

## Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism

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### Abstract

**Objectives** To assess the effects of surgery compared with conservative treatment (no surgery) for primary hyperparathyroidism.

**Design** Cohort study.

**Setting** Nationwide Danish cohort.

**Participants** 3213 patients, mean age 61 (SD 16) years, with a diagnosis of primary hyperparathyroidism between 1980 and 1999. 1934 (60%) underwent surgery and 1279 (40%) were treated conservatively.

**Main outcome measures** Occurrence of fractures, osteoporosis, kidney or urinary tract stones, acute myocardial infarction, angina pectoris, cardiac arrhythmias, arterial hypertension, heart failure, stroke, acute pancreatitis, stomach or duodenal ulcers, muscle pain, malignant diseases, psychiatric disorders, and mortality.

**Results** At diagnosis of primary hyperparathyroidism, patients who subsequently underwent surgery had a lower prevalence of previous fracture (odds ratio 0.64, 95% confidence interval 0.51 to 0.80), acute myocardial infarction (0.59, 0.42 to 0.83), stroke (0.57, 0.37 to 0.88), psychiatric disorders (0.54, 0.31 to 0.94), and painful muscle disorders (0.44, 0.26 to 0.76), whereas kidney stones (2.49, 1.93 to 3.23) and acute pancreatitis (2.77, 1.33 to 5.76) were more prevalent. After diagnosis, the risks of fractures (hazards ratio 0.69, 0.56 to 0.84) and gastric ulcers (0.59, 0.41 to 0.84) were lower in patients treated surgically than those treated conservatively. Events involving kidney or urinary tract stones were more prevalent in patients treated surgically than patients treated conservatively (1.87, 1.30 to 2.68). Mortality was lower in patients treated surgically (0.65, 0.57 to 0.73).

**Conclusions** Patients treated surgically for primary hyperparathyroidism have a lower prevalence of fractures and gastric ulcers than patients treated conservatively. The type of treatment had no effect on the occurrence of cardiovascular events.

### Introduction

The high levels of parathyroid hormone in primary hyperparathyroidism cause demineralisation of bone and increase the risk of fracture.<sup>1</sup> Hypercalcaemia increases the risk of kidney and urinary tract stones.<sup>2</sup> The high calcium and parathyroid hormone levels

have been associated with atherosclerosis and acute myocardial infarction.<sup>3-7</sup> Arterial hypertension, which does not regress with surgery, has also been reported in primary hyperparathyroidism, as have stomach and duodenal ulcers and acute and chronic pancreatitis.<sup>8-11</sup>

Most intervention studies on the effect of surgery in primary hyperparathyroidism are uncontrolled cohort or before and after trials comparing changes in left ventricular size, fracture risk, bone mineral density, and incidence of kidney stones.<sup>1 2 12 13</sup> They therefore have not evaluated the difference between surgically and non-surgically (conservatively) treated patients. One small randomised study of 53 patients evaluated the effects of surgery and conservative treatment on bone mineral density and found an increase in bone mineral density and quality of life scores in surgically treated patients.<sup>14 15</sup> We collected data on a large cohort of patients with primary hyperparathyroidism and evaluated the long term outcome of hard end points in surgically treated patients compared with conservatively treated patients.

### Materials and methods

Data were obtained from the Danish national hospital discharge database. This central database contains information on patients admitted to hospital according to their unique identification number and type of disease (international classification of diseases, eighth and 10th revisions; the ninth revision was never used in Denmark).<sup>16</sup> Any surgical procedures are also entered in the database. We were therefore able to obtain data on both diagnosis and admissions for concurrent illnesses in patients with primary hyperparathyroidism.

We retrieved information on patients with a first time diagnosis of primary hyperparathyroidism (ICD-8 codes: 252.00, 252.01, 252.03-05, 252.08, 252.09, and ICD10 codes: E21.0, E21.2, E21.3) for the period 1 January 1980 to 31 December 1999, and identified 3225 patients. Twelve (0.4%) were excluded: 10 were not Danish citizens, precluding follow up; the identification number was incorrect in one; and one had emigrated. This left 3213 for analysis. We identified 1934 patients (60%) who had undergone surgery and 1279 (40%) who had not. Information was obtained on all hospital contacts for these 3213 patients from 1 January 1977 to 31 December 1999. Our primary end points of interest were fractures, osteoporosis, kidney and urinary tract stone events, acute myocardial

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infarction, angina pectoris, cardiac arrhythmias, arterial hypertension, cardiac insufficiency, stroke, stomach or duodenal ulcers, acute pancreatitis, poorly defined muscular pain, cancer, and psychiatric illness (psychoses and dementia) or neurotic disorders. We assessed whether any such contact had taken place before or after the date when primary hyperparathyroidism was diagnosed. We also obtained information on whether patients had died or emigrated during this period from the ministry of the interior. Total follow up time after diagnosis was 19 565 (median 6.1) years. Before diagnosis the observation time was 47 063 (median 15.9) years. The precision of the disease codes is generally considered to be high.<sup>16-18</sup> Screening a random sample of 33 patients showed that the register based diagnosis of primary hyperparathyroidism was correct in 95% (n = 19) of surgically treated patients and 85% (n = 14) of conservatively treated patients. Screening a random sample of 35 patients with fracture diagnoses showed that 97% of register diagnoses agreed with hospital records. From a previous study the validity of a registered diagnosis of acute myocardial infarction was almost 90%.<sup>19</sup>

### Statistics

Crude odds ratios were calculated for all outcomes. We used a Cox proportional hazard model to analyse differences between surgically and conservatively treated patients. We entered as potential confounders in the model, age at diagnosis of primary hyperparathyroidism for patients aged 50 or over compared with those under 50, sex, and presence of the end point in question before the time of diagnosis. The presence of an end point before the time of diagnosis presents a special problem. In some cases, the patient may have more than one end point—for example, fractures occurring several times during follow up, and a fracture before diagnosis may be a risk factor for sustaining a new fracture after primary hyperparathyroidism was diagnosed. However, in other instances a prior end point may be a chronic disease for which the individual simply returns to receive medical attention (for example, cancer). We analysed the dataset both with the end points before the time of diagnosis and without. The results were similar for both approaches. We used logistic regression (likelihood ratio method) to evaluate difference in the prevalence of concurrent diseases at the time primary hyperparathyroidism was diagnosed, adjusted for age ( $\geq 50$  v  $< 50$  years) and sex (female v male). We computed the models with all vari-

ables, entered using SPSS version 10.0. We compared the observed survival in the cohort of patients with that of the age matched and sex matched normal population using survival tables from the National Bureau of Statistics.<sup>20</sup> The Charlson comorbidity index was used to assess survival in surgically treated compared with conservatively treated patients.<sup>21</sup> This index comprises 19 comorbid conditions, including cardiovascular disease, cerebrovascular disease, peripheral artery disease, lung disease, liver disease, kidney diseases, dementia, cancer, and diabetes.

### Results

Table 1 shows baseline characteristics at the time of diagnosis in all patients with primary hyperparathyroidism, stratified by treatment. The median time from diagnosis to surgery was 0.09 years (31 days), range 0-14 years. Table 2 shows the presence of any end point before diagnosis and whether these risk factors were unevenly distributed among the groups. Table 3 shows the effect of surgery on the occurrence of a variety of end points after diagnosis. The risk of fractures was 31% (hazard ratio 0.69) lower in surgically treated patients than in conservatively treated patients whereas the risk of stomach and duodenal ulcers was 41% (0.59) lower. A history of any of the end points increased the risk of having a recurrent episode of that end point. More episodes of kidney stones occurred after diagnosis among those who had surgery than among those who did not. The results were not changed by including the Charlson comorbidity index as a confounder.

After adjustment for potential confounders, the risk of death was lower in surgically treated patients than in conservatively treated patients (hazards ratio 0.65, 95% confidence interval 0.57 to 0.73; table 4). The risk of death was lower in patients with a history of kidney stones. Prior myocardial infarction, hypertension, cardiac failure, arrhythmia, cancer, fracture, and ulcer were associated with an increased risk of death (see table 4). The results were not changed by including the Charlson comorbidity index (0.62, 0.55 to 0.70 for surgical compared with conservative treatment) instead of the confounders. Survival was higher in surgically treated patients than in conservatively treated patients (figure). In both groups the observed survival was significantly lower than in the general population. However, the relative loss of expected life time was higher among conservatively treated patients than among surgically treated patients (mean 20% or 2.7 years v 14% or 2.1 years,  $P < 0.01$ ) after adjustment for age and sex. The proportion undergoing surgery decreased with time: 66% of patients diagnosed from 1980 to 1989 underwent surgery compared with 56% of those diagnosed between 1990 and 1999 ( $P < 0.01$ ).

### Discussion

Surgical treatment for primary hyperparathyroidism led to fewer fractures and episodes of gastroduodenal ulcers and lower mortality than conservative treatment. Surgery was not, however, associated with a change in risk of cardiovascular events.

**Table 1** Characteristics of patients at time primary hyperparathyroidism was diagnosed stratified by surgery or conservative treatment (no surgery). Values are numbers (percentages) unless stated otherwise

Variable	Surgery (n=1934)	No surgery (n=1279)	P value
Mean (SD) age (years)	58.3 (15.2)	64.2 (17.4)	<0.01*
Men	500 (26)	293 (23)	0.06†
Women	1434 (74)	986 (77)	
Charlson index‡:			<0.01†
0	1385 (72)	852 (67)	
1	259 (13)	199 (16)	
2	204 (11)	142 (11)	
3	59 (3)	53 (4)	
≥4	27 (1)	33 (3)	

\*Two sided t test.

† $\chi^2$  test.

‡0=no comorbidity; 1-4=increasing comorbidity.

**Table 2** Presence of end points before diagnosis of primary hyperparathyroidism stratified by surgery or conservative treatment (no surgery). Values are numbers (percentages) of patients unless stated otherwise

Variable	Surgery (n=1934)	No surgery (n=1279)	Crude odds ratio for surgery v no surgery (95% CI)*	Odds ratio (95% CI)		
				Adjusted for age†	Adjusted for sex	Adjusted for surgery‡
Fractures	172 (9)	176 (14)	0.61 (0.49 to 0.76)	2.07 (1.49 to 2.87)	1.14 (0.86 to 1.50)	0.64 (0.51 to 0.80)
Kidney stones	297 (15)	83 (7)	2.61 (2.04 to 3.35)	0.59 (0.47 to 0.75)	0.49 (0.39 to 0.61)	2.49 (1.93 to 3.23)
Stroke	38 (2)	46 (4)	0.54 (0.35 to 0.83)	6.37 (2.32 to 17.48)	0.64 (0.39 to 1.03)	0.57 (0.37 to 0.88)
Hypertension	85 (4)	58 (5)	0.97 (0.69 to 1.36)	1.52 (0.98 to 2.38)	0.76 (0.52 to 1.11)	0.99 (0.70 to 1.39)
Acute myocardial infarction	65 (3)	75 (6)	0.54 (0.39 to 0.76)	6.48 (3.00 to 13.97)	0.52 (0.36 to 0.75)	0.59 (0.42 to 0.83)
Angina	59 (3)	50 (4)	0.77 (0.53 to 1.13)	4.98 (2.29 to 10.80)	0.56 (0.37 to 0.84)	0.81 (0.55 to 1.20)
Heart failure	29 (2)	42 (3)	0.45 (0.28 to 0.72)	19.45 (2.76 to 137.17)	1.19 (0.65 to 2.19)	0.49 (0.30 to 0.79)
Arrhythmias	55 (3)	50 (4)	0.72 (0.49 to 1.06)	6.05 (2.45 to 14.95)	1.12 (0.69 to 1.82)	0.78 (0.53 to 1.15)
Pancreatitis	38 (2)	9 (1)	2.83 (1.41 to 5.69)	0.77 (0.41 to 1.47)	1.02 (0.52 to 2.00)	2.77 (1.33 to 5.76)
Ulcers	99 (5)	56 (4)	1.18 (0.84 to 1.65)	2.68 (1.60 to 4.49)	0.85 (0.58 to 1.23)	1.24 (0.88 to 1.74)
Muscle pain	23 (1)	34 (3)	0.44 (0.26 to 0.74)	1.25 (0.63 to 2.44)	0.72 (0.40 to 1.29)	0.44 (0.26 to 0.76)
Osteoporosis	35 (2)	27 (2)	0.85 (0.51 to 1.42)	7.81 (1.90 to 32.06)	8.52 (2.08 to 34.91)	0.96 (0.57 to 1.59)
Cancer	135 (7)	119 (9)	0.73 (0.57 to 0.95)	3.49 (2.21 to 5.51)	1.13 (0.82 to 1.55)	0.78 (0.60 to 1.01)
Psychiatric disorder	23 (1)	29 (2)	0.52 (0.30 to 0.89)	2.35 (0.99 to 5.57)	0.71 (0.39 to 1.31)	0.54 (0.31 to 0.94)
Neuroses	33 (2)	36 (3)	0.60 (0.37 to 0.96)	3.01 (1.53 to 5.94)	7.63 (3.30 to 17.65)	0.70 (0.42 to 1.15)

Adjustment performed by logistic regression.

\*Unadjusted for age and sex.

†Aged ≥50 v &lt;50 years at diagnosis.

‡Surgery v no surgery.

### Advantages and disadvantages of study

The major advantage of our study is that we looked at a population based representative sample, allowing assessment of multiple outcomes over an extended period. Our study was not randomised, but relied on observational data from an administrative system collected for other purposes. Another major limitation was the lack of information on important confounders such as smoking. Thus bias may have affected the outcomes significantly. Selection bias could have affected the results in several ways. It is unlikely that the population was selected, as all cases of primary hyperparathyroidism in Denmark are managed in hospital and thus are included in the register. Selection bias is, however, a significant factor in deciding who should have surgery and who should be managed conservatively.

Surgery is the treatment of choice in patients with symptoms of primary hyperparathyroidism. Guidelines recommend that patients with asymptomatic primary hyperparathyroidism undergo surgery when there is a high concentration of serum calcium (> 1 mg/dl above normal range), high urine calcium output, and organ involvement (reduced kidney function or reduced bone mineral density).<sup>22</sup> Thus those selected for surgery are more likely to have advanced disease with symptoms in contrast with those selected for conservative management, who will often have asymptomatic disease with a low risk of any end point. This would underestimate any difference between surgical and conservative treatment. On the other hand, some patients may simply be too unwell to tolerate surgery, and this would mean that some of

**Table 3** Presence of end points after diagnosis stratified by surgery or conservative treatment (no surgery) for primary hyperparathyroidism and test of effects of surgery versus no surgery. Values are numbers (percentages) unless stated otherwise

Variable	Surgery	No surgery	Crude odds ratio* (95% CI)	Hazard ratio (95% CI)†			
				Age‡	Sex	Prior event§	Surgery¶
Fractures	235 (12)	170 (13)	0.90 (0.73 to 1.11)	1.90 (1.46 to 2.48)	1.66 (1.26 to 2.17)	2.76 (2.14 to 3.55)	0.69 (0.56 to 0.84)
Kidney stones	174 (9)	37 (3)	3.32 (2.35 to 4.68)	0.69 (0.52 to 0.91)	0.82 (0.61 to 1.09)	8.62 (6.51 to 11.43)	1.87 (1.30 to 2.68)
Stroke	128 (7)	74 (6)	1.15 (0.86 to 1.55)	5.95 (3.49 to 10.15)	0.87 (0.63 to 1.21)	3.61 (2.03 to 6.41)	0.90 (0.68 to 1.21)
Hypertension	96 (5)	35 (3)	1.86 (1.26 to 2.74)	0.98 (0.67 to 1.44)	0.81 (0.56 to 1.19)	7.41 (4.73 to 11.61)	1.30 (0.88 to 1.91)
Acute myocardial infarction	98 (5)	53 (4)	1.23 (0.88 to 1.74)	3.83 (2.26 to 6.52)	0.57 (0.40 to 0.80)	5.11 (3.29 to 7.95)	0.96 (0.69 to 1.35)
Angina	94 (5)	56 (4)	1.12 (0.80 to 1.57)	2.48 (1.59 to 3.88)	0.45 (0.32 to 0.62)	12.80 (8.45 to 19.40)	0.84 (0.60 to 1.18)
Heart failure	87 (5)	57 (5)	1.01 (0.72 to 1.42)	6.19 (3.12 to 12.27)	1.01 (0.68 to 1.52)	10.25 (5.98 to 17.55)	0.81 (0.58 to 1.14)
Arrhythmias	99 (5)	44 (3)	1.51 (1.06 to 2.17)	2.24 (1.40 to 3.60)	0.63 (0.44 to 0.91)	13.78 (8.97 to 21.15)	1.16 (0.81 to 1.66)
Pancreatitis	18 (1)	8 (1)	1.49 (0.65 to 3.42)	0.75 (0.33 to 1.71)	0.60 (0.26 to 1.36)	45.22 (19.94 to 102.53)	0.82 (0.35 to 1.95)
Ulcers	69 (4)	55 (4)	0.82 (0.57 to 1.18)	2.31 (1.41 to 3.80)	0.73 (0.49 to 1.08)	3.78 (2.28 to 6.25)	0.59 (0.41 to 0.84)
Muscle pain	34 (2)	25 (2)	0.90 (0.53 to 1.51)	1.32 (0.71 to 2.45)	1.41 (0.73 to 2.75)	3.51 (0.84 to 14.58)	0.68 (0.40 to 1.15)
Osteoporosis	36 (2)	29 (2)	0.82 (0.50 to 1.34)	4.45 (1.59 to 12.44)	3.39 (1.22 to 9.42)	14.88 (8.13 to 27.24)	0.63 (0.38 to 1.03)
Cancer	270 (14)	127 (10)	1.47 (1.18 to 1.84)	2.45 (1.84 to 3.28)	0.69 (0.55 to 0.86)	5.17 (4.06 to 6.59)	1.11 (0.90 to 1.37)
Psychiatric dis.	44 (2)	33 (3)	0.88 (0.56 to 1.39)	3.01 (1.53 to 5.94)	0.70 (0.42 to 1.15)	7.63 (3.30 to 17.65)	0.66 (0.42 to 1.04)
Neuroses	20 (1)	18 (1)	0.73 (0.39 to 1.39)	0.46 (0.24 to 0.90)	1.75 (0.76 to 4.04)	12.06 (5.49 to 26.46)	0.61 (0.32 to 1.16)

Hazard ratios are mutually adjusted.

\*Unadjusted for age and sex.

†Cox regression model.

‡Aged ≥50 v &lt;50 years at diagnosis.

§Sustaining new end point after diagnosis if event had already occurred before diagnosis.

¶Surgery v no surgery.

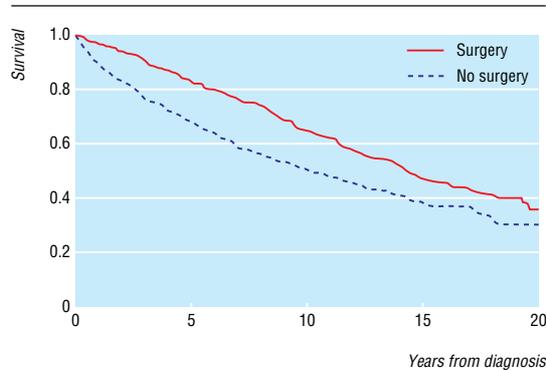
**Table 4** Variables of significance to risk of death during follow up after surgery or conservative treatment (no surgery) for primary hyperparathyroidism

Variable	Hazard ratio (95% CI)*
Surgery v no surgery	0.65 (0.57 to 0.73)
Age (≥50 v <50 years)	3.85 (3.14 to 4.72)
Sex (women v men)	0.70 (0.61 to 0.80)
Medical history:	
Kidney stones	0.57 (0.46 to 0.71)
Cancer	1.57 (1.27 to 1.93)
Myocardial infarction	1.34 (1.02 to 1.74)
Angina pectoris	1.06 (0.75 to 1.49)
Cardiac failure	2.21 (1.56 to 3.14)
Arrhythmia	1.48 (1.07 to 2.03)
Hypertension	1.82 (1.40 to 2.36)
Stroke	1.34 (0.95 to 1.88)
Stomach or duodenal ulcer	1.40 (1.09 to 1.79)
Acute pancreatitis	0.97 (0.57 to 1.64)
Fracture	1.29 (1.06 to 1.57)

\*Cox proportional hazard analysis. Hazard ratios are mutually adjusted. Results not changed by replacing preoperative conditions with Charlson index.

those managed conservatively actually have a higher risk of death than those undergoing surgery. It is also possible that some patients did not want to undergo surgery, particularly those with psychiatric disorders. A trend was, however, shown towards a decrease in occurrence of psychiatric disorders in surgically treated patients.

Information bias seems to pose a smaller problem for fractures and acute myocardial infarction, as the precision of diagnoses was high. Precise data for the validity of certain end points, such as stomach ulcers, were not available. The lower precision of the diagnoses in those not undergoing surgery would tend to underestimate any effect of surgery because some of the patients did not have primary hyperparathyroidism. Although many of the conditions studied are managed in hospital (for example, acute myocardial infarction, cardiac arrhythmias, fractures), hypertension, muscle pain, neuroses, and gastric ulcers are often managed by general practitioners and are therefore not reflected in the data presented here. This may lead to a significant underestimation of these types of comorbidity. A special feature of bias is confounding by indication, when patients with urinary tract stones were more likely to undergo surgery than those without



Kaplan-Meier plot of survival in surgically and conservatively treated patients with primary hyperparathyroidism. Death during follow up occurred in 591 (31%) surgically treated patients and 474 (37%) conservatively treated patients

### What is already known on this topic

The risk of death is increased in primary hyperparathyroidism mainly due to an excess of deaths from cardiovascular causes

Bone mineral density increases after parathyroid surgery

Little is known on outcomes from cardiovascular events after surgery

### What this study adds

Patients treated surgically for primary hyperparathyroidism have a lower risk of fractures and stomach and duodenal ulcers than those treated conservatively

Surgery was not associated with a change in the risk of cardiovascular events

The risk of kidney and urinary stones was higher both before and after surgery in those undergoing surgery

Mortality was lower in surgically treated patients

after the recommendations from international guidelines. Those who did not undergo surgery were older and had a higher mortality—that is, they may not have been offered surgery owing to their health and comorbidity.

### Effects of surgery on hard end points

In contrast with the present study, we have presented the results of a study on patients only surgically treated for primary hyperparathyroidism.<sup>1,2</sup> Although the risk of fracture was increased before surgery and returned to that of the general population within one year after surgery, it took 10 years or more for the risk of kidney stones to return to that of the general population.<sup>1,2</sup> This may be caused by permanent damage to the urinary tract from strictures, persistent infections, or untreated stones. Although we tried to adjust for prior kidney stones, this may not have excluded patients with asymptomatic kidney stones, those whose pain was misdiagnosed as simple stomach pain, or those who did not at seek medical attention for the pain. Therefore, although some of the basis for recurrent stone formation (hypercalcaemia and hypercalciuria) is removed after parathyroidectomy, other factors may continue to induce stone formation. The risk of being admitted for gastric and duodenal ulcers decreased by 41% after surgery, although patients who underwent surgery tended to have more ulcers before diagnosis than those who did not have surgery. In accordance with our study, previous studies have shown that blood pressure is unchanged after surgery for primary hyperparathyroidism, probably indicating irreversible vascular or renal changes.<sup>9</sup> The lack of effect on this important risk factor for other cardiovascular diseases may partly explain the absence of treatment effect on overall cardiovascular risk in our study.

The risk of death was smaller in surgically treated patients even after adjustment for several important confounders such as cardiovascular disease, cancer,

and hypertension. Those not selected for surgery may have had a shorter expected lifespan than those selected for surgery. However, surgery did improve survival by decreasing serum calcium and serum parathyroid hormone levels. In our study those with prior kidney stones had a lower risk of death, a finding that agrees with another study.<sup>23</sup> The reason for this remains unclear.

#### Effect of time

The incidence of primary hyperparathyroidism has changed significantly over time, because of increased access to measurements of serum calcium.<sup>24</sup> The diagnostic criteria of increased serum calcium and serum parathyroid hormone levels have not changed over time, but milder cases are now diagnosed, and many of these do not require surgical management—reflected by the decrease in the proportion undergoing surgery. With the advent of milder cases the difference in the risk of end points between surgically and conservatively treated patients must be larger than if the cases were more balanced. However, the effects of surgery on these mild cases must be expected to be less than those on the more severe cases in our study.

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