Received: 30 September 2021 | Revised: 9 January 2022 | Accepted: 11 January 2022

DOI: 10.1111/cen.14703

ORIGINAL ARTICLE

WILEY

Reduced fracture incidence in patients having surgery for primary hyperparathyroidism

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Funding information
Anna-Lisa och Sven Eric Lundgrens stiftelse för medicinsk forskning; Stiftelsen Thelma Zoégas fond för medicinsk forskning, Grant/Award Numbers: TZ2015-0080, TZ2017-0093; SUS stiftelser och donationer; Thorsten Birger Segerfalks Stiftelse; Carl J Michaelsens Donationsfond

Abstract

Objective: The indication of surgery in primary hyperparathyroidism has been controversial, as many patients experience mild disease. The primary aim was to evaluate fracture incidence in a contemporary population-based cohort of patients having surgery for primary hyperparathyroidism. The secondary aim was to investigate whether preoperative serum calcium, adenoma weight or multiglandular disease influence fracture incidence.

Design: A retrospective cohort study with population controls. Primary outcomes, defined by discharge diagnoses and prescriptions, were *any fracture* and *fragility fracture*, secondary outcomes were *multiple fractures anytime* and *osteoporosis*. Subjects were followed 10 years pre- and up to 10 years postoperatively (or 31 December 2015). Multiple events per subject were allowed. Fracture incidence rate ratios (IRRs) for patients pre- and postoperatively were tabulated and evaluated with mixed-effects Poisson regression. Secondary outcomes were evaluated using conditional logistic regression.

Patients: A Swedish nationwide cohort of patients having surgery for primary hyperparathyroidism ($n = 5009$) from the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery between 2003 and 2013 was matched with population controls ($n = 14{,}983$). Data were cross-linked with Statistics Sweden and the National Board of Health and Welfare.

Measurements: Preoperative serum calcium and adenoma weight at pathological examination.

Results: Patients had an increased incidence rate of any fracture preoperatively, IRR 1.27 (95% confidence interval: 1.11–1.46), highest in the last year before surgery. Fracture incidence was not increased postoperatively. Serum calcium, adenoma weight and multiglandular disease were not associated with fracture incidence.

Conclusions: Fracture incidence is higher in patients with primary hyperparathyroidism but is normalized after surgery.

KEYWORDS

adenoma, bone/epidemiology, calcium, fractures, bone/epidemiology, hyperparathyroidism, primary/complications, hyperparathyroidism, primary/surgery

1 | INTRODUCTION

Primary hyperparathyroidism (pHPT) is one of the most common endocrine disorders requiring surgical intervention. Parathyroidectomy was performed on 15.5 per 100,000 inhabitants in Sweden in 2019.[1] pHPT is associated with complications ranging from secondary osteoporosis, fractures, urinary stones, cardiovascular events, cancer, excess mortality, gastrointestinal to neuropsychiatric symptoms.[2–4] Previous studies have, in various settings and subgroups, shown increased incidence of fractures and cardiovascular events in pHPT cohorts,[5–11] and reduced incidence after parathyroidectomy.[7,8] A recent meta-analysis demonstrated a twofold increase in fracture risk among patients with pHPT compared to controls.[12]

Since the 1970s, there has been a shift in the presentation of pHPT towards less advanced disease with lower levels of serum calcium and parathyroid hormone (PTH), as well as lower adenoma weight and fewer complications at diagnosis.[13–23] An almost eightfold decrease in adenoma weight and an absolute and relative reduction of severe skeletal disease (*osteitis fibrosa cystica*) has been demonstrated in a meta-analysis of surgical cases from the United States during the years 1930–2000.[17] This is most likely caused by automatized biochemical assays for calcium and PTH and a growing awareness of pHPT and hypercalcemia as causes of morbidity, although there also might be other explanations such as dietary supplementation of vitamin D and calcium.[17] Further, there is an underlying assumption that early intervention might prevent severe complications such as secondary osteoporosis, cardiovascular events, cancer and excess mortality.

The primary aim of this study is to investigate whether the reduced fracture incidence after surgery observed in previous studies can be demonstrated in a modern setting, in patients with less advanced disease compared to previously studied cohorts.[5–7,9,11] Secondly, we investigated if fracture incidence relates to disease severity, measured as serum calcium or adenoma weight at histopathology and to multiglandular disease. In addition, we studied the prevalence of osteoporosis and medications affecting bone metabolism in the cohort.

2 | MATERIALS AND METHODS

This study was performed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[24]

TABLE 1 Demography and comorbidity among pHPT patients and matched controls

	Patients (*N*)	Mean ± SD, median (IQR), *n* (%)	Controls (*N*)	Mean ± SD, median (IQR), *n* (%)
Age (years)	5009	61.7 ± 13.7	14,983	61.7 ± 13.7
Male sex (*n*)	5009	1129 (22.5)	14,983	3380 (22.6)
Year of surgery	5009		14,983	
2003–2007		1428 (28.5)		4272 (28.5)
2008–2010		1756 (35.1)		5249 (35.0)
2011–2013		1825 (36.4)		5462 (36.5)
Osteoporosis[a]	5009	481 (9.6)	14,983	601 (4.0)
Bisphosphonates (*n*)				
Preoperatively	4564	435 (9.5)	13,639	553 (4.1)
Postoperatively (10 years)	5000	309 (6.2)	14,940	548 (3.7)
Systemic glucocorticoids (*n*)				
Preoperatively	4564	636 (13.9)	13,639	1392 (10.2)
Postoperatively (10 years)	5000	514 (10.3)	14,940	1258 (8.4)
Oestrogens (*n*)				
Preoperatively	4564	1146 (25.1)	13,639	2915 (21.4)
Postoperatively (10 years)	5000	434 (8.7)	14,940	1085 (7.3)
Charlson's score (*p*)	5009	0 (0–1)	14,983	0 (0–0)
Unmarried (*n*)	4982	2346 (47.1)	14,851	7053 (47.5)
Disposable income (SEK)	5009	167,845 (121,327–241,683)	14,981	166,782 (119,899–243,049)
Elementary school only (*n*)	4955	1324 (26.7)	14,738	4304 (29.2)

Abbreviations: IQR, interquartile range; pHPT, primary hyperparathyroidism.

[a]Inpatient diagnosis or prescription of bisphosphonates preoperatively.

2.1 | Study population

A nationwide cohort of patients operated for pHPT in the years 2003–2013 was extracted from the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) as described previously.[25] Patients with hereditary hyperparathyroidism, parathyroid carcinoma on histology, or lithium treatment were not eligible, even though they had been registered as cases of pHPT. For each patient, three controls, matched for sex, age and municipality, were selected by Statistics Sweden. The controls were alive at the date of surgery, to avoid immortal time bias. Patients with unmatchable personal identification number (incorrect or reused), negative surgical exploration, biochemical evidence of persistent disease, reoperation or missed to follow-up were excluded with their respective controls. Socioeconomic data (marital status, disposable income, educational level), data on hospitalizations, prescriptions and time and cause of deaths for patients and their controls were retrieved by cross-linking with Statistics Sweden, the National Patient Register, the Swedish Prescribed Drug Register (in operation since 1 July 2005) and the Swedish Cause of Death Register held by the National Board of Health and Welfare. After linkage, controls who had undergone parathyroid surgery not registered in SQRTPA were also excluded.

Controls were assigned the date of surgery of the patients. End of follow-up was 31 December 2015 or 10 years after surgery, whichever came first. A longitudinal Charlson's comorbidity score[26,27] was calculated from hospital discharge diagnoses up until on date of surgery, using the algorithm described by Quan et al.[28]

2.2 | Fractures and osteoporosis

Fractures were retrieved from the hospital discharge diagnoses of the National Patient Register (ICD-9/10). Fractures were grouped as any fracture, fragility fracture and multiple fractures; *any fracture* includes all fractures with the exceptions of skull and digits and defined by anatomical fracture site; *fragility fracture* was defined as vertebral, proximal humerus, distal upper extremity, pelvic or hip fracture and *multiple fractures anytime* as several fracture discharge diagnoses at either the same or separate occasions. The ICD-9/10 codes used for each fracture site are given in Table S1. *Osteoporosis* was defined by either of discharge diagnosis (ICD-9 7330–1, ICD-10 M80–2) or more than one expedited prescription of bisphosphonates as registered in the National Patient Register and the Swedish Prescribed Drug Register. Exposure to bone density affecting medications, such as oestrogens or systemic glucocorticoids, were similarly defined as >1 expedited prescription to avoid including patients with only limited exposure (e.g., due to adverse effects or low compliance). At least 6 months of observation in the Swedish Prescribed Drug Register was required to exclude prescription; prescription derived variables were otherwise defined as missing.

2.3 | Ethics

The study was approved by the local ethical committee at Lund University (diary number 2016/26).

2.4 | Statistics

Descriptive statistics are presented as mean ± standard deviation for normally distributed and median (interquartile range [IQR]) for skewed variables. Skewness was assessed visually. Parametric and nonparametric tests were used as appropriate to test differences between groups. Temporal trends in age and sex distribution, preoperative serum calcium and adenoma weight were assessed by dividing the patient cohort in three groups by year of surgery (2003–2007, 2008–2010 and 2011–2013).

Fracture incidence rate was tabulated for patients versus controls, preoperatively with time-of-entry defined as 10 years before date of surgery or the corresponding date for controls. Postoperatively, time-of-entry was date of surgery and exit was death, emigration or end of follow-up. Multiple events were allowed per subject. Mixed-effects Poisson regression (two-level random-intercept models, corrected for observation time) was used to evaluate fracture incidence rate for patients and controls pre- and postoperatively in relation to socioeconomy (age over 50 years, sex, marital status, educational level, disposable income), and comorbidity using Charlson's comorbidity score (divided as 0, 1 or ≥2 points). For patients, fracture and fragility fracture incidence rate was also evaluated in relation to serum calcium, preoperative osteoporosis, multiglandular disease, adenoma histology and adenoma weight.

Multivariable mixed-effects Poisson regression models were fitted for fracture incidence rate for patients versus controls preoperatively and postoperatively, adjusted for sex, age (in 10-year time bands as this proved statistically stronger than age over 50 years), Charlson's comorbidity score and marital status, each model refinement evaluated by likelihood ratio tests. Educational level, disposable income and period of surgery were not included as they did not strengthen the model.

To assess change in fracture incidence postoperatively, mixed-effects Poisson regression models for fracture incidence (*any fracture* and *fragility fracture*) were fitted for patient status, time period (postoperatively vs. preoperatively) and the interaction between them.

The secondary outcomes *multiple fractures anytime* and *osteoporosis* were analysed with logistic regression conditional on patient-control sets. Multivariable models were fitted adjusted for sex, age over 50 years, Charlson's comorbidity score (0, 1 or ≥2 points) and marital status.

Sensitivity analysis excluding patients with pre- and postoperative prescriptions of bisphosphonates, oestrogens and systemic glucocorticoids was performed for fracture incidence.

For all statistical analyses, STATA SE 16.1 (StataCorp LLC) was employed. All tests were two-sided. A $p < .05$ was considered significant.

TABLE 2 Preoperative calcium and histology, in pHPT patients

	N	Mean ± SD, median (IQR) *n* (%)
Total calcium (mmol/L)	4958	2.78 ± 0.199
Multiglandular disease	4101	394 (9.61)
Adenoma on histologic examination	4970	4359 (87.7)
Adenoma weight (g)	3702	0.58 (0.30–1.15)

Abbreviations: IQR, interquartile range; pHPT, primary hyperparathyroidism.

3 | RESULTS

3.1 | Cohort

Patients with unmatchable personal identification number ($n = 15$), negative exploration ($n = 224$), persistent disease ($n = 358$), reoperation ($n = 149$) or missed to follow-up ($n = 337$) were excluded, as were their respective matched controls ($n = 3237$) and controls having experienced parathyroid surgery ($n = 42$). The remaining cohort consisted of 5009 patients and 14,983 matched controls, as previously described.[25] Preoperatively, patients were followed for 49,522 and controls for 148,319 person-years; postoperatively, patients were followed for 29,322 and controls for 86,423 person-years, respectively. Patients and controls were observed for a median of 15.7 (IQR: 13.7–17.9) years.

3.2 | Perioperative characteristics and comorbidity

Demography, socioeconomic characteristics, and Charlson's comorbidity score for patients and controls are summarized in Table 1, together with preoperative osteoporosis, prescriptions of bisphosphonates and related medications, systemic glucocorticoids and oestrogens. Preoperative calcium and results of the histological examination are summarized in Table 2. Mean preoperative serum calcium was significantly lower in the later periods than in the first, whereas the sex, age and adenoma weight distributions did not differ (Table S2).

3.3 | Fracture incidence

Fracture incidence pre- and postoperatively is summarized in Table 3, and reported as incidence rate ratios (IRRs). Univariable mixed-effects Poisson regressions of *any fracture* and patient status, comorbidity and socioeconomics are presented in Table 4. Similarly, univariable mixed-effects Poisson regressions of *any fracture* in patients in relation to disease-specific factors, that is, preoperative serum calcium, adenoma weight, and multiglandular disease are presented in Table 5. The results were largely identical for *fragility fracture* (Tables S3 and S4).

The incidences of *any fracture* and *fragility fracture* were significantly higher in patients before surgery, and most pronounced in the year immediately preceding surgery. Postoperatively, fracture incidence was not higher in patients compared to controls, Figures 1 and S1. When analysed by fracture site, the incidence of upper extremity fractures (except

TABLE 3 IRR of fractures, patients versus controls

	Fractures preop (*n*)			Fractures postop (*n*)			
Fracture site	Patients	Controls	IRR (95% CI)	Patients	Controls	IRR (95% CI)	*p* Value[a]
Vertebral	43	113	1.1 (0.8–1.6)	60	194	0.9 (0.7–1.2)	.379
Rib	15	64	0.7 (0.4–1.2)	33	56	1.7 (1.1–2.7)*	.014
Proximal humerus	34	72	1.4 (0.9–2.2)	32	90	1.1 (0.7–1.6)	.312
Distal upper extremity	76	123	1.9 (1.4–2.5)*	41	113	1.1 (0.7–1.5)	.021
Upper extremity incl. shoulder	47	87	1.6 (1.1–2.3)*	34	97	1.0 (0.7–1.5)	.117
Hand	7	28	0.7 (0.3–1.8)	3	14	0.6 (0.1–2.3)	.831
Pelvic	19	61	0.9 (0.5–1.6)	31	80	1.1 (0.7–1.8)	.544
Hip	95	228	1.2 (1.0–1.6)	123	370	1.0 (0.8–1.2)	.141
Lower extremity	93	267	1.0 (0.8–1.3)	59	205	0.9 (0.6–1.1)	.258
Foot	11	14	2.4 (1.0–5.6)	4	19	0.6 (0.2–1.9)	.052
Other	142	356	1.2 (1.0–1.5)	92	303	0.9 (0.7–1.1)	.062
Any fracture	408	995	1.2 (1.1–1.4)*	400	1,160	1.0 (0.9–1.1)	.010
Fragility fracture[b]	255	575	1.3 (1.1–1.5)*	278	818	1.0 (0.9–1.2)	.005

Note: Fracture sites defined by ICD-8/9/10 codes given in Table S1.

Abbreviations: CI, confidence interval; IRR, incidence rate ratios.

[a]Mixed-effects Poisson regression of interaction patient status × postoperative time-period.

[b]Fractures of vertebrae, proximal humerus, distal upper extremity, pelvis or hip.

*$p < .05$

TABLE 4 Univariable mixed-effects Poisson regression of *any fracture*, patients and controls

	Preoperatively		Postoperatively	
	IRR (95% CI)	*p* Value	IRR (95% CI)	*p* Value
Patient	1.27 (1.11–1.46)	.001	0.99 (0.86–1.14)	.859
Sex				
Male	1.00 (ref)		1.00 (ref)	
Female	1.48 (1.26–1.75)	<.001	1.63 (1.38–1.92)	<.001
Age				
Continuous (years)	1.06 (1.05–1.06)	<.001	1.09 (1.08–1.10)	<.001
<50 years	1.00 (ref)		1.00 (ref)	
>50 years	3.76 (2.95–4.78)	<.001	7.22 (5.37–9.70)	<.001
Charlson's score				
Continuous (*p*)	1.40 (1.35–1.46)	<.001	1.44 (1.38–1.51)	<.001
0	1.00 (ref)		1.00 (ref)	
1	2.39 (2.08–2.75)	<.001	2.51 (2.18–2.89)	<.001
≥2	4.81 (3.97–5.83)	<.001	4.93 (3.99–6.10)	<.001
Disposable income (SEK)				
q1 (–36,079–)	2.53 (2.09–3.06)	<.001	3.53 (2.89–4.32)	<.001
q2 (120,261–)	2.39 (1.97–2.89)	<.001	3.20 (2.61–3.93)	<.001
q3 (167,058–)	1.40 (1.14–1.73)	.001	1.43 (1.15–1.79)	.002
q4 (242,669–)	1.00 (ref)		1.00 (ref)	
Civil status				
Married	1.00 (ref)		1.00 (ref)	
Unmarried	1.70 (1.49–1.93)	<.001	1.74 (1.53–1.97)	<.001
Educational level				
Elementary school	2.01 (1.71–2.37)	<.001	2.60 (2.19–3.08)	<.001
Upper secondary school	1.15 (0.97–1.35)	.101	1.46 (1.23–1.73)	<.001
Higher education	1.00 (ref)		1.00 (ref)	

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

proximal humerus) was higher in patients preoperatively, whereas the incidence of rib fractures was higher postoperatively. Distal upper extremity fractures of radius and ulna was the fracture site most increased among patients preoperatively. The test for fracture incidence reduction yielded an interaction variable (*patient status × postoperative time period*) with IRR 0.80 (0.68–0.95) for *any fracture* and IRR 0.75 (0.61–0.92) for *fragility fracture*, interpreted as a significant effect. In the multivariable model, the higher incidence rates for patients were only slightly diminished and remained significant at the same level (Tables S5 and S6).

In conditional logistic regression of *multiple fractures anytime*, there was no increase for patients compared with controls in the complete period odds ratio (OR): 1.05 (0.92–1.21), preoperatively OR: 1.17 (0.97–1.40), or postoperatively OR: 0.95 (0.78–1.15).

There was no association between fracture incidence and preoperative total calcium, multiglandular disease, adenoma on histology or adenoma weight (Tables 5 and S4).

3.4 | Osteoporosis

Osteoporosis was more prevalent among patients during the complete observation time OR: 2.43 (2.19–2.69), preoperatively OR: 2.77 (2.42–3.16), and postoperatively OR: 1.93 (1.69–2.20) when analysed using conditional logistic regression. This did not change substantially with adjustment for sex, age over 50 years, Charlson's comorbidity score (0, 1 or ≥2 points) and marital status.

3.5 | Sensitivity analysis

After exclusion of patients and controls with prescriptions of bisphosphonates, oestrogens and glucocorticoids ($n = 8597$), the IRRs of *any fracture*, *fragility fracture* and *multiple fractures anytime* were similar, but the interaction variables *patient status × postoperative time period* were no longer significant.

TABLE 5 Univariable mixed-effects Poisson regression of *any fracture*, patients only

	Preoperatively		Postoperatively	
	IRR (95% CI)	*p* Value	IRR (95% CI)	*p* Value
Total calcium				
Continuous (mmol/L)	0.96 (0.55–1.70)	.897	0.80 (0.42–1.55)	.508
Delta 6 months			0.92 (0.46–1.85)	.818
2.17–	1.00 (ref)		1.00 (ref)	
2.69–	0.78 (0.58–1.03)	.080	0.71 (0.52–0.97)	.032
2.82–	1.06 (0.81–1.39)	.681	0.95 (0.71–1.28)	.756
Osteoporosis preoperatively	3.44 (2.59–4.56)	<.001	2.59 (1.83–3.67)	<.001
Multiglandular disease	1.38 (0.93–2.03)	.108	0.84 (0.52–1.37)	.482
Adenoma on histology	0.84 (0.60–1.16)	.281	1.35 (0.90–2.03)	.150
Adenoma weight				
Continuous (g)	1.02 (0.98–1.06)	.313	0.96 (0.88–1.03)	.251
0.05–	1.00 (ref)		1.00 (ref)	
0.38–	1.11 (0.80–1.54)	.522	1.13 (0.79–1.62)	.498
0.89–	1.18 (0.85–1.63)	.319	1.10 (0.77–1.58)	.601

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

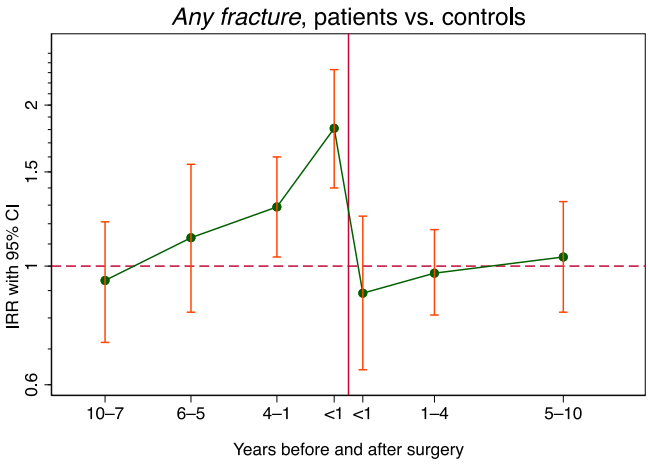

FIGURE 1 Incidence rate ratio (IRR) of any fracture pre- and postoperatively. CI, confidence interval

4 | DISCUSSION

In this study, based on a contemporary cohort of patients with pHPT undergoing surgery, a higher fracture incidence was found already several years before surgery compared to controls. After surgery, the fracture incidence was reduced, a reduction which was sustained during the follow-up period. The fracture incidence in patients and controls remained similar up to ten years. Generally, our study confirms earlier findings that fracture incidence is increased in pHPT.[5–7,9–12] The increased fracture incidence is most evident in the year immediately preceding surgery, which could reflect that fragility fracture and investigation of suspected osteoporosis is a common presentation in patients with pHPT. Although this could be interpreted as a detection bias, this is contradicted by the continuous increase in the fracture incidence during 10 years preceding surgery.

However, fracture incidence was not associated with preoperative serum calcium levels, adenoma weight or multiglandular disease. This finding did not change when patients and controls who were prescribed drugs affecting bone metabolism were excluded from the analysis. The lack of association between calcium and fracture incidence is in line with previous findings.[29] A potential explanation might be that patients with biochemically more severe disease, manifested as symptomatic hypercalcemia, are more likely to be diagnosed and undergo surgery within a shorter time frame. The trend of decreasing serum calcium over time could reflect that patients are diagnosed and referred to surgery in an earlier, milder, course of disease.[23]

The proportions of patients and controls prescribed systemic glucocorticoids and oestrogens were high, possibly reflecting more general trends in medical therapy (e.g., short term glucocorticoid therapy for lower respiratory tract symptomatology and hormone replacement therapy in menopause).

This study is foremost applicable to surgically treated patients, since it does not include any nonsurgically treated patients. However, previous longitudinal observational studies of patients with pHPT managed conservatively show deteriorating bone mineral density in trabecular and cortical bone,[30–33] and patients sustain an increased fracture risk.[6,11]

It is an interesting observation that the incidence of distal upper extremity fractures is most increased, a fracture site we a priori envisioned would be difficult to detect since it is predominantly managed in the outpatient setting. In contrast, we were not able to

demonstrate an increased rate of vertebral fractures which has been described previously.[6,7,10]

4.1 | Strengths and limitations

There are several strengths of this study, including that we studied a large nationwide cohort and with matched population controls, enabling us to evaluate fracture incidence in pHPT patients in routine care.

The most important limitation of this register study is that it solely relies on discharge diagnoses, that is, diagnoses after hospital stay, whereas many fractures, including fragility fractures, are treated in outpatient care. Even though Swedish discharge diagnoses have been validated and found to be of high quality (positive predictive value of hip fracture 95%–98.4%),[34] registration of outpatient diagnoses has been unreliable. Hence, a large number of upper extremity, vertebral and rib fractures events are likely not detected for the present cohort. There should, however, be no difference between patients and controls in this respect.

In the analyses of fracture incidence post- versus preoperatively, we have not accounted for the competing risk of death postoperatively, other than subjects being censored from the analysis. In our previous analysis of mortality in this cohort,[25] we observed that the patients' survival was not inferior than their matched controls'. Thus, it seems unlikely that an analysis allowing for the competing risk of death would yield a different result.

In general, register studies offer an opportunity to evaluate medical care and interventions in a real-world setting, ensuring that results are generally applicable. However, as data is collected retrospectively, and from many different facilities, measurements and other detailed data points are not easily validated. For a cohort of almost 20,000 subjects, it is not feasible to scrutinize X-ray results or biochemistry. Unfortunately, the SQRTPA database does not include PTH, vitamin D status, alkaline phosphatase or bone densitometry which would have been relevant for analysis of the fracture incidence.

5 | CONCLUSION

Fracture incidence is increased in patients before surgery for pHPT, with the highest incidence in the year immediately preceding parathyroid surgery. Postoperatively, the fracture incidence seems to normalize. We did not find any firm evidence that preoperative serum calcium levels or adenoma weight is associated with fracture incidence pre- or postoperatively.

ACKNOWLEDGEMENTS

The authors would like to thank all the departments of Surgery and Ear, Nose and Throat Surgery that participate and register in the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery. In addition, the authors would like to thank Jenny Sandgren and Anna Åkesson at Clinical Studies Sweden, Forum South for valuable statistical advice. Funding for this study was generously granted from Thelma Zoégas Fond för Medicinsk forskning, Thorsten Birger Segerfalks Stiftelse, Carl J. Michaelsens Donationsfond, Anna-Lisa och Sven Eric Lundgrens stiftelse för medicinsk forskning and SUS stiftelser och donationer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

This study was planned jointly by Martin Nilsson, Elin Ståhl, Kristina E. Åkesson, Mark Thier, Martin Almquist and Anders Bergenfelz. Erik Nordenström is the registered holder of SQRTPA. Martin Nilsson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The results were interpreted by Martin Nilsson, Kristina E. Åkesson, Erik Nordenström, Martin Almquist and Anders Bergenfelz. The paper was written by Martin Nilsson and revised by Martin Nilsson, Elin Ståhl, Kristina E. Åkesson, Mark Thier, Erik Nordenström, Martin Almquist and Anders Bergenfelz.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of some or all data generated or analysed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Nilsson M, Ståhl E, Åkesson KE, et al. Reduced fracture incidence in patients having surgery for primary hyperparathyroidism. *Clin Endocrinol (Oxf)*. 2022;97: 276-283. doi:10.1111/cen.14703