surgical quality register and of a local, prospectively collected cohort of surgically treated patients have been analysed. This means that the generalisability is reduced since the studies have no information on patients not treated surgically.

Current international guidelines on surgical treatment of pHPT provide the following indications for surgery in pHPT: 1) symptomatic pHPT, 2A) hypercalcemia >0.25 mmol/L above upper reference; supported by our finding that increasing total serum is associated with mortality, BMD recovery and cardiovascular morbidity, 2B) vertebral fracture or T-score <-2.5 at any site; supported by our finding that fracture incidence is increased in untreated pHPT and normalize following surgery, and that BMD improve following surgery, 2C) renal involvement with impaired kidney function, nephrocalcinos or nephrolithiasis, hypercalciuria >250 mg/d for women and >300 mg/d for men; supported by our finding that 24-hour urine calcium predicts reduced fractures and improved BMD following surgery, 2D) age <50 years; supported by our finding that untreated pHPT carries an increased cardiovascular disease burden which is in part reversible, 2E) patient's choice.[10]

Strengths and limitations

Paper	Strengths	Limitations
I	Nation-wide cohort, large series	No non-surgical controls
	Outcomes from Swedish Cause of Death Register, high data quality	Scarce biochemical data, no PTH or predictors of cardiovascular morbidity
	Patients with unsuccessful surgery excluded	
	MICE used to handle missing data	
II	Nation-wide cohort, large series	No non-surgical controls
	Outcomes from National Patient Register, high data quality	Scarce biochemical data, no PTH or 24-hour urine calcium
	Patients with unsuccessful surgery excluded	
III	Prospectively collected single-center cohort, consequetive series	Changing biochemical methods during the study period
	Detailed biochemical data and BMD measurements with follow-up	BMD measurement from only part of the series
	Patients with unsuccessful surgery excluded	Retrospective
IV	Nation-wide cohort, large series	No non-surgical controls
	Outcomes from National Patient Register, SwedeHeart and RiksStroke, high data quality	Scarce biochemical data, no PTH or predictors of cardiovascular morbidity
	Patients with unsuccessful surgery excluded	

Conclusions

Paper I

Overall mortality is not increased among patients with pHPT compared to population controls following surgery, any over-risk from disease complications is reduced with successful treatment. Total serum calcium predicts mortality, supporting the international recommendations for surgical management of pHPT.

Paper II

Fracture incidence is increased up to 4 years before surgery for pHPT and normalize following successful surgery. None of the proposed disease-specific factors were associated with fracture incidence.

Paper III

24-hour urine calcium predicts reduced fracture incidence and BMD recovery following surgery in patients with pHPT, supporting the international recommendations for surgical management of pHPT. Findings on total serum calcium is contradictory; PTH, osteocalcin and adenoma histology were associated with BMD recovery.

Paper IV

Major CVD events were not increased among patients with pHPT, before or after surgery. The incidence rates of *TIA*, *heart failure* and *mitral valve stenosis* were increased before surgery and were reduced after surgery. The incidence of *aortic aneurysm* was increased in untreated pHPT but was not affected by surgery. Higher total serum calcium was associated with increased incidence rates of *aortic aneurysm* preoperatively and *acute myocardial infarction, coronary artery* disease, and *heart failure* postoperatively, supporting the international recommendations for surgical management of pHPT.

Future perspectives

Given the shift in disease presentation and increasing number of diagnosed patients, largely related to biochemical screening and demographic changes in Western countries with aging populations, it would be interesting and important to evaluate the present situation in Sweden with decreasing availability for surgical treatment for benign disorders.

Especially patients with comorbidities necessitating inpatient perioperative care at a hospital with an available intensive care unit, i.e. patients with cardiovascular, respiratory or chronic kidney disease, experience very long waiting lists to surgery. None of the measures so far passed and implemented by the Swedish government or regional authorities have managed to increase the availability for this patient group.

In several US reports, the utilization of parathyroidectomy in pHPT has been investigated, finding low overall utilization, 12.8% to 32% in different settings, and low rates even among patients clearly fulfilling the international guidelines criteria for surgical treatment of pHPT (33%).[160-162] A similar evaluation investigating temporal trends, adherence to international and national recommendations and the impact of parathyroidectomy on major outcomes should be feasible using the Swedish population-based registers.

Generally, limitations in observational study design affect the ability to conclude whether observed differences are causal. In Paper I, we cannot conclude whether the observed indifference in overall mortality is a result from biochemical cure, or if there was no effect due to the fact that contemporary patients are operated with milder disease. Similarly, in Papers II & IV, we can only make the assumption, that observed changes in incidence rates after parathyroidectomy is related to the biochemical cure by surgery.

To affirm this, there is still a need for further well-conducted RCTs. The largest RCT so far, the SIPH study failed in proving treatment effects in most areas. At our department, a single-center RCT has been conducted on mild pHPT (ionized serum calcium <1.50 mmol/L, normal renal function, no evidence of osteoporosis and age >65 years at inclusion) evaluating the treatment effect of parathyroidectomy over two years by biochemistry, BMD, renal function, cardiac function, atherosclerosis and cognitive tests. Now finally closed, this study can hopefully provide valuable evidence.

Individualized treatment by preoperative measures to prognose treatment effects is another interesting trend. Koman et al predicted the treatment effect of surgery for pHPT on neuromuscular, cognitive and affective symptomatology, using short-term calcimimetics treatment preoperatively.[163, 164] This seems likely to be a valuable addition in preoperative work-up for patients with diffuse symptomatology, not fulfilling the international criteria for surgical treatment.

Errata

Paper I

In Methods, p 859, second column, lines 7–8, it is stated that CCI score was included in the multivariable models as “0, 1, 2 or more”, should be “0, 1–2, more than 2”.

Paper II

In Material and Methods, p 278, second column, lines 23–24, it is stated that univariable Poisson models were fitted for Charlson's comorbidity score “divided as 0, 1 or ≥2 points”, should be “0, 1–2, >2 points”.

Acknowledgements

Hereby, I would like to express my gratitude and appreciation to all, who, in one way or another, helped med to achieve this doctoral thesis.

Martin Almquist, main supervisor, always optimistic and enthusiastic, and co-supervisors Anders Bergenfelz, Erik Nordenström and Mark Their, for your generous help, support, and endless revising of too long manuscripts.

Kristina Åkesson, Gustav Smith, Elin Ståhl, Kerstin Höfler, co-authors, for important input in designing the thesis projects and, again, revising my long manuscripts. Åsa Westrin, for the planning of a psychiatric project, which have not quite happened yet.

Pall Hallgrímsson, Lo Hallin Thompson and Farhad Salem, present and former colleagues on the Endocrine and Sarcoma unit, for your support and understanding. All staff in the outpatient clinic, present and former, for all your help, flexibility and a fika now and then.

Gabriel Börner, former clinical supervisor, and Hans Mårtensson, for making me a surgeon. Maria Cornelius, for making sure I was not laid off even though I had been practically fired in advance on the third day of my first temporary job, and Per-Anders Larsson, for complying.

Henrik Bergenfeldt, colleague and long-time friend, for interesting research discussions and valuable help with the multiple imputation for Paper I.

Adam Zeyara, my colleague and roommate, for interesting discussions on life, work, research and everything there in between.

Jonas Björk, for help with the basics of epidemiology and standardized mortality ratio. Jenny Sandgren and Anna Åkesson at Clinical Studies Sweden, for your valuable statistical advice on mixed-effects Poisson regression for Papers II–IV. Ian White of UCL, for advice on multiple imputation for mixed-effects Poisson regression, not yet used.

Last, and not least, my family —

Selma, Kerstin, Vidar & Gro, for your endurance in endless days and nights consumed by the thesis, and my parents, Anders Nilsson and Maria Nyman-Nilsson, for your dedication and support.

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Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

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Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:37
ISBN 978-91-8021-530-5
ISSN 1652-8220