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## Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study

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### Abstract

**Aim** To study the risk of renal stone episodes and risk factors for renal stones in primary hyperparathyroidism before and after surgery.

**Design** Register based, controlled retrospective follow up study.

**Setting** Tertiary hospitals in Denmark.

**Participants** 674 consecutive patients with surgically verified primary hyperparathyroidism. Each patient was compared with three age- and sex-matched controls randomly drawn from the background population. Hospital admissions for renal stone disease were compared between patients and controls. Risk factors for renal stones among patients were assessed.

**Main outcome measures** Number of renal stone episodes; comparison of hospital admissions for renal stones in patients and controls; assessment of risk factors for renal stones.

**Results** Relative risk of a stone episode was 40 (95% confidence interval 31 to 53) before surgery and 16 (12 to 23) after surgery. Risk was increased 10 years before surgery, and became normal more than 10 years after surgery. Stone-free survival 20 years after

surgery was 90.4% in patients and 98.7% in controls (risk difference 8.3%, 4.8% to 11.7%). Patients with preoperative stones had 27 times the risk of postoperative stone incidents than controls. Before surgery, males had more stone episodes than females and younger patients had more stone episodes than older patients. Neither parathyroid pathology, weight of removed tissue, plasma calcium levels, nor skeletal pathology (fractures) influenced the risk of renal stones. After surgery, younger age, preoperative stones and ureteral strictures were significant risk factors for stones.

**Conclusions** The risk of renal stones is increased in primary hyperparathyroidism and decreases after surgery. The risk profile is normal 10 years after surgery. Preoperative stone events increase the risk of postoperative stones. Stone formers and non-stone formers had the same risk of skeletal complications.

### Introduction

Primary hyperparathyroidism is associated with increased risk of renal stones. As the clinical picture of primary hyperparathyroidism has shifted towards milder and even asymptomatic cases with the advent of



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biochemical screening, the prevalence of stone disease has declined from around 80% in early series to 7-20% in more recent series.<sup>1 2</sup>

It is generally accepted that parathyroidectomy reduces the risk of recurrent stone disease provided that normocalcaemia is obtained.<sup>3</sup> However, a 30-50% risk of recurrence after an observation period of three to five years has been reported,<sup>4 5</sup> bringing into question the effect of parathyroidectomy in a substantial proportion of the patients.

The objective of this study was to investigate the whether the risk of renal stones is higher in patients with primary hyperparathyroidism before surgery than in the general population; the extent to which patients with and without renal stones differ in variables such as age, sex, severity of disease, histopathology, and skeletal symptoms; and whether surgery decreases the future risk of stone disease.

## Methods

The study was designed as a register based, controlled retrospective follow up study.

### Patients

The cohort consisted of 674 consecutive white patients with surgically verified primary hyperparathyroidism treated at Aarhus University Hospital between 1979 and 1997, at Odense University Hospital between 1979 and 1990, and at Copenhagen University Hospital, Rigshospitalet, between 1991 and 1997. Of the 674 patients, 97% (653) were operated on within one year after the diagnosis was first registered. All patients included were normocalcaemic after surgery.

### Controls

For each of the 674 patients, three white controls frequency matched for age (birth year), sex, and status were drawn from population lists of people residing in Denmark between 1 January 1979 and 31 December 1997. The status match regarded death or emigration. The follow up period of the controls was then divided into the period before and after this date.<sup>6</sup>

### Outcome variables

For both patients and controls, all inpatient and outpatient discharge diagnoses concerning kidney or urinary tract stones (see bmj.com) between 1 January 1978 and 31 December 1997 were retrieved from the National Patient Register under the Danish National Board of Health.<sup>7</sup> Only discharges in which renal stone disease was the main diagnosis were considered for statistical evaluation.

Furthermore, for both patients and controls, information on any fracture diagnosis or osteoporosis (ICD-8 code 723.09; ICD-10 codes M80.0-M81.9) was retrieved from the same source.

Data on serum calcium were retrieved from patients' files. All calcium values reported were measured the day before surgery.

## Statistics

The Mann-Whitney test or the  $\chi^2$  test for contingency tables were used to compare numbers where appropriate. Incidence rates were calculated as the number of participants with at least one stone-related admission divided by the observation time and were compared as incidence rate ratios by Mantel-Haenszel-type statistics. Differences between proportions were calculated by Fischer's exact test. Incidence rate ratios were compared by using Poisson regression. Risk factors were analysed by using logistic regression and Cox regression. Stone-free survival was determined from Kaplan-Meier plots.

## Results

Women made up 74% of the cohort, of whom 90% (451) had parathyroid adenoma and 10% (50) had hyperplasia. The amount of removed tissue varied greatly. Male patients were younger and had larger adenomas and a higher incidence of stone disease than female patients (table).

### Risk of stone disease and effect of parathyroid surgery

The incidence rate ratio of contact with hospital because of stone disease was 40 (95% confidence interval 31 to 53) before parathyroid surgery and 17 (12 to 24) after surgery ( $P < 0.01$ ). The risk of stone disease was highest within the four years before and in the four years after surgery, with a peak in risk immediately before diagnosis and treatment (fig 1). As much as 10 years before the diagnosis of primary hyperparathyroidism, the risk of a stone event was significantly increased. From five to 10 years after surgery the risk of stone events remained at the same level as five to 10 years before surgery. However, more than 10 years after surgery the risk of

Clinical characteristics and operative findings in 674 patients with primary hyperparathyroidism. Values are mean (SD) unless otherwise stated

| Characteristic                           | All patients (n=674) | Men (n=173)       | Women (n=501)  |
|--|----------------------|-------------------|----------------|
| Age (years)                              | 58.2 (15.0)          | 54.8 (16.6)       | 59.4 (14.3)    |
| No (%) with adenomas                     | 606 (90)             | 155 (90)          | 451 (90)       |
| No (%) with hyperplasia                  | 68 (10)              | 18 (10)           | 50 (10)        |
| Adenoma weight (g)                       | 2.11 (5.18)          | 3.03 (8.79)       | 1.80 (3.13)    |
| Median (range)                           | 1.00 (0.02-87)       | 1.20 (0.03-87)    | 1.00 (0.02-40) |
| Hyperplasia weight (g)                   | 3.59 (6.53)          | 3.57 (4.29)       | 3.60 (7.09)    |
| Median (range)                           | 1.50 (0.10-42)       | 2.82 (0.80-17.61) | 1.48 (0.10-42) |
| Stone disease mentioned in file          | 167 (25)             | 58 (34)           | 109 (22)       |
| Serum calcium (ionised), mmol/l*         | 1.58 (0.17)          | 1.59 (0.15)       | 1.57 (0.17)    |
| Postoperative observation period (years) | 5.4 (4.4)            | 6.9 (4.4)         | 5.3 (4.3)      |

\*Measured on day before surgery.

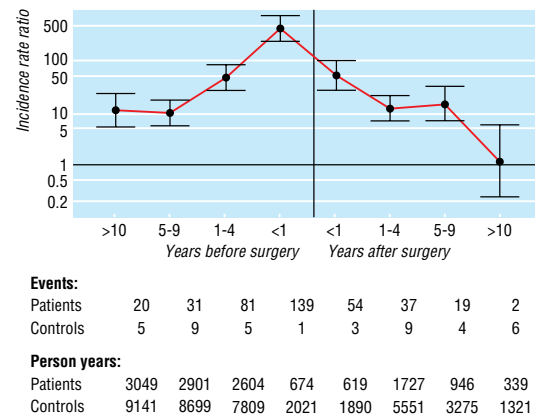
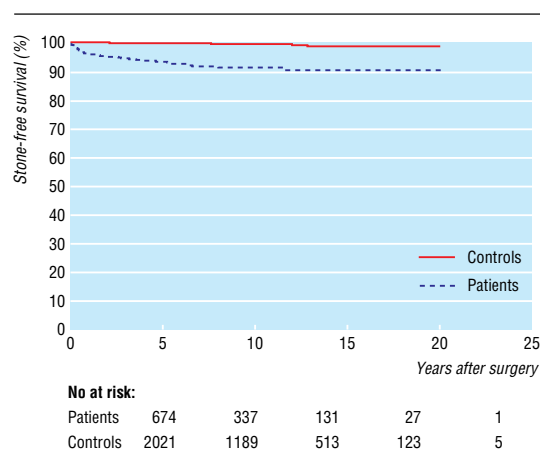


Fig 1 Renal stone events among patients compared with controls before and after parathyroid surgery. Bars indicate 95% confidence intervals; vertical line indicates time of surgery



**Fig 2** Stone-free survival after surgery

stone events in patients did not differ from the risk among controls.

The stone-free survival after surgery was 98.7% in controls and 90.4% in patients 20 years after surgery, yielding a risk difference of 8.3% (4.8–11.7%) (fig 2).

Patients with preoperative stones had 27 times the risk of postoperative stone incidents (incidence rate ratio 75.9; 45.8 to 125.5) of patients without preoperative stones (2.8; 1.5 to 5.5).

The risk of strictures of the ureters and hydronephrosis was higher in patients than in controls both before and after parathyroid surgery. All three patients with ureteral stricture or hydronephrosis before diagnosis also had urinary tract stones; one of the three patients diagnosed as having postoperative strictures or hydronephrosis did not have concomitant urinary tract stones.

#### Differences between stone formers and non-stone formers

Apart from a significantly lower age at diagnosis (53 (SD 16) years *v* 60 (15) years,  $P < 0.01$ ) and a higher proportion of men among patients with stones (35/167 (21%) *v* 23/506 (5%),  $P < 0.01$ ), no significant differences were evident in patients with and without renal stones. The groups did not differ in parathyroid pathology, weight of removed tissue, or plasma calcium concentrations. Skeletal complications in terms of fractures or a diagnosis of osteoporosis were similar in the two groups.

#### Risk factors for renal stones

Before surgery, men had more stone episodes than women (adjusted odds ratio 1.83; 1.11 to 3.00), and younger patients (< 60 years) had more stone episodes than older patients (0.33; 0.20 to 0.54). Neither the weight of removed parathyroid tissue nor preoperative plasma calcium was related to the risk estimate. Also, after surgery younger patients had more stone episodes than older patients. Furthermore, a history of stones was associated with more stone episodes after surgery (adjusted hazard ratio 5.89; 3.04 to 11.41).

## Discussion

Patients with primary hyperparathyroidism had a greater risk of renal stone disease even 10 years before the diagnosis was registered than did a population

based control group matched for sex and age. This is in accordance with the higher risk of fractures observed in the same population 10 years before diagnosis.<sup>6</sup> These findings suggest that the disease has started several years before diagnosis and emphasises the importance of early diagnosis and treatment. This view is further supported by the finding of a higher risk of stone events before diagnosis. Parathyroid adenomas were larger and preoperative serum calcium concentrations were higher in our patients than in other surgical series,<sup>8,9</sup> supporting the theory of a delay in diagnosis.

After surgical treatment of primary hyperparathyroidism, hospital admissions due to stone episodes were reduced. Without randomisation to surgery or no surgery, one cannot determine whether this reduction in stone episodes is caused by the treatment, by the natural course of the disease, or by the synchronisation effect induced by a possible Berkson's bias. In our study, the risk of new renal stone episodes before, as well as after, parathyroid surgery was lower with older age. However, the reduction of stone events after diagnosis and surgery was significantly higher than could be explained by the average increase in age during follow up, suggesting a treatment effect of around 8%. The risk of hospital admission because of stone disease returned to normal more than 10 years after surgery (fig 1).

Patients also had a higher risk of strictures of the ureters and of hydronephrosis than the controls both before and after surgery. This could indicate that stones caused anatomical damage to the urinary tract. These structural changes could increase the risk of having stones subsequently even though the biochemical abnormalities had been normalised by surgery.

Our data accord with recent studies that have shown that patients with primary hyperparathyroidism and renal stones may continue to produce stones after parathyroid surgery even though normocalcaemia has been established.<sup>4,5</sup> Patients with renal stones who have primary hyperparathyroidism have a higher renal calcium excretion than those without stones who have similar concentrations of plasma calcium.<sup>10</sup> Finally, three years after parathyroidectomy, patients who continue to form stones have higher average renal calcium

#### What is already known on this topic

Patients with primary hyperparathyroidism have an increased risk of renal stone events

The extent to which parathyroid surgery reduces the risk of further stones is unclear

#### What this study adds

The risk of a new stone event was 8.3% higher in patients than in controls after surgery

In patients with stone disease before operation the risk rate for a postoperative stone event was 27 times that in controls

The risk of a renal stone event was higher than the risk among controls until more than 10 years after surgery

excretion than those without stones. This suggests again that idiopathic renal hypercalciuria could have a pathogenic role in patients with recurrent stone formation.<sup>11</sup>

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## Insecticide impregnated curtains to control domestic transmission of cutaneous leishmaniasis in Venezuela: cluster randomised trial

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### Abstract

**Objective** To measure the impact on transmission of leishmaniasis of curtains impregnated with insecticide. **Design** Cluster randomised controlled trial: household interview survey, observational study of people's behaviour, entomological study with light trap captures of sandflies inside houses.

**Setting** 14 urban sectors in Trujillo, Venezuela.

**Participants** 2913 inhabitants of 569 houses.

**Intervention** Sectors were paired according to their 12 month cumulative incidence of cutaneous leishmaniasis, one sector in each pair was randomly allocated to receive polyester curtains impregnated with lambda-cyhalothrin (intervention group) while the other sector received curtains without insecticide or no curtains (control groups). After 12 months a follow up household survey was conducted.

**Main outcome measures** Reduction in abundance of sandflies indoors and 12 month incidence of clinical cases of cutaneous leishmaniasis.

**Results** Transmission of cutaneous leishmaniasis occurred mainly in the domestic setting, with the incidence over 12 months of 4%. The mean number of sandflies per trap per night was 16. After follow up the 12 month incidence of cutaneous leishmaniasis was 0% in the intervention group and 8% in the six pairs in the control group that received unimpregnated curtains (mean difference 8, 95% confidence interval 4.22 to 11.78; P=0.001). There were significantly fewer sandflies in the intervention group (2 v 15, mean difference 13 sandflies per trap; 9 to 17; P<0.001).

**Conclusion** Curtains impregnated with insecticide provide a high degree of protection against indoor transmission of cutaneous leishmaniasis.

### Introduction

American cutaneous leishmaniasis is transmitted by sandflies in rain forest areas mainly among mammals and occasionally humans. However, deforestation has brought vectors and some animal hosts closer to humans, and domestic animals have emerged as alternative reservoirs resulting in an increase in cases of cutaneous leishmaniasis in urban areas.<sup>1</sup> This trend has been described for several countries.<sup>2-8</sup>

The domestication of transmission has also increased the opportunities for control. Indoor house spraying in Peru,<sup>9</sup> space spraying in Venezuela,<sup>10</sup> and curtains impregnated with pyrethroid insecticide in Burkina Faso,<sup>11</sup> Sudan,<sup>12 13</sup> and Colombia<sup>14</sup> have considerably reduced sandfly populations.

We carried out a study in an urban area of Venezuela with intense transmission of cutaneous leishmaniasis. We assessed any reduction in abundance of sandflies indoors and of clinical cases in areas with houses protected by curtains impregnated with pyrethroid insecticide compared with areas with houses using non-impregnated curtains or with no curtains at all. Curtains are preferred to bed nets in urban areas. We received approval for the study from the ethics committee at the Universidad de los Andes, Venezuela.

### Methods

#### Study area

Trujillo, Venezuela, is 800 metres above sea level, has 33 399 inhabitants, and is divided into 22 sectors. It has an annual average temperature of 23.3°C and two annual rainfall periods (July and November) of 750 mm each. The city has many green areas where opossum and other woodland reservoir hosts of *Leishmania* live.