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PRIMARY HYPERPARATHYROIDISM - COMORBIDITY AND OUTCOME AFTER PARATHYROID ADENOMECTOMY

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In memory of my grandfather, Mille
ABSTRACT

Primary hyperparathyroidism (pHPT) is associated with increased mortality in certain malignant tumours. Breast cancer is the most common and a shared aetiology has been suggested. In a register-based nested case-control study, we compared breast cancer in patients with and without a previous operation for pHPT. Neither tumour size or stage, nor lymph node metastases differed, nor did breast cancer specific survival.

Longer life expectancy and a lower threshold for referral of pHPT patients to surgery have lead to an increasing proportion of elderly patients. In a large cohort study of the period 1961-2004, all-cause mortality within 30 days and one year after surgery for pHPT was analysed. The entire Swedish population, standardized for age, sex and time period, served as control. During the study period, 30-day mortality decreased from 4.2% to 0.4% and mean age increased by 11 years (53-64 years). Cardiovascular disease was the dominant cause of death in both sexes and all age groups.

Patients with pHPT have lower bone mineral density and display several risk factors of cardiovascular disease. Vitamin D deficiency is more common in pHPT and could aggravate the complications. In a randomized clinical trial, we examined the effect of vitamin D supplementation on bone mineral density, blood pressure and metabolic risk factors after curative surgery for pHPT. 150 patients were randomized to either calcium and vitamin D or calcium alone. Surgery had a positive effect on bone mineral density and insulin resistance and a small positive effect on systolic blood pressure. There was no obvious additive effect of vitamin D supplementation.

Conclusions: Breast cancer in pHPT patients seems to have the same characteristics and prognosis as in the general population. Parathyroidectomy is a safe operation, even in the elderly, and leads to improvements in bone mineral density, insulin resistance and to a lesser extent in systolic blood pressure. Vitamin D supplementation after surgical cure had no obvious beneficial effect.
LIST OF PUBLICATIONS

This thesis is based on the following original studies, which will be referred to in the text by their Roman numerals:

I. **Perioperative mortality in parathyroid surgery in Sweden during five decades – improved outcome despite older patients**
   Norenstedt S., Ekbom A., Zedenius J., Nilsson I-L.
   European Journal of Endocrinology (2009) 160; 295-299

II. **Breast cancer associated with primary hyperparathyroidism – a nested case control study**
    Clinical Epidemiology (2011) 3; 103-106

III. **Primary hyperparathyroidism and metabolic risk factors: impact of parathyroidectomy and vitamin D supplementation; results of a randomized double-blind study**
     Submitted

IV. **Parathyroidectomy increases bone mineral density in primary hyperparathyroidism – no additive effect of vitamin D supplementation – a randomized double-blind study**
    Submitted
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LIST OF ABBREVIATIONS

%CV  coefficient of variation in per cent
1,25(OH)2D  1,25-dihydroxyvitamin D
24h ABP  24-hour ambulatory blood pressure
25-OH-D  25-hydroxyvitamin D
βCTx  c-terminal telopeptide of type 1 collagen
BMC  bone mineral content
BMD  bone mineral density
BMI  body mass index
BP  blood pressure
Ca2+  serum ionized calcium
CI  confidence interval
D-  group treated with calcium carbonate
D+  group treated with cholecalciferol and calcium carbonate
DBP  diastolic blood pressure
DXA  dual x-ray absorptiometry
GFR  glomerular filtration rate
HDL  high density lipoprotein
HOMA-IR  the homeostatic model assessment insulin resistance
HR  heart rate
HR-pQCT  high-resolution peripheral quantitative computed tomography
ICD 7  International Classification of Diseases 7th revision
IGF-I  insulin-like growth factor I
IGFBP-1  insulin-like growth factor binding protein 1
IQR  inter quartile range
IU  international units
LBM  lean body mass
LDL  low density lipoprotein
n  number
P  phosphate
P1NP  procollagen type I aminoterminal propeptide
pHPT  primary hyperparathyroidism
PTH  parathyroid hormone
<table>
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<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>PTX</td>
<td>parathyroid adenomectomy</td>
</tr>
<tr>
<td>RIA</td>
<td>radioimmunoassay</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>SMR</td>
<td>standard mortality ratio</td>
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<tr>
<td>TG</td>
<td>triglycerides</td>
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<tr>
<td>UD</td>
<td>ultra distal</td>
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1 INTRODUCTION

1.1 PRIMARY HYPERPARATHYROIDISM

1.1.1 Clinical presentation of primary hyperparathyroidism

Primary hyperparathyroidism (pHPT) is a common endocrine disorder, characterized by elevated or “high normal” serum calcium in combination with an inappropriately high level of parathyroid hormone (PTH). It is caused by excessive, incompletely regulated secretion of PTH from one or more of the parathyroid glands. In more than 80% of the cases there is a single, benign parathyroid adenoma: in the remaining cases, multiglandular involvement is seen. Parathyroid cancer is rare (0.5% of the cases).

PHPT is mostly a sporadic disease, but a small percentage of the cases is part of a hereditary multiple endocrine neoplasia type I or IIa, HPT-jaw tumour syndrome or other rare hereditary disorders. The introduction of automated serum analyses of calcium in the early 1970s, led to a sharp increase in the observed prevalence of pHPT. Today the prevalence is around 1%, with a female:male ratio of 3:1. It increases with age in both sexes, with a prevalence up to 3.4% or even higher, in postmenopausal women.

In a Swedish screening study on premenopausal women, the prevalence of assumed mild pHPT was as high as 5.1%, and 2.7% on repeated measures.

Besides the increased prevalence, the clinical picture has changed from the classic symptoms of severe osteoporosis or osteitis fibrosa cystica, gastrointestinal symptoms, muscle weakness, psychiatric symptoms, kidney stones and nephrocalcinosis to a more or less asymptomatic disease in a majority of the patients. By definition, asymptomatic pHPT presents without overt clinical signs. However, these patients often have reduced bone mineral density (BMD), preferentially in cortical bone, cardiovascular disturbances and metabolic abnormalities. Asymptomatic or normocalcaemic patients may have an early form of the disease, with smaller adenomas.

Long-term follow-up of conservatively treated pHPT patients shows that in most cases the disease is relatively stable. Progression has been documented in one fifth to one third of the patients. Lowe et al. followed 37 normocalcaemic pHPT patients for 1-9 years and found that as many as 40% developed evidence of disease progression.
Patients with pHPT also have an increased risk of death from mainly cardiovascular disorders and certain malignancies, of which breast cancer is the most frequent\textsuperscript{26,27,28-30}.

1.1.2 Treatment

The only curative treatment of pHPT is surgical removal of the affected parathyroid gland(s). With improved techniques for preoperative localization, such as ultrasound and scintigraphy, and assays for intraoperative PTH monitoring, the surgery has become less extensive. Both the traditional four-gland exploration and minimally invasive surgery have a success rate of >95% and very low morbidity in the hands of experienced surgeons\textsuperscript{31,32}. Since life expectancy and awareness of the disease have risen, an increasing proportion of elderly patients are referred to surgery.

The change in the disease profile has lead to controversies over the advisability of recommending surgery to all patients, especially if they are asymptomatic and the diagnosis is discovered incidentally. This has resulted in the development of international guidelines for the surgical treatment of asymptomatic pHPT, in order to select patients with an expected beneficial effect. The current criteria are: age < 50 years, serum calcium levels > 0.25 nmol/l above the upper limit of normal, creatinine clearance < 60 ml/min and BMD detected T-score < -2.5 at any site or previous fragility fracture\textsuperscript{33}.

After curative surgery, 9-62\% of patients, depending on the time after surgery, have a persistently elevated PTH despite normocalcaemia\textsuperscript{34,35}. Postoperative PTH elevation is associated with higher preoperative PTH, higher bone turnover markers and lower vitamin D levels\textsuperscript{34,36}. The underlying aetiology is probably multifactorial. Possible causes are an increased need of calcium and phosphate in the remineralization of bone (hungry bone), vitamin D deficiency causing secondary hyperparathyroidism and reduced peripheral sensitivity to PTH\textsuperscript{35,37,38}. The high preoperative PTH and low vitamin D levels suggest a beneficial effect of postoperative vitamin D supplementation in these patients, but there are no randomized trials which address this issue.

1.1.3 Calcium and parathyroid hormone

Calcium has several important physiological functions. One is to provide the mineral structure of bones and teeth and another is metabolic. Soluble calcium ions (Ca$^{2+}$) in the
extracellular fluid are essential in a large number of enzymatic reactions, cell signalling and electrical membrane potentials necessary for normal cellular function. The skeleton serves as a reservoir of calcium. Precise control of the calcium level is critical and involves the parathyroid glands, the kidneys, the skeleton and the gut. The principal regulators of calcium homeostasis are PTH and 1,25-dihydroxyvitamin D (1,25(OH)₂D). The free extracellular Ca²⁺ concentration is maintained within a narrow range (1.15-1.33 nmol/l). Approximately 50% of the total amount of circulating calcium is free: 40% is bound to proteins, mainly albumin, and about 10% to anions such as sulphate and citrate.

Parathyroid hormone is secreted by the chief cells of the parathyroid glands. It is initially synthesized as pre-pro-parathyroid peptide, which then undergoes post-translational modifications, resulting in the biologically active 84-aminoacid protein. PTH has a short half-life and is degraded by the liver and kidney. It exerts its action through binding to widely distributed PTH receptors, mainly expressed in bone and the kidneys.

PTH is a major regulator of calcium and phosphate homeostasis. Its main function is to maintain the extracellular calcium concentration within physiological limits through actions on bone metabolism, renal function, vitamin D activation and gastrointestinal absorption.

Ca²⁺ exerts its action on the parathyroid glands by binding to a surface-bound G-coupled receptor, the calcium sensing receptor (CaSR). A change in the secretory rate of PTH in response to low Ca²⁺ takes place in a matter of seconds and the net rate of PTH synthesis increases within 30 minutes. PTH elevates serum Ca²⁺ concentrations by increasing calcium reabsorption in the loop of Henle and the distal tubule of the kidney and by stimulating the conversion of 25-hydroxyvitamin D (25-OH-D) to the active 1,25(OH)₂D in the proximal tubule. PTH also releases Ca²⁺ and phosphate from the skeleton. At the same time, PTH has a phosphaturic effect by stimulating the excretion of phosphate in the proximal tubule of the kidney (Figure 1). This is thought to compensate for the extra phosphate released from the skeleton.

PTH production is increased by phosphate and inhibited by Ca²⁺ and 1,25(OH)₂D.
1.2 ASSOCIATION TO BREAST CANCER

PHPT is associated with an increased risk of developing malignant disorders. Certain malignant tumours are overrepresented, for example breast cancer, colon cancer, cancer in the kidneys and non-melanotic skin cancer. The increased risk of breast cancer persists for at least 15 years after parathyroid adenomectomy (PTX). Breast cancer patients have a high incidence of hypercalcaemia, and pHPT may be one of the causes apart from bone metastases. PHPT was found to be more common in a breast cancer population than in patients with differentiated thyroid cancer and it was unrelated to clinical stage or anti-tumour therapy. In a group of untreated breast cancer patients, the association was no longer significant when age was taken into account. Serum calcium and 25-OH-D concentrations have also been associated with an increased risk of breast cancer, but data are not consistent. Breast cancer and pHPT share several other characteristics: both typically affect postmenopausal women and both are associated with ionized radiation and obesity.
These common features suggest potential shared etiological pathways or risk factors of pHPT and breast cancer, such as predisposing genetic or environmental factors. There could also be an increased susceptibility to one disease as a consequence of the other, but that is less likely because the risk of breast cancer persists after surgically treated pHPT\textsuperscript{27}. Little is known about any possible causal relationship. Familial accumulations of pHPT and breast cancer, as well as isolated cases with high penetrance susceptibility genes, have been reported\textsuperscript{59,60}.

Whether pHPT affects the aggressiveness of breast cancer is not known. One study found an association between serum calcium levels and increased tumour aggressiveness in premenopausal and/or overweight women\textsuperscript{61}.

### 1.3 VITAMIN D

Vitamin D supplies in humans come from exposure to sunlight and dietary intake. Ultraviolet radiation from the sun converts 7-dehydrocholesterol to cholecalciferol (vitamin D3) in the skin. The quantity of vitamin D3 formed in the skin depends on the duration and intensity of sunlight exposure. Vitamin D3 can be stored in fat and in the liver. Vitamin D is hydroxylated twice, first in the liver to 25-hydroxyvitamin D (25-OH-D) and a second time in the kidney, where it is converted by 1α-hydroxylase to its biologically active form, 1,25-dihydroxyvitamin D (1,25(OH)\textsubscript{2}D). 25-OH-D is used to determine a person’s vitamin D status since it is more stable and its serum concentration is 500-1000 times higher than 1,25(OH)\textsubscript{2}D’s. 1,25(OH)\textsubscript{2}D binds to the vitamin D receptor, an intracellular hormone receptor, to exert its effect. Vitamin D is involved in the regulation of cellular metabolism and differentiation, bone metabolism and inflammation. It plays a role in calcium homeostasis, where 1,25(OH)\textsubscript{2}D increases serum calcium concentrations by enhancing absorption from the intestine and resorption of calcium from bone (Figure 1). PTH stimulates the conversion to 1,25(OH)\textsubscript{2}D, while 1,25(OH)\textsubscript{2}D has a negative effect on PTH secretion. Other regulators of 1,25(OH)\textsubscript{2}D are phosphorus, calcium and fibroblast growth factor \textsuperscript{23,44,62,63}.

There is no globally accepted cut-off defining vitamin D deficiency and insufficiency. The most widely used (recommended by the Institute of Medicine, USA\textsuperscript{64} and the
Danish Sundhedsstyrelsen) is deficiency defined as a 25-OH-D concentration below 25 nmol/l and insufficiency as $\leq 50$ nmol/l. Attempts to define vitamin D deficiency are often based on studies aimed at determining the point at which vitamin D cannot further suppress the PTH level, resulting in a wide range of values $^{65-67}$. Other studies on 25-OH-D levels in relation to clinical outcomes, such as BMD, fractures and colorectal cancer, found advantages at 25-OH-D concentrations above 50-75 nmol/l $^{68,69}$. A large cross-sectional analysis on more than 300,000 individuals showed a continuous decline in PTH with rising 25-OH-D and no inflection point or plateau $^{70}$.

Vitamin D insufficiency is one of the causes of secondary hyperparathyroidism. A chronic, low vitamin D concentration has an adverse effect on the skeleton, leading to rickets in children and osteoporosis/osteomalacia in adults. Many extra-skeletal conditions, such as autoimmune diseases, malignancies and cardiovascular morbidity and mortality, have been associated with low vitamin D levels in observational studies $^{51,71-73}$. However, the existing data are inconclusive as to causality.

Supplementation with vitamin D and calcium has a putative positive effect on bone health and fracture prevention, but the evidence is inconsistent $^{74,75}$. In a recent pooled analysis of eleven randomized clinical trials, looking at quartiles of actual intake of vitamin D, high-dose vitamin D supplementation ($\geq 800$ IU daily) was somewhat better for preventing hip fracture and any non-vertebral fracture in patients 65 years of age or older $^{76}$. There is not enough evidence for benefits of vitamin D and/or calcium supplementation in extra-skeletal conditions and mortality $^{64,77,78}$. In a pooled analysis, vitamin D and calcium reduced mortality, but data did not support an effect of vitamin D alone $^{79}$.

A low concentration of vitamin D is more prevalent in patients with pHPT than in geographically matched populations $^{80-83}$. Vitamin D deficiency seems to be associated with more severe pHPT, in terms of higher PTH levels, larger adenomas and lower BMD $^{82,83}$. It is also associated with a persistent PTH elevation after curative surgery $^{36}$. Possible explanations for the relationship between pHPT and low vitamin D levels are stimulation of adenoma growth or inhibition of the production of vitamin D in skin and liver by the elevated level of 1,25(OH)$_2$D, caused by an increased conversion to 1,25(OH)$_2$D in the kidney. Enhanced inactivation of 25-OH-D in the liver has also been suggested $^{84}$. 
The Guidelines for management of asymptomatic pHPT recommend repletion to a 25-OH-D concentration > 50 nmol/l to distinguish primary from secondary hyperparathyroidism\textsuperscript{33}. Supplementation with vitamin D in untreated pHPT patients may decrease PTH levels and bone turnover, but there are no randomized trials to prove any beneficial effects\textsuperscript{85}. Since low vitamin D is common in pHPT patients and associated with a persistent elevation of PTH after surgery, postoperative vitamin D supplementation might have positive effects on bone health and metabolic disturbances associated with pHPT.

However, studies on repletion after parathyroid surgery are sparse and no randomized trial has been conducted. A reduction in PTH concentration has been shown, but no effect on BMD\textsuperscript{86,87}.

1.4 METABOLIC AND CARDIOVASCULAR COMPLICATIONS

1.4.1 Cardiovascular morbidity and mortality

Serum levels of PTH have been associated with cardiovascular morbidity and mortality in the general population\textsuperscript{88-90}. An increase in cardiovascular mortality in patients with pHPT has been well documented in European studies\textsuperscript{9,26,91-96}. North American studies are incongruent with these results but an association has been demonstrated between high calcium levels and increased cardiovascular mortality\textsuperscript{97,98}. A possible explanation is that patients diagnosed in more recent years have less severe disease. However, Yu et al. found that patients with untreated mild pHPT, diagnosed between 1997 and 2006, had an increased cardiovascular morbidity and mortality compared to the general population, but mortality data in mild pHPT are scanty\textsuperscript{99}.

Most studies indicate that PTX results in a lower mortality\textsuperscript{26,100,101}. The pathogenesis of the increased risk of cardiovascular disease in pHPT has not been established. PHPT has been associated with cardiac abnormalities in structure and function, such as left ventricular hypertrophy, diastolic dysfunction and conduction disturbances\textsuperscript{28}. Several aspects of the metabolic syndrome have been linked to pHPT, such as increased body weight\textsuperscript{57}, hypertension, dyslipidaemia, glucose intolerance and insulin resistance\textsuperscript{102-105}. 


PTH in normocalcaemic patients is also independently associated with hypertension, dyslipidemia, body mass index (BMI) and insulin sensitivity\textsuperscript{106,107}.

1.4.2 Hypertension and pHPT

Hypertension is common in pHPT even in its mild form\textsuperscript{105,108,109}. The cause of this association is not entirely clear, but possible mechanisms are increased total peripheral resistance, disturbances in the renin-angiotensin-aldosterone axis\textsuperscript{110} and endothelial dysfunction\textsuperscript{16,111,112}. Associations with other cardiovascular risk factors such as diabetes complicate interpretations. Both prolonged elevation of calcium and PTH are associated with an increase in blood pressure\textsuperscript{113-115}. Reversible endothelial dysfunction seems to precede structural vascular changes in pHPT\textsuperscript{111,112}. Studies on PTX’s effect on hypertension have produced contradictory results, where some report a decrease in blood pressure\textsuperscript{102,105,108,116} and others show no effect\textsuperscript{117,118}. Ambulatory monitoring of blood pressure (ABP) is superior to single office measurements in predicting the risk of cardiovascular complications\textsuperscript{119}. Data on ABP in pHPT are scanty and not conclusive\textsuperscript{108,117,118,120,121}. In view of the lack of agreement concerning PTX’s effect on hypertension, the presence of hypertension in pHPT patients is currently not an indication for PTX\textsuperscript{122}.

1.4.3 Glucose metabolism and pHPT

Data on insulin resistance in pHPT, especially mild pHPT, are sparse and contradictory\textsuperscript{123}. Increased incidences of non-insulin dependent diabetes mellitus, insulin resistance and decreased glucose tolerance have been reported\textsuperscript{19,103,124-126}. PTH levels are associated with insulin sensitivity assessed by the hyperglycaemic clamp\textsuperscript{107}. A plausible biological mechanism could be that PTH influences intracellular calcium levels and thereby insulin sensitivity. Both hypercalcaemia and hypophosphataemia have been linked to reduced insulin sensitivity\textsuperscript{103,127}. PTX has been found to reduce abnormalities in glucose metabolism\textsuperscript{125,126,128} but not in all studies\textsuperscript{129}. In a study of patients with mild pHPT, PTX had a positive effect on BMD, but did not benefit insulin resistance and other metabolic risk factors\textsuperscript{130}.

Insulin-like growth factor I (IGF-I) plays an important role in the regulation of cell proliferation and differentiation. It is synthesized mainly in the liver and regulated by
growth hormone. It exerts its effect in most tissues, where it is involved in the pathogenesis of insulin resistance, metabolic syndrome and cardiovascular disease\textsuperscript{131}. IGF binding protein 1 (IGFBP-1), a protein of predominantly hepatic origin, modulates the bioactivity of IGF-I. In addition, IGFBP-1 seems to have insulin-sensitizing, blood-pressure lowering and anti-atherosclerotic properties on its own\textsuperscript{132,133}. IGFBP-1 is a marker of insulin secretion\textsuperscript{134}. Increasing levels of IGFBP-1 seem to have favourable effects on insulin sensitivity, hypertension and other cardiovascular risk factors\textsuperscript{133,135}. There are just a few studies on IGFBP-1 and pHPT. Jehle et al. reported higher concentrations of IGFBP-1 in pHPT patients than in healthy controls\textsuperscript{136} but a smaller study found no difference\textsuperscript{137}. In the latter study, on 13 patients and nine controls, the response of IFGBP-1 to oral glucose suggests an improvement in insulin sensitivity after PTX.

1.5 EFFECTS ON BONE

PTH has both anabolic and catabolic effects on bone, depending on whether the exposure to PTH is continuous as in pHPT (catabolic effects) or intermittent as during treatment with exogenous PTH in osteoporosis (anabolic effects). Intermittent exposure to PTH has an anabolic effect through enhanced osteoblast formation and survival whereas chronic PTH stimulation, as in pHPT, stimulates osteoclast formation, activity and survival\textsuperscript{138}. The anabolic effects of PTH are at least partially mediated by a local synthesis of insulin-like growth factor I (IGF-I) in the osteoblasts\textsuperscript{139}. In the Western world today, severe skeletal disease in pHPT, such as osteitis fibrosa cystica, is rare. However, many patients suffer from osteopenia or osteoporosis and the current guidelines cite the latter as an indication for surgery in asymptomatic pHPT\textsuperscript{33}.

In pHPT, there is a 50-60\% increase in bone turnover and number of osteoclasts and osteoblasts, but decreased activity of the individual bone cells, leading to a prolonged active formation period and a tendency to a longer remodelling period, resulting in shallower resorption sites\textsuperscript{140,141}. There is also a disturbed mineralization, which may be due to hypophosphataemia induced by PTH or low concentrations of 25-OH-D.

Most studies on BMD using dual X-ray absorptiometry (DXA), microcomputed tomography and analyses of iliac crest bone biopsies in patients with pHPT, show that
cortical bone undergoes reductions of cortical width and porosity that recover after PTX, while the cancellous bone is relatively preserved\textsuperscript{14,142-144}. BMD measured by DXA, typically shows the greatest reduction in sites rich in cortical bone, such as the 1/3 proximal forearm, and a more modest reduction or even preserved BMD in the lumbar spine, dominated by cancellous bone\textsuperscript{141}. Recently, studies using high-resolution peripheral quantitative computed tomography (HR-pQCT) have demonstrated both trabecular and cortical abnormalities at the radius and tibia, resulting in decreased whole bone and trabecular stiffness\textsuperscript{145,146}.

After PTX, bone turnover decreases, with an early fall in the concentration of resorption markers, while markers of bone formation decrease more slowly\textsuperscript{147-149}. As a result, the BMD increases, predominantly in the lumbar spine and hip, and to a lesser extent in the forearm\textsuperscript{130,146,150-153}. The greatest improvement occurs during the first postoperative year\textsuperscript{154}. The majority of the patients in these studies have mild pHPT, and BMD improved after PTX even in patients who did not meet the criteria for surgical treatment\textsuperscript{153}. Patients randomized to observation had a stable or slightly decreased BMD during follow-up (one or two years)\textsuperscript{130,152,153,155}. In an observational study of patients with pHPT for 10 to 15 years, BMD decreased significantly after 5-10 years\textsuperscript{23,24}. A quarter to one third of the patients met at least one criterion for surgery according to guidelines during the follow-up.

Bone mineral density is an important predictor of fracture risk. A number of cohort studies have reported an increased risk of fractures at several sites in patients with pHPT, even 10 years before diagnosis\textsuperscript{156-158}. The fracture risk is increased not only at sites rich in cortical bone, as suggested by the DXA findings, but also in sites rich in cancellous bone, such as the lumbar spine and hip. This is in accordance with the above-mentioned recent finding of trabecular abnormalities.

No randomized study has been published on the effect of surgery on fracture risk in pHPT, but three cohort studies show a decreased risk of fractures of the hip, femur, forearm and upper arm\textsuperscript{159-161}. 
2 AIMS OF THE THESIS

• To analyse all-cause mortality within 30 days and one year after parathyroid adenomectomy during five decades.

• To investigate whether a history of primary hyperparathyroidism affects the risk of mortality or factors predictive of prognosis and response to therapy in women with a subsequent breast cancer.

• To study the effects of surgery and postoperative vitamin D supplementation on insulin resistance, ambulatory blood pressure and other cardiovascular risk factors in patients with primary hyperparathyroidism.

• To study the effect of postoperative vitamin D supplementation on parathyroid hormone levels and bone mineral density in patients with primary hyperparathyroidism.
3 PATIENTS AND METHODS

3.1 STUDIES I AND II

3.1.1 Quality registers

The Swedish Cancer Registry is a well-validated register with 3-4% underreporting\textsuperscript{162}. Since 1958, all malignant and a few benign tumours, including parathyroid adenomas, are reported to the register, by both the treating physician and the pathologist establishing the diagnosis. The registry includes date of diagnosis and type of tumour. Diagnoses are coded using the International Classification of Diseases 7\textsuperscript{th} revision (ICD-7).

Causes of death are reported to the Cause of Death Registry at the National Board of Health and Welfare. The registry includes all deaths from 1952 onwards among registered Swedish residents. It also contains the underlying and contributory causes of death from the physician’s death certificate in accordance with ICD-7, 8 and 9 and date of death. Underreporting is 0.5\% and the proportion of misclassification was 1.2\pm0.3\% (year 1998, www.socialstyrelsen.se).

Matching between registers can be achieved by means of the individual National Registration Number that is allocated to every Swedish resident.

3.1.2 Design and patients: Study I

In a cohort study of 14,635 patients subjected to PTX, generated from the Swedish Cancer Registry during January 1961 to December 2004, postoperative mortality within 30 days and one year was analysed. All patients had a histopathologically verified, single parathyroid adenoma. Neither cancer, nor hyperplasia were included. Date and cause of death were derived from the National Cause-of-Death Registry.

3.1.3 Statistical analysis: Study I

The person-year at risk was counted from the date of entry into the cohort until death, emigration or the end of the observation period, i.e. 31 December 2004. The entire
Swedish population, standardized for age, gender and time period was used as control to calculate standard mortality ratios (SMR). SMR were calculated as the ratio of the observed to the expected number of deaths and used as an indicator of risk. Nationwide statistics from the Causes-of-Death Registry include annual sex- and age-specific mortality rates for different ICD codes. The expected number of deaths in the observed population was calculated by multiplying the number of person-years at risk for each 5-year age group, gender and calendar year, by the corresponding age, gender and calendar year-specific mortality rates in the general population. The 95% confidence interval (CI) of SMR was calculated on the assumption that the number of deaths in various categories followed the Poisson distribution. Various stratification studies were conducted, using age and calendar year at entry, the duration of follow-up, attained age, gender and various combinations.

3.1.4 Design and patients: Study II

This was a nested case-control study comparing breast-cancer patients with and without a history of surgically cured pHPT. The study population was retrieved from the Swedish Cancer Registry. Requisites for inclusion of cases were parathyroid adenomectomy of a single parathyroid adenoma (ICD-7 1951) and a subsequent diagnosis of invasive breast cancer (ICD-7 170). For each patient, five control subjects with breast cancer but no history of pHPT, matched for age and time period, were enrolled. To minimize confounding by diagnosis, we excluded all cases with a breast cancer diagnosis discovered prior to primary hyperparathyroidism (n=59). All males were excluded, as were all women with a diagnosis of breast carcinoma in situ. The national registration number, a unique identifier for each Swedish resident, was used for linkage to the regional breast cancer registers in Stockholm and Uppsala and the Swedish Cause of Death Registry. Data on tumour size, stage, lymph node and hormonal receptor status, date and cause of death were retrieved from the registers.

Seventy-one women with breast cancer diagnosed after surgery for pHPT and 338 controls were identified during the period from January 1 1992 to December 31 2006. The American Joint Committee on Cancer’s staging system for breast cancer was used\textsuperscript{163}. 
3.1.5 Statistical analysis: Study II

Statistical analysis was performed with the PASW for Windows statistical package 18.0 (PASW Inc; Chicago, IL, USA). Student’s two-tailed, unpaired $t$-test was used to compare mean tumour size between the cases and control subjects. The distribution of tumour characteristics of cases and controls was compared by Pearson’s chi-square test. When cells had expected counts less than 5, a corresponding exact test was applied.

Survival time was calculated as the number of months between the date of diagnosis and whichever occurred first: date of death, date or end of follow-up. Breast cancer survival is presented in a Kaplan-Meier plot and tested with the Logrank test. $P < 0.05$ was considered to be statistically significant.

3.2 STUDIES III AND IV

3.2.1 Design

A randomized double-blind clinical trial (ClinicalTrials.gov Identifier: NCT00982722) to evaluate the effect of vitamin D supplementation after PTX was conducted at the Karolinska University Hospital during the period from April 2008 to November 2010. After successful PTX the patients were randomized to either one year of treatment with daily oral cholecalciferol 800 IU x 2 and calcium carbonate 1 g x 2 (D+) or calcium carbonate 1 g x 2 alone (D-) (Figure 2). The study was blinded for all the researchers, physicians, nurses and patients.

The primary end-point was the change in PTH after PTX and treatment with the study medication. For study III, secondary end-points were vitamin D levels, changes in metabolic risk factors, body composition and ambulatory blood pressure. Secondary end-points for study IV were vitamin D levels, biochemical markers of bone turnover and bone mineral density.
3.2.2 Patients

Patients with pHPT planned for surgery were eligible for the study. Exclusion criteria were age under 18, manifest osteoporosis at pHPT diagnosis, persistent hypercalcaemia after surgery, postoperative hypocalcaemia requiring vitamin D treatment, glomerular filtration rate (GFR) <40 ml/min., pregnancy, breast-feeding or if the treating physician considered it unsuitable for the patient to participate for other reasons. Patients on vitamin D treatment, prescribed for medical reasons, were not included in the study.

A total of 159 consecutive patients were enrolled, but after PTX, nine of them met exclusion criteria; 150 patients were randomized, 75 patients in each arm. They were followed during one year. 135 patients had a complete follow-up: the fifteen who
dropped out were followed for median 6 months (min-max 1-9 months). Reasons for termination were patient’s own will (n=11), emigration (n=1), deceased (n=2) and symptomatic vitamin D deficiency (n=1).

BMI was calculated at baseline as weight (kilograms) divided by the square of height (metres). Patients with insulin treatment (n=2) were excluded from the analyses of glucose, insulin and HOMA-IR.

All patients gave written consent to participation. The study complied with the Ethical Principles of the World Medical Association Declaration of Helsinki, and was approved by the Medical Products Agency in Sweden and by the Local Ethics Committee, Regionala etikprövningsnämnden, EPN, of Stockholm, Sweden.

3.2.3 Methods

3.2.3.1 Laboratory methods

Blood and urine samples were collected after an overnight fast at six ± two weeks before surgery, at randomization and after six and twelve months of treatment. Plasma concentrations of intact PTH, insulin-like growth factor I (IGF-I) and insulin and serum concentrations of procollagen type 1 aminoterminal propeptide (P1NP) and c-terminal telopeptide of type 1 collagen (βCTx) were determined with electrochemiluminescence immunoassay on the Modular E system (Roche Diagnostics GmbH, Mannheim, Germany). Serum ionized calcium (Ca²⁺) was analysed on ABL 800 (Radiometer, Copenhagen, Denmark). Plasma concentrations of phosphate, creatinine, glucose, total cholesterol, triglycerides (TG), HDL and LDL were measured using the Synchron LX 20 system (Beckman Coulter Inc., Brea, CA). Serum concentrations of 25-OH-D were measured by chemiluminescence on Liaison XL® (DiaSorin, Inc Stillwater, USA); values below 50 nmol/l were considered to represent vitamin D insufficiency. The inter-assay coefficient of variation (%CV) is 4.6% at 15.5 nmol/L and 2.7% at 68.3 nmol/l; intra-assay %CV is 4.4% at 15.5 nmol/l and 2.6% at 68.3 nmol/l.

Estimated renal function (GFR ml/min/1.73 m²) was derived by Cockroft-Gault’s formula: GFR = (140-age in years) x (weight in kilograms/plasma creatinine) x (1.23 in men or 1.04 in women). An in-house radioimmunoassay (RIA) according to the method of Povoia et al. determined IGFBP-1 concentrations in serum. The sensitivity of the RIA was 3 µg/l and the intra- and inter-assay CVs were 3% and 10%, respectively.
Estimates of insulin resistance were calculated using the homeostatic model assessment (HOMA-IR): insulin resistance = fasting glucose x fasting insulin/22.5 after conversion of insulin levels from pmol/l to µU/ml by multiplication with a factor 6.945165.

3.2.3.2 Bone mineral density and body composition
Areal bone mineral density (BMD, g/cm²) of the total body, total hip, femoral neck, lumbar spine, non-dominant forearm (ultradistal (UD) and 1/3 proximal radius) and body composition was estimated using dual energy x-ray absorptiometry (DXA). The same instrument (Lunar Prodigy Advance, #PA+41562, GE Healthcare) was used for all the patients. Osteoporosis was defined as a T-score at any site -2.5 standard deviations below the value for white women aged 20-29 years. The precision error was 0.009 SD g/cm² in the lumbar spine, 0.010 SD g/cm² in the total hip and 0.007 SD g/cm² in the femoral neck. The precision error of the forearm was not measured.

3.2.3.3 Ambulatory blood pressure
Ambulatory blood pressure monitoring (24h ABP) was performed with a standardized ambulatory blood pressure device (Meditech ABPM-04 monitor (PMS Instruments, Maidenhead, United Kingdom) that was applied around the patient’s non-dominant arm. Daytime was defined as the time from wakening to bedtime (07.00-23.00 in most cases) and night-time as the time the study participant spent in bed. The ambulatory device was set to record ABP and heart rate (HR) at 30-minute intervals during daytime and 60-minute intervals during night-time. If the recording failed, a new measurement was automatically done after 2 minutes. Patients were instructed to continue their usual daily activities while wearing the device and to continue any anti-hypertensive treatment. 125 patients completed pre-and postoperative AMB.

3.2.4 Statistical analysis and sample size calculation
Statistical analysis was performed with the IBM SPSS Statistics version 20. Since data did not follow a normal distribution, they were expressed as median and interquartile range. Intra-individual analyses were performed with the Wilcoxon signed rank sum test. Comparison between groups was performed with the Mann-Whitney U-test for unpaired data; the Kruskal-Wallis one-way analysis of variance was used for comparison of more than two independent continuous variables and the chi-square test was used for analysis of the distribution of categorical variables. Univariate analyses of relationships between variables were assessed with Spearman’s ρ-correlation test.
Partial correlations were used to assess the relationship between delta BMD and PTH and 25-OH-D (controlling for age, gender, weight, smoking and creatinine). All tests were done two-tailed, and \( p<0.05 \) was considered to be statistically significant.

The size of the cohort was determined by a power analysis. Based on data from a European study showing that 90% of a population of patients with pHPT had a vitamin D insufficiency\(^8\) and a Swedish study where 28% of the patients had an increased level of PTH 8 weeks after PTX\(^{16,6}\), we expected PTH to be within the normal range, after PTX, in 72% of patients not receiving vitamin D and in 97% of those treated with vitamin D. Since data on the effect of vitamin D on postoperative PTH levels are scarce, we assumed a normal PTH level in two-thirds of the patients with vitamin D supplementation. Thus, with a significance level of 0.05 and a power of 80%, we calculated a sample size of 71 patients in each group. To compensate for dropouts during the study, we chose to enrol 75 patients per group.
4 RESULTS

4.1 STUDY I

Of the 14,635 pHPT patients in the cohort, 79% were women. The observation time was more than 166,000 person-years. The mean age of the patients increased from 53 years in the period 1961–71 to 64 years in 1992–2004 (p<0.0001). Nearly 3000 of the pHPT patients were 75 years of age or more at the time of PTX and this age group constituted more than a quarter of the cases in the most recent period (1997-2004) (Figure 3).

**Figure 3** Age distribution in different time periods

During the entire study period, 185 patients died within one month after PTX and 365 died during the next eleven months. An analysis of the 30-day mortality over time
showed a decrease from 4.2% during 1961-1976 to 0.4% 1997-2004. Mortality in the period from day 31 to day 365 after PTX ceased to be significantly increased from 1987 onwards (Table 1).

**Table 1.** Standard mortality ratio with 95% confidence interval in different time periods, after parathyroid adenomectomy.

<table>
<thead>
<tr>
<th></th>
<th>1st month</th>
<th>2-12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>1961-1976</td>
<td>105</td>
<td>4.2%</td>
</tr>
<tr>
<td>1977-1986</td>
<td>36</td>
<td>0.9%</td>
</tr>
<tr>
<td>1987-1996</td>
<td>31</td>
<td>0.6%</td>
</tr>
<tr>
<td>1997-2004</td>
<td>13</td>
<td>0.4%</td>
</tr>
<tr>
<td>Total number</td>
<td>185</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Table 2 shows the 30-day mortality in different age and calendar year groups. Mortality within 30 days after PTX in the period 1997–2004 among patients 75 years or older was 1.0%. The dominant causes of mortality during the first month after PTX were cardiovascular (37%), endocrine (32%) and malignancy-related (17%), demonstrable in both genders and in all the investigated age groups (Figure 4). Of the patients who died within the first year after PTX, 51% did so from a cardiovascular disorder.

**Figure 4** Causes of death during the first month after parathyroidectomy.
Table 2. Parathyroid adenoma cohort by calendar-year period, with the total number of registered individuals (n) and their age distribution.

<table>
<thead>
<tr>
<th>Calender years</th>
<th>15-54 yrs</th>
<th></th>
<th>55-74 yrs</th>
<th></th>
<th>75+ yrs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>SMR</td>
<td></td>
<td>95%CI</td>
<td></td>
</tr>
<tr>
<td>1961–76</td>
<td>906</td>
<td>12</td>
<td>52.7</td>
<td></td>
<td>27.2-92.1</td>
<td></td>
</tr>
<tr>
<td>1977–86</td>
<td>920</td>
<td>5</td>
<td>23.5</td>
<td></td>
<td>7.6-54.9</td>
<td></td>
</tr>
<tr>
<td>1987–96</td>
<td>1119</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0.0-17.8</td>
<td></td>
</tr>
<tr>
<td>1997–2004</td>
<td>796</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0.0-27.8</td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>3741</td>
<td>17</td>
<td>21.8</td>
<td></td>
<td>12.7-34.9</td>
<td></td>
</tr>
</tbody>
</table>

\[\#\] = number of deaths during the first postoperative month
4.2 STUDY II

The mean age at diagnosis of breast cancer was 69 years in both groups (standard deviation (SD) 11 years, 95% confidence interval (95%CI) 68-70 years). The mean interval between parathyroid adenoma operation and breast cancer diagnosis was 91 months (SD 68 months, 95%CI 72-111 months), ranging from 1 to 292 months.

Tumour size, stage, axillary lymph node status and hormone receptor status are presented in Table 3.

Table 3 Tumour characteristics in women with pHPT + breast cancer (cases) and women with breast cancer only (controls).

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=71)</th>
<th>Controls (n=338)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour size (mm±SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td><strong>Axillary lymph node status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>35 (59%)</td>
<td>176 (65%)</td>
<td></td>
</tr>
<tr>
<td>1-3 positive nodes</td>
<td>11 (19%)</td>
<td>63 (23%)</td>
<td></td>
</tr>
<tr>
<td>≥4 positive nodes</td>
<td>13 (22%)</td>
<td>32 (12%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>12 (17%)</td>
<td>67 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (T1+N0)</td>
<td>29 (46%)</td>
<td>149 (51%)</td>
<td></td>
</tr>
<tr>
<td>IIa (T1+N1 or T2+N0)</td>
<td>25 (40%)</td>
<td>77 (27%)</td>
<td></td>
</tr>
<tr>
<td>IIb (T2+N1 or T3+N0)</td>
<td>9 (14%)</td>
<td>49 (17%)</td>
<td></td>
</tr>
<tr>
<td>III (T3+N1 or T4)</td>
<td>0 (0%)</td>
<td>4 (1%)</td>
<td></td>
</tr>
<tr>
<td>IV (M1)</td>
<td>0 (0%)</td>
<td>11 (4%)</td>
<td>0.13*</td>
</tr>
<tr>
<td><strong>Undefined</strong></td>
<td>8 (11%)</td>
<td>48 (14%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hormone receptor status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>46 (88%)</td>
<td>217 (84%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6 (12%)</td>
<td>42 (16%)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>19 (27%)</td>
<td>79 (23%)</td>
<td></td>
</tr>
</tbody>
</table>

*a ER positive, PR positive or negative according to local laboratory and clinical standards
*b ER and PR negative
*Exact Pearson Chi-Square test

None of the prognostic factors analysed in this study differed between the women with and those without a history of pHPT. Mean time of follow-up was 80 months (SD 59 months, 95%CI 74-86). At December 31 2009, 29 (41%) cases and 150 (44%) controls
had died. There was no statistically significant difference between the two groups in the cumulative breast cancer specific survival (Figure 5).

**Figure 5** Kaplan-Meier plot of breast cancer specific survival in women with pHPT+breast cancer (cases) and women with breast cancer only (controls).
4.3 STUDIES III AND IV

Patient characteristics and biochemical data at baseline and after PTX are shown in Tables 4 and 5. The calcium level was normalized six weeks after PTX in all patients, but 50% had a persistently high PTH (>65 ng/l). Vitamin D levels were lower in patients with a high postoperative PTH (25-OH-D 39 nmol/l (31-44) vs. 42 nmol/l (32-52), p=0.027) and they had larger adenomas (534 g (310-1038) vs. 333 g (204-819), p=0.003) and their preoperative PTH levels were higher (141 ng/l (119-169) vs. 94 (82-108), p<0.001) but creatinine did not differ (data not shown). The incidence of 25-OH-D below 50 nmol/l at baseline was 76% and was similar in men and women.

Table 4. Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>n=150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median (min-max))</td>
<td>60 (30-80)</td>
</tr>
<tr>
<td>Women / men (n)</td>
<td>119 / 31</td>
</tr>
<tr>
<td>Women ≤50 yrs / &gt;50 yrs (n)</td>
<td>19 / 100</td>
</tr>
<tr>
<td>BMI (kg/m2, median (min-max))</td>
<td>26 (17-44)</td>
</tr>
<tr>
<td>Weight of adenoma (mg, median (min-max))</td>
<td>450 (75-27800)</td>
</tr>
<tr>
<td>Multiglandular disease (n)</td>
<td>4</td>
</tr>
<tr>
<td>Vitamin D &lt; 50 nmol/l (n (%))</td>
<td>114 (76%)</td>
</tr>
<tr>
<td>Osteoporosis (n (%))</td>
<td>69 (46%)</td>
</tr>
<tr>
<td>Smokers (n (%))</td>
<td>23 (15%)</td>
</tr>
<tr>
<td>Diabetes (n (%))</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>26 (17%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>31 (21%)</td>
</tr>
<tr>
<td>Betablockers</td>
<td>32 (21%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>Other relevant medication</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>24 (16%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Oestrogen, systemic</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>

BMI=body mass index
## Table 5. Biochemistry before and after parathyroid adenomectomy (PTX)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>After PTX</th>
<th></th>
<th>p (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
<td></td>
</tr>
<tr>
<td>S-25-OH-D (75-250 nmol/l)</td>
<td>40</td>
<td>31-49</td>
<td>42</td>
<td>33-54</td>
<td>0.004</td>
</tr>
<tr>
<td>P-PTH (10-65 ng/l)</td>
<td>116</td>
<td>89-145</td>
<td>65</td>
<td>53-68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-Ca²⁺ (1.15-1.33 mmol/l)</td>
<td>1.43</td>
<td>1.39-1.43</td>
<td>1.25</td>
<td>1.22-1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-Phosphate (0.75-1.4 mmol/l)</td>
<td>0.83</td>
<td>0.74-0.92</td>
<td>1.0</td>
<td>0.92-1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-Creatinine (♀&lt;90, ♂&lt;100 µmol/l)</td>
<td>65</td>
<td>56-76</td>
<td>67</td>
<td>58-75</td>
<td>0.400</td>
</tr>
<tr>
<td>GFR Creatinine (ml/min)</td>
<td>97</td>
<td>79-117</td>
<td>95</td>
<td>79-115</td>
<td>0.900</td>
</tr>
<tr>
<td>P-Glucose (4.0-6.0 mmol/l)</td>
<td>5.2</td>
<td>4.9-5.6</td>
<td>5.2</td>
<td>4.8-5.6</td>
<td>0.022</td>
</tr>
<tr>
<td>S-Insulin (18-173 pmol/l)</td>
<td>66</td>
<td>43-97</td>
<td>58</td>
<td>37-95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR²</td>
<td>2.2</td>
<td>1.4-3.3</td>
<td>1.8</td>
<td>1.2-3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-IGF-I (110–270 µg/l)</td>
<td>144</td>
<td>117-179</td>
<td>138</td>
<td>115-172</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-IGFBP1</td>
<td>30</td>
<td>21-49</td>
<td>37</td>
<td>21-54</td>
<td>0.046</td>
</tr>
<tr>
<td>S-Cholesterol (3.3-7.8 mmol/l)</td>
<td>5.6</td>
<td>4.8-6.1</td>
<td>5.5</td>
<td>4.9-6.3</td>
<td>0.134</td>
</tr>
<tr>
<td>P-HDL (♀01.0-2.7, ♂0.8-2.1 mmol/l)</td>
<td>1.4</td>
<td>1.2-1.8</td>
<td>1.4</td>
<td>1.2-1.8</td>
<td>0.825</td>
</tr>
<tr>
<td>P-LDL (1.4-5.3 mmol/l)</td>
<td>3.5</td>
<td>2.8-4.1</td>
<td>3.5</td>
<td>2.8-4.1</td>
<td>0.161</td>
</tr>
<tr>
<td>S-Triglycerides (0.45–2.6 mmol/l)</td>
<td>0.98</td>
<td>0.75-1.40</td>
<td>0.96</td>
<td>0.70-1.52</td>
<td>0.256</td>
</tr>
<tr>
<td>S-P1NP (µg/l)</td>
<td>62</td>
<td>47-89</td>
<td>57</td>
<td>42-78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-βCTx (ng/l)</td>
<td>545</td>
<td>388-707</td>
<td>318</td>
<td>216-455</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*a* patients with insulin treatment were excluded from the analysis.

W=Wilcoxon signed rank sum test for paired data
25-OH-D=25-hydroxyvitamin D, PTH=parathyroid hormone, Ca²⁺=ionized calcium, GFR=glomerular filtration rate, HOMA-IR=homeostatic model assessment insulin resistance, IGF-I=insulin-like growth factor 1, IGFBP1=IGF binding protein 1, HDL=high density lipoprotein, LDL=low density lipoprotein

At follow-up after twelve months, the D+ group had a significantly higher level of vitamin D and lower PTH (Table 6). 19 % (n=26) had a persistently high concentration of PTH (D+ n=9, D- n=17). Only two patients had 25-OH-D below 50 nmol/l in the D+ group, compared to 36 patients in the D- group. 12 patients, all in the D- group, had a combination of high PTH and 25-OH-D < 50 nmol/l.
<table>
<thead>
<tr>
<th>Year</th>
<th>Randomization One Year</th>
<th>Randomization One Year</th>
<th>Randomization One Year</th>
<th>Randomization One Year</th>
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</tr>
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<tr>
<td></td>
<td>p (M vs W)</td>
<td>p (M vs W)</td>
<td>p (M vs W)</td>
<td>p (M vs W)</td>
<td>p (M vs W)</td>
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<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
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</tr>
</tbody>
</table>

Table 6. Biomarkers at randomization and after one year of study medication.
4.3.1 Study III

Patients with 25-OH-D in the lowest quartile at baseline (< 31 nmol/l) had higher levels of fP-glucose (median 5.4 (IQR 5.1-6.3) vs. 5.2 (4.9-5.5) mmol/l), insulin (79.4 (53.5-129.0) vs. 60.5 (43.1-87.9), HOMA-IR (2.7 (1.7-5.2) vs. 2.0 (1.4-3.1) and triglycerides (1.3 (0.9-1.8) vs.0.9 (0.7-1.2); p<0.05 for all parameters. Plasma glucose, insulin, HOMA-IR and IGF-I decreased after PTX, while IGFBP1 increased. △IGFBP-1 correlated to △PTH (r=0.18; P=0.03) and was inversely correlated to △insulin (r=-0.26; p=0.002) and △HOMA-IR (r=-0.25; p=0.002).

After one year of study medication, the D+ group had a lower serum concentration of IGF-1 than the D- group (Table 6). All other biochemistry (except PTH and vitamin D, as mentioned above) was unchanged compared with six weeks after surgery.

*Ambulatory blood pressure*

Data on 24h ABP are presented in Table 6. Median 24h SBP at baseline was significantly correlated to baseline PTH (r=0.24), serum insulin (r=0.29) and TG (r=0.37), p<0.01, and inversely to IGFBP-1 (r=-0.19; P<0.005). 24h SBP decreased in both groups. The change in 24h SBP was not correlated to changes in PTH, ionized calcium or 25-OH-D (data not shown). Eleven patients, equally distributed between the D+ and the D- group, were able to either cease or reduce their antihypertensive treatment. Vitamin D supplementation did not give any additive effect.

*Body composition*

Total body BMC increased in both D+ and D- (△BMC: D+ 68 g (-16-127), p<0.001; D- 56 g (-32-108), p=0.013). The changes in BMC, LBM and fat mass did not correlate to the change in either 25-OH-D or Ca²⁺, but there was an inverse correlation between delta PTH and delta BMC (r=-0.30, p=0.002).

4.3.2 Study IV

*Bone mineral density*

BMD at baseline was similar in the D+ and D- groups. After twelve months of study medication, median BMD had increased significantly in the lumbar spine, the total hip and the femoral neck in both the D+ and the D- group (Table 7). Patients in the D+
group also increased their BMD of the ultra-distal forearm. The increase in BMD did not differ either between patients with or without osteoporosis, or between men and women (data not shown).

BMD at baseline and the change in BMD did not differ between patients with or without vitamin D insufficiency (25-OH-D<50nmol/l). In both groups BMD improved in the lumbar spine and hips; the insufficient patients had an increased BMD in the ultra-distal forearm as well. No significant additive effect of vitamin D supplementation was observed. For patients with insufficient vitamin D levels after 1 year, BMD was lower in the lumbar spine, 1/3 proximal forearm and ultra-distal forearm (p<0.05).

The changes in BMD, especially in the hips, were correlated to the baseline concentrations of PTH, ionized calcium and bone turnover markers, but not to vitamin D (Figure 6). This correlation remained significant when controlling for age, gender, smoking, weight and creatinine (r=0.38, p<0.001).

Patients with PTH > 65 ng/l 6±2 weeks after PTX had a greater improvement in BMD in the total hip, femoral neck and distal forearm than patients with normalized PTH levels. In patients with PTH > 65 ng/l after PTX, BMD increased at all measured sites in the D+ group, but not in the forearm (ultra-distal and 1/3 proximal forearm) in the D- group, without regard to vitamin D status at baseline.
Table 7. Bone mineral density sex weeks before surgery (baseline) and after one year of study medication.

<table>
<thead>
<tr>
<th></th>
<th>Vitamin D+</th>
<th></th>
<th>Vitamin D-</th>
<th></th>
<th>D+ vs D-</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change at 1 year</td>
<td>Baseline</td>
<td>Change at 1 year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
<td>p^</td>
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<td>BMD lumbar spine (g/cm²)</td>
<td>1.067</td>
<td>0.951-1.242</td>
<td>1.042</td>
<td>0.938-1.182</td>
<td>0.180</td>
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<td>Z-score</td>
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<td>-0.4</td>
<td>-1.2-0.3</td>
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<td>T-score</td>
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<td>-1.9-0.3</td>
<td>-1.1</td>
<td>-2.2-0</td>
<td>0.013</td>
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<tr>
<td>BMD hip, total (g/cm²)</td>
<td>0.915</td>
<td>0.823-1.018</td>
<td>0.889</td>
<td>0.797-0.971</td>
<td>0.194</td>
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<tr>
<td>Z-score</td>
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<td>T-score</td>
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<td>-1.6-(-0.1)</td>
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<td>-1.9-(-0.4)</td>
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<td>BMD femoral neck (g/cm²)</td>
<td>0.852</td>
<td>0.773-0.948</td>
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<td>Z-score</td>
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<td>-2.0-(-0.7)</td>
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<td>BMD radius UD (g/cm²)</td>
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<td>0.330-(-0.458)</td>
<td>0.371</td>
<td>0.331-0.440</td>
<td>0.192</td>
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<td>-1.3</td>
<td>-2.1-(-0.7)</td>
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<td>T-score</td>
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<td>BMD radius 33% (g/cm²)</td>
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<td>-1.2-0.5</td>
<td>-0.5</td>
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<td>0.911</td>
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<tr>
<td>T-score</td>
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<td>-2.6-(-0.5)</td>
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IQR=inter quartile range
^ Wilcoxon sign rank sum test, paired data
^ Mann-Whitney U-test, unpaired data
**Figure 6** Correlations between delta BMD total hip and baseline PTH, Ca\(^{2+}\) and bone turnover markers.

![Correlation plots](image)

**Biochemical markers of bone turnover**

In 79 patients, P1NP and \(\beta\)CTx were within the normal range at baseline, while 70 patients had an increased level of P1NP (n=46), \(\beta\)CTx (n=1) or both (n=23). Patients with bone turnover markers above the normal range at baseline had higher PTH, ionized calcium and ALP (PTH: 120 (101-152) vs. 105 (84-133), ionized calcium: 1.46 (1.41-1.51) vs. 1.42 (1.38-1.44), ALP: 1.3 (1.1-1.6) vs. 1.2 (0.9-1.4), p<0.05).

\(\beta\)CTx and P1NP decreased significantly in both groups from baseline to six weeks and one year after PTX (Table 5 and 6). \(\beta\)CTx changed most after PTX, while the decrease in P1NP was more pronounced after one year. Both bone turnover markers were correlated to the change in BMD (Figure 6). There was no correlation between the bone turnover markers and 25-OH-D, except for a weak inverse correlation six weeks after PTX between 25-OH-D and \(\beta\)CTx (r=-0.21, p<0.05).
5 DISCUSSION

5.1 STUDY I

Postoperative mortality after parathyroid adenomectomy in Sweden has decreased from 4.2 % to 0.4 % since 1961, notwithstanding a simultaneous 11-year increase in patients’ mean age. Similar postoperative mortality data have been reported. There are several plausible explanations. Measurements of serum calcium became routine in the 1970’s and lead to earlier diagnosis and less severe disease at the time of surgery. Modern anaesthetic procedure and better postoperative care may also affect the postoperative mortality. Better preoperative localization techniques have paved the way for focused surgery, even under local anaesthesia. However, in our country, 99% of PTX are still performed under general anaesthesia. Improved medical treatment of a number of chronic diseases has made it possible to operate patients despite a certain degree of comorbidity. Surgery in the elderly seems to be safe and beneficial.

The dominant cause of death, for all ages and both genders, within the first month and the following year after PTX was cardiovascular disease. This is in line with the 30-day mortality of other elective surgical procedures, such as groin hernia repair. Several risk factors for cardiovascular disease are overrepresented in pHPT and an increased mortality in cardiovascular disorders has been demonstrated. It may be assumed that the duration of the disease is important for the prognosis, since mortality risk has been associated with the degree of hypercaemia and the weight of the adenoma.

Postoperative mortality after PTX was higher than for other elective surgical procedures, such as inguinal hernia repair, thyroidectomy for benign goitre and cataract. After PTX, an increased mortality persists for at least 15 years.

Hypercaemic crisis could also affect mortality rates, since it is associated with a significant mortality, especially in patients with extremely high serum calcium levels. In a study of 1055 patients who underwent PTX from 1969 to 2004, the prevalence of hypercaemic crisis was estimated to be 4%.
5.1.1 Strengths and limitations

The registries used are well validated and the size of the investigated cohort provides good statistical power. A limitation is that the cohort does not represent the entire pHPT population in Sweden, since the registry does not include either conservatively treated patients or patients with multiglandular disease, comprising approximately 15% of the pHPT population. Neither are there any data on the degree of hypercalcaemia, symptoms, surgical procedure or postoperative serum calcium levels. In a long-term follow-up of Swedish patients, 95% had reversed hypercalcaemia after PTX\textsuperscript{178,179}.

5.2 STUDY II

The results in this nested case-control study indicate that factors predictive of prognosis and response to therapy did not differ between patients with breast cancer and previous surgery for pHPT and matched controls without previous PTX, although none of the cases had stage III or IV disease.

PHPT and breast cancer have several characteristics in common. Both mainly affect postmenopausal women and have been associated with obesity and increased calcium and 25-OH-D levels\textsuperscript{48-51,57,58,180}. The mammary gland has receptors for both calcium\textsuperscript{181}, PTH\textsuperscript{182} and vitamin D\textsuperscript{183}. A causal relationship between calcium and/or PTH levels and breast cancer seems less likely, since unlike cardiovascular mortality, the risk of breast cancer remains unchanged at least 15 years after PTX\textsuperscript{26,27}. Neither did Almquist et al. find any association between PTH level and breast cancer in a nested case-control study of 764 patients with breast cancer\textsuperscript{48}.

Vitamin D deficiency is a factor that could contribute to the aetiology of both breast cancer and pHPT. 1,25-(OH)\textsubscript{2}-D has the ability to inhibit proliferation, invasion and angiogenesis and promote differentiation and apoptosis\textsuperscript{184,185}. There is a potential link between vitamin D deficiency and both the development and prognosis of breast cancer\textsuperscript{185-187} as well as an aggravated clinical presentation of pHPT and larger parathyroid adenomas\textsuperscript{82,188}. Two meta-analyses of serum vitamin D and breast cancer risk found an inverse association with 25-OH-D measured after diagnosis of breast cancer. However, this could not be confirmed in prospective studies with measurements of 25-OH-D years before diagnosis\textsuperscript{50,51}. Neither have studies on a possible association
between vitamin D intake and breast cancer risk yielded consistent results. A meta-analysis of observational studies found a possible positive effect of higher intakes of vitamin D\textsuperscript{189} but a nested case-control study of calcium and vitamin D supplementation versus placebo during seven years (mean) did not show any protective effect\textsuperscript{190}. However, 57% of the subjects in the placebo arm took personal supplements, and a re-analysis restricted to the women not taking any extra calcium and/or vitamin D, showed a 14-20% decrease in the risk of breast cancer in the calcium and vitamin D arm\textsuperscript{191}. Many factors may complicate the interpretation of data on vitamin D status, such as age, BMI, liver and kidney function, chronic illness and sun exposure\textsuperscript{192}.

Obesity is another factor associated with both pHPT\textsuperscript{57}, an increased risk of postmenopausal breast cancer\textsuperscript{180,193} and vitamin D deficiency\textsuperscript{194}. In addition to oestrogen, hyperinsulinaemia is suggested to be a contributory risk factor for breast cancer in obese postmenopausal women\textsuperscript{193,195} and is also associated with pHPT\textsuperscript{19}.

5.2.1 Strengths and limitations

The strengths of the study are the use of well-validated registers, including two of the most important prognostic factors – tumour size and lymph node involvement. The risk of confounding by diagnosis was minimized by excluding cases with a breast cancer diagnosis before pHPT. Other strengths are the relatively large number of observations with five controls per case and the long follow-up.

The main weakness lies in the scope of the data in the registers. Data on HER-2/neu and the cell proliferation marker Ki67 were incomplete. Elston-Ellis tumour grading could not be properly analysed because of too many missing data, especially in the early period. Neither did the register include any information on risk factors for breast cancer, treatment modalities and biochemical data in the register. However, bias because of differences in treatment is likely to be negligible, since the compliance with the regional and national treatment guidelines is excellent and controls were matched for region. Misclassification of controls may affect isolated cases, based on the comparatively low incidence of pHPT in the population\textsuperscript{9}. 
5.3 STUDIES III AND IV

The major findings in this randomized, double-blind study were that PTX had beneficial effects on insulin resistance, blood pressure and bone mineral density. However, despite a high prevalence of vitamin D insufficiency (76 % < 50 nmol/l) in the cohort, postoperative supplementation with vitamin D had no obviously beneficial effect. Preoperative SBP and the increase in BMD correlated with the preoperative PTH concentration.

Vitamin D supplementation did lower the level of PTH in the D+ group. At follow-up this group had a significantly higher concentration of 25-OH-D, indicating an adequate dose of vitamin D.

50 % of the patients had a persistently high concentration of PTH six weeks after PTX. The clinical importance of persistent PTH elevation after curative PTH is still an open question\textsuperscript{36}. Several factors are probably causally involved. One is the interval after PTX and another is secondary hyperparathyroidism due to vitamin D deficiency, which was the case in some, but not all patients. High postoperative levels of PTH have been associated with larger adenomas and high preoperative PTH, as in the patients in the present study, and may be due to an increased need of calcium in the remineralization of the bone or to an increased peripheral resistance to PTH\textsuperscript{37,38}.

The cause and clinical importance of the persistent PTH elevation in nearly 20% of the patients more than one year after PTX are more complicated. Not all of them had a low vitamin D concentration and only one showed obvious signs of recurrent disease. Our results are in line with other long term follow-up studies after PTX\textsuperscript{36,196,166}.

Vitamin D supplementation resulted in a lower PTH concentration at follow-up after one year. It cannot be excluded that the higher PTH concentration in the D- group has negative effects in the long term. In the general population, PTH in the upper normal range has been associated with an increased risk of cardiovascular complications\textsuperscript{88,89,197}, increased blood pressure\textsuperscript{198,199} and decreased insulin sensitivity\textsuperscript{107,200}. Furthermore, a
high PTH level in combination with low vitamin D has been associated with an increased risk of fractures\textsuperscript{201}.

Among patients with pHPT, those with low vitamin D levels and a higher PTH concentration have also been found to have greater catabolic effects in cortical bone and greater anabolic effects in cancellous bone\textsuperscript{202}.

5.3.1 Insulin resistance and pHPT

Available reports on the relationship between pHPT and insulin resistance and the effect of PTX are contradictory\textsuperscript{123,124,128,130}. The simultaneous reduction of HOMA-IR, glucose, insulin and IGF-I and the increase in IGFBP-1 seen postoperatively and remaining at follow-up, support a possible reversibility of the impaired glucose metabolism coupled to pHPT. The underlying mechanism is not clear, since both PTH and calcium are associated with insulin sensitivity\textsuperscript{200,203}.

In a randomized study on vitamin D supplementation to women with insulin resistance and vitamin D deficiency, vitamin D had a positive effect on insulin resistance and sensitivity; the optimal vitamin D concentration was $\geq 80\text{ nmol/l}$\textsuperscript{204} (von Hurst 2010). In the present study, the median 25-OH-D concentration at one year was 76 nmol/l. Even so, effects of vitamin D on insulin resistance could not be seen, beyond the positive effect of PTX.

5.3.2 Blood pressure and pHPT

Control of hypertension appears to be crucial for the prevention of cardiovascular complications. The Framingham Study has confirmed that the risk of cardiovascular complications increases incrementally with blood pressure even within the normal range and that SBP is a more important risk factor than DBP\textsuperscript{205,206}. It is also well established that 24h ABP is superior to single office measurements in predicting a risk of cardiovascular morbidity and mortality\textsuperscript{119}. The available information on 24h ABP in pHPT is limited to a few studies, with contradictory results\textsuperscript{108,117,118,120,121}. Recently, Luigi et al. compared patients with pHPT to patients with essential hypertension and to normal subjects, 30 in each group\textsuperscript{108}. They found a strong correlation between PTH and SBP and a high prevalence of the metabolic syndrome in patients with pHPT, with
significant improvements after parathyroid surgery. Others have also reported a high percentage of alterations in the normal circadian rhythm of 24h ABP in pHPT\textsuperscript{117,120}. Our patients had a small but significant decrease in SBP, regardless of vitamin D levels. The results may be biased by the high proportion of patients with hypertensive medication, but similar findings were obtained in another study with selected patients without known cardiovascular risk factors\textsuperscript{80}. A positive effect on blood pressure after surgery has been demonstrated among patients with pHPT and hypertension\textsuperscript{105}. However, few studies have been able to show any effect of PTX on blood pressure. Partially irreversible vascular changes may be a possible explanation\textsuperscript{122}.

The coexistence with other risk factors seems to be important and the combination of high PTH, hypertension and insulin resistance could potentiate the risk of cardiovascular complications in pHPT.

5.3.3 Bone and pHPT

Vitamin D supplementation had no obviously beneficial effect on bone recovery after PTX. The increase in BMD did not differ either between patients with or without vitamin D insufficiency or between patients with or without osteoporosis or between genders. Instead, the change in BMD correlated with the preoperative concentrations of PTH, ionized calcium and bone turnover markers. This is in accordance with other studies\textsuperscript{146,147,151,207}.

The results of the present study are comparable to previously reported effects of parathyroid surgery only, confirming the positive effects on BMD in sites rich in cancellous bone, such as the lumbar spine and total hip\textsuperscript{130,150,154,208,209}.

Studies using DXA and analyses of iliac crest bone biopsies in patients with pHPT, show a reduction of cortical width and cortical bone porosity, while the cancellous bone is relatively preserved\textsuperscript{14,143}. Recent studies using HR-pQCT found both trabecular and cortical abnormalities, resulting in decreased whole bone and trabecular stiffness\textsuperscript{145} and improvements in the microarchitecture after PTX in both cortical and trabecular bone\textsuperscript{146}. The potential for improvements in the microarchitecture and bone strengths was related to the baseline levels of PTH and bone turnover markers. These findings
are consistent with the strong correlation between △BMD and the baseline concentration of PTH and bone turnover markers in our patients.

There is a possibility that vitamin D supplementation has a beneficial effect in certain subgroups, for example those with a high PTH level after PTX; they showed a greater improvement in BMD and a beneficial effect in the forearm from vitamin D supplementation. The entire group with vitamin D supplementation also had a positive effect on BMD of the ultra-distal forearm. This raises the question of whether vitamin D and/or PTH have differential effects on different skeletal compartments, for example weight-bearing and non-weight-bearing skeletal sites or stage of maturation of the bone cells. In a Danish study on patients with pHPT, high levels of 1,25(OH)2D were inversely correlated to BMD in the distal radius.

5.3.4 Strengths and limitations

To the best of my knowledge, this is the first randomized study on vitamin D supplementation after PTX in patients with pHPT. The strengths of this interventional study are the prospective randomized design, the close and standardized follow-up with good compliance and the achievement of adequate vitamin D levels in the D+ group. Furthermore, the diagnosis was verified by PTX in all cases and the loss to follow-up was 10%. The advantage of a proper randomization is that it could eliminate bias in treatment assignment, especially selection bias and confounding. In this study, the groups were comparable in all studied parameters except for the 24h ABP, which was higher in the D+ group. However, the number of patients with medication for hypertension was the same in D- and D+ (n=33 vs 34) and both groups showed the same decrease in SBP. This is in accordance with a study on selected patients with pHPT but without known cardiovascular risk factors and another study with a high proportion of patients with hypertension.

The study was blinded to patients, investigators and assessors to further minimize the risk of bias (information bias).

The use of calcium carbonate instead of placebo could be a limitation, since one cannot definitely exclude the possibility that the calcium supplementation interfered with the results. However, the changes in insulin resistance were detected before the start of
study medication and remained stable during the study period and the positive effects of PTX on BMD and blood pressure have been reported by others\textsuperscript{108,130,209}.

Another limitation may be the time interval between operation and randomization. It is our clinical routine to check biochemical parameters after six weeks and we chose to randomize the patients at this time point to ensure that they were cured before starting the study medication. In some patients, for example those with significant vitamin D deficiency or hungry bone, a shorter interval might have been favourable for the early mineralization of the bone.

There is a potential risk of type II error, considering the precision errors of the DXA and blood pressure devices and the %CV of the assays of the biochemical parameters. The sample size was based on the change in PTH (primary end-point), and could therefore be too small to detect differences in secondary end-points.
6 CONCLUSIONS

• Parathyroid adenomectomy is a safe procedure today, even in older patients. Chronological age *per se* is no reason for abstaining from surgical treatment of pHPT.

• A history of primary hyperparathyroidism does not seem to affect factors predictive of prognosis and response to therapy in women with subsequent breast cancer.

• Parathyroid adenomectomy has beneficial effects on insulin resistance, blood pressure and bone mineral density.

• Supplementation with vitamin D and calcium after parathyroid adenomectomy lowers the levels of parathyroid hormone, but no obviously beneficial effect was found on blood pressure, metabolic factors or bone mineral density.


Medelåldern hos patienterna steg från 53 till 64 år, samtidigt som dödligheten inom 30 dagar efter operation sjönk från 4.2% till 0.4%. Under senare år var en fjärdedel av patienterna 75 år och äldre. Den vanligaste dödsorsaken var hjärt- och kärlsjukdom.

Patienter med pHPT har också en ökad risk att drabbas av vissa cancerformer, varav bröstcancer är den vanligaste. I en registerstudie jämfördes bröstcancer hos kvinnor med och utan tidigare operation p.g.a. pHPT avseende prognostiska faktorer och dödlighet. Grupperna skilde sig inte åt avseende tumörstorlek, hormonreceptorstatus, lymfkörtelengagemang eller dödlighet i bröstcancer.

En hög andel av patienter med pHPT har brist på D-vitamin, vilket kan förvärra sjukdomens komplikationer. Efter botande operation av pHPT återhämtar sig bentätheten till viss del. Huruvida riskfaktorerna för hjärt- kärlsjukdom påverkas eller ej är inte helt klarlagt. De studier som finns är motstridiga. I avhandlingen undersöks om man kan påskynda och/eller förbättra återhämtningen i skelett och metabola
faktorer som blodtryck och blodsockerregering, genom att ge D-vitamintillskott efter operationen. Av 150 patienter fick hälften kalcium och D-vitamin och hälften enbart kalcium under ett år efter botande operation för pHPT. Själva operationen hade en gynnsam effekt på bentätthet, blodtryck och blodsockerregering men D-vitamin verkar inte tillföra någon ytterligare effekt, utom möjligen på bentättheten. D-vitamintillskott sänkte nivån av PTH, vilket i sig skulle kunna vara gynnsamt på lång sikt, då PTH åt det högre hållet är kopplat till t. ex. ökad risk för frakturer och hjärt- kärlsjukdom.

Sammanfattningsvis har vi sett att prognosen hos patienter med bröstcancer inte verkar skilja sig mellan de som har eller inte har haft pHPT. Nuförtiden är operation av primär hyperparatyreoïdism säker, även hos äldre personer. Ålder i sig bör inte utesluta att patienten får genomgå en potentiellt botande behandling av pHPT. Kirurgisk behandling av pHPT har en gynnsam effekt på PTH-nivå, bentätthet och blodsockerregering samt till viss del blodtryck. Någon säker vinst av D-vitamintillskott efter operation har inte kunnat påvisas, mer än en sänkning av PTH, vilket skulle kunna ha positiva effekter i sig.
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