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Parathyroid

Skeletal effects of failed parathyroidectomy

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Background. Parathyroidectomy improves bone mineral density and decreases risk for fracture in patients with primary hyperparathyroidism. The aim of this study was to determine skeletal consequences of failed parathyroidectomy.

Methods. A retrospective, cohort study of patients with biochemically confirmed primary hyperparathyroidism within a vertically integrated health system was performed (1995–2014). Failed parathyroidectomy was defined by hypercalcemia within 6 months of initial parathyroidectomy. Time-varying Cox regression was used to estimate the risk for any fracture and hip fracture in 3 comparison groups: observation, successful parathyroidectomy, and failed parathyroidectomy. Bone mineral density changes also were compared.

Results. The cohort included 7,169 patients, of whom 5,802 (81%) were observed, 1,228 underwent successful parathyroidectomy (17%), and 137 underwent failed parathyroidectomy (2%). The adjusted risk for any fracture (hazard ratio, 1.28; 95% confidence interval, 0.85–1.92) and hip fracture (hazard ratio, 1.63; 95% CI, 0.77–3.45) associated with failed parathyroidectomy was similar to that associated with observation. Successful parathyroidectomy was associated with a decrease in any fracture (hazard ratio, 0.68; 95% confidence interval, 0.57–0.82) and hip fracture (hazard ratio, 0.43; 95% confidence interval, 0.27–0.68) compared with observation. Bone mineral density changes in the failed parathyroidectomy group paralleled those associated with observation.

Conclusion. Failed parathyroidectomy is associated with a high risk for fracture similar to that seen with observation.

Primary hyperparathyroidism (PHPT) is a common condition that affects 1 in 400 women and 1 in 1,200 men in the United States.[1] Consequences of long-standing PHPT include loss of bone mineral density (BMD), increased risk for fracture, nephrolithiasis, neuropsychiatric disturbances, and cognitive impairment.[2] We reported previously that parathyroidectomy (PTx) improves BMD and decreases the risk for fracture in patients with PHPT.[3] The success rate of PTx is >95% in expert hands and 75% to 90% in community practice.[4-8]

Patients who have undergone failed PTx (FPTx), defined by hypercalcemia within 6 months of initial PTx, have been difficult to identify historically because the majority do not present for reoperation.[9] Hence, the clinical consequences of FPTx remain obscure. We previously have used electronic screening of biochemical follow-up data on patients who have undergone PTx to accurately assess the rate of persistent and recurrent PHPT within a large population.[9] The aim of this study was to examine skeletal outcomes in patients who have undergone FPTx in comparison with those who have undergone successful PTx (SPTx), as well as patients who were managed nonoperatively. We hypothesize that patients undergoing FPTx will have outcomes similar to those in the observation group.

Methods

Study participants

Patients with PHPT were identified using the Kaiser Permanente Southern California (KPSC) Laboratory Management System. KPSC is an integrated health system that covers ~20% of the population of the Los Angeles metropolitan area and demographically and

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socioeconomically reflects the region. Patients meeting criteria for inclusion were those with hypercalcemia (serum total calcium concentration >2.63 mmol/L [> 10.5 mg/dL]) and parathyroid hormone excess (>65 ng/L) during the period between January 1, 1995 and December 31, 2014. We excluded patients who were members for <6 months, those <20 years of age, and those with secondary (renal) hyperparathyroidism (serum creatinine concentration >221 μmol/L [> 2.5 mg/dL]). We identified patients with tertiary hyperparathyroidism by excluding any patient with ≥2 tests for immunosuppressant levels.

Fracture outcomes

For fracture outcomes, we included those patients who had adequate biochemical follow-up of ≥1 year after PTx. Patients who had a diagnosis of fracture entered on the same day as a diagnosis of PHPT were excluded. Three cohorts were created: (1) observation patients who did not undergo PTx within the study period, (2) SPTx patients who underwent PTx and were either continuously eucalcemic or who at most had 1 increased serum calcium concentration followed by 3 consecutive normal calcium levels within 1 year of surgery, and (3) FPTx patients who had increased serum calcium concentrations within 6 months of PTx. Patients with a fracture before PTx contributed events to the observation group.

Patients in each cohort were followed from the inception date (date of first increased serum calcium concentration) until fracture, disenrollment from KPSC, death, or the end of the follow-up period (September 30, 2016). Fractures were categorized into hip and non-hip by using International Classification of Diseases (ICD)-9 diagnostic codes and an ICD-9 to ICD-10 crosswalk for fractures occurring before and after October 2015, respectively.

BMD outcomes

The KPSC database was queried for data on BMD. For this study, only total hip BMD was examined. Records within 2 years of the index date of biochemical diagnosis for observation patients and within 2 years of initial PTx for the FPTx and SPTx cohorts were defined as the baseline BMD for each patient. When multiple BMD measurements were made within this 4-year time window, we used data from the BMD examination that was closest temporally to the 2 respective time points. Changes in BMD were studied over 4 discrete periods: 0 to 2 years, 2 to 5 years, 5 to 8 years, and >8 years from baseline BMD.

Statistical analysis

Modeling and analyses were carried out using SAS Enterprise Guide 5.1 (SAS Institute, Atlanta, GA). We calculated standardized differences to compare the baseline characteristics among the 3 groups using the SAS macro provided by Yang and Dalton.[10] Cohen[11] suggested that indices of 0.2, 0.5, and 0.8 can be used to represent small, medium, and large effect sizes, respectively. Fracture rates were compared between the 3 cohorts using a time-varying Cox model in which 2 group indicators, SPTX and FPTX, were coded as binary, time-dependent variables to reflect status change from observation to PTX during study follow-up, with the observation group being the reference. Risk adjustments were made for age, sex, and ethnicity. Percent change in BMD from baseline was compared between the 3 cohorts using linear regression with group being the primary predictor, controlling for age, sex, and race/ethnicity. For all analyses, bisphosphonate use for >1 year was considered a covariate. This study was approved by the institutional review boards of KPSC and the University of California, Los Angeles.

Results

Risk for fracture

Biochemical screening revealed 7,392 patients with PHPT (Fig 1). After exclusion criteria were applied, 7,167 were followed for skeletal outcomes. The study cohort was 78% female and 44% nonwhite (Table I). The median age was 69 years (interquartile range [IQR] 59–77) for the observation group, 61 years (IQR 52–70) for SPTx group, and 60 years (IQR 52–68) for the FPTx group. Fifty-seven percent of the observation group, 39.4% of the SPTx group, and 38.2% of the FPTx group had Charlson Comorbidity Index scores >0. Baseline BMD was normal in 55% of patients, and 60% of patients were treated with bisphosphonates for >1 year.

PTx was undertaken in 1,506 patients (21%). Of these patients, 141 had a fracture before PTx and thus contributed their outcomes to the observation group. For these 141 patients, the median time from biochemical diagnosis of PHPT to fracture was 1.88 years (IQR 0.44–3.53 years). For fracture analyses, 5,802 patients were in the observation group, 1,228 in the SPTx group, and 137 in the FPTx group (Fig 1). The median postoperative parathyroid hormone was 92 ng/L (IQR 55–143 ng/L) for the FPTx group and 55 ng/L (IQR 35–78 ng/L) for the SPTx group. The rate of any fracture was 36 events/1,000 person-years in the observation group, 14/1,000 person-years in the SPTx group, and 26.6/1000 person-years in the FPTx group. The rate of hip fracture was 8.8 events/1,000 person-years in the observation group, 1.7/1,000 person-years in the SPTx group, and 7.1/1,000 person-years in the FPTx group. Using time-varying survival analysis, the hazard ratio (HR) for total risk for fracture after SPTX was 0.56 (95% confidence interval [CI], 0.47–0.66) and FPTX was 1.18 (95% CI, 0.79–1.77) compared with observation. After adjusting for age, sex, and race/ethnicity, the HR for SPTX was 0.68 (95% CI, 0.57–0.82) and FPTX was 1.28 (95% CI, 0.85–1.92). Further

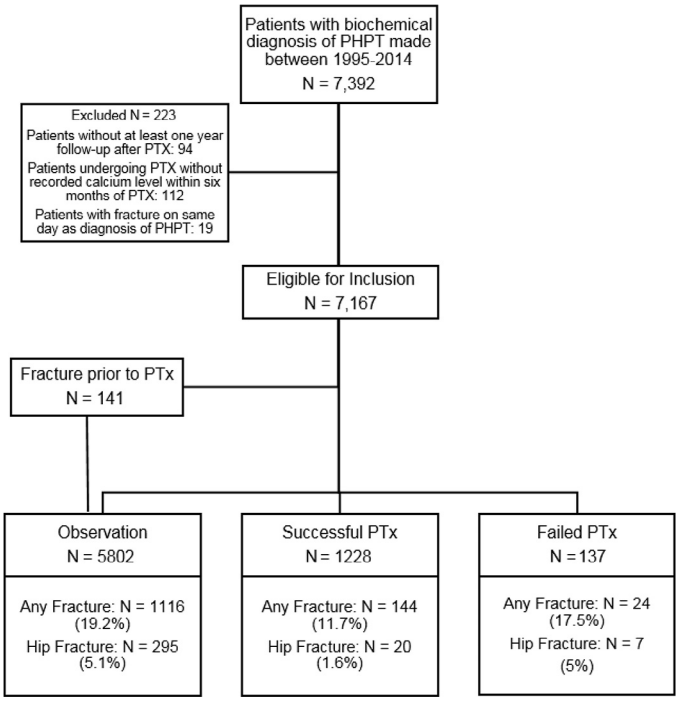

Fig 1. Flow chart depicting observation, successful parathyroidectomy, and failed parathyroidectomy groups and fracture rates.

Table I
Standardized differences: effect size indices of 0.2, 0.5, and 0.8 can be used to represent small, medium, and large effect sizes, respectively[12,13]

Baseline demographic data	Observation n = 5,802	Failed PTx n = 137	Successful PTx n = 1,228	Standardized difference
Age, mean y ± SD	67.7 ± 13	60.1 ± 13.1	59.8 ± 11.6	–0.59
Age, median (Q1–Q3)*	69 (59–77)	61 (52–70)	60 (52–68)	
Sex, *n* (%)				–0.017
Female	4533 (78.1)	108 (78.8)	949 (77.3)	
Male	1269 (21.9)	29 (21.2)	279 (22.7)	
Race/ethnicity, *n* (%)				0.25
White	3261 (56.2)	82 (59.9)	686 (55.9)	
Asian	255 (4.4)	4 (2.9)	70 (5.7)	
Black	1090 (18.8)	25 (18.2)	208 (16.9)	
Hispanic	873 (15)	24 (17.5)	250 (20.4)	
Other	323 (5.6)	2 (1.5)	14 (1.1)	
Charlson Comorbidity Index, *n* (%)				0.41
0	2473 (42.6)	83 (60.6)	759 (61.8)	
1–2	1605 (27.7)	33 (24.1)	313 (25.5)	
> = 3	1724 (29.7)	21 (15.3)	156 (12.7)	
Bisphosphonate use, *n* (%)				0.19
None	689 (11.9)	12 (8.8)	113 (9.2)	
≤1 y	1641 (28.3)	50 (36.5)	345 (28.1)	
>1 y	3472 (59.8)	75 (54.7)	770 (62.7)	
Bone density, *n* (%)				0.14
Normal	1,394 (53.3)	44 (56.4)	427 (60.6)	
Osteopenia	792 (30.3)	25 (32.1)	183 (26)	
Osteoporosis	427 (16.3)	9 (11.5)	95 (13.5)	
Not measured	3189	59	523	
Serum calcium concentration				
Mean (SD)	11 (0.59)	13.4 (25.19)	11.2 (0.55)	0.13
Median (Q1–Q3)	10.9 (10.7–11.2)	11.2 (10.8–11.6)	11.1 (10.8–11.4)	
Serum PTH				
Mean (SD)	123.5 (74)	165.2 (127)	150.0 (90)	0.40
Median (Q1–Q3)	101 (80–138)	120 (92–174)	125 (96–169)	

* Q1–Q3: Interquartile range.
PTH, parathyroid hormone.

adjusting for bisphosphonate use, the HR for SPTX was 0.69 (95% CI, 0.58–0.82) and FPTX was 1.31 (95% CI, 0.8795% CI, 1.96; Table II).

Changes in BMD

For 745 patients, at least 2 measurements of BMD in the femoral neck were reported during the follow-up period. In the observation group, adjusted BMD in the femoral neck BMD decreased by 3% (95% CI, –4.2% to –1.9%) at 2 to 5 years, by 4.6% (95% CI, –6.2% to –2.9%) at 5 to 8 years, and by 6.8% (95% CI, –9.7% to –4%) >8 years (Fig 2). SPTx was associated with an increase in BMD of 2.5% at 2 to 5 years (95% CI, 0.7%–4.4%), 1.3% at 5 to 8 years (95% CI, –1.0 to 3.8%), and 1.1% (95% CI, –2.8% to 4.9%) >8 years. In the FPTx group, BMD changes closely mirrored those of observed patients (Fig 2), and no significant

Table II
Fracture risk of three groups

Risk for fracture	Any fracture			
	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)	Adjusted HR‡ (95% CI)
Observation	1	1	1	1
Failed PTX	1.18 (0.79–1.77)	1.28 (0.85–1.92)	1.31 (0.87–1.96)	1.37 (0.91–2.06)
Successful PTX	0.56 (0.47–0.66)	0.68 (0.57–0.82)	0.69 (0.58–0.82)	0.72 (0.60–0.86)
Hip fracture				
	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)	Adjusted HR‡ (95% CI)
Observation	1	1	1	1
Failed PTX	1.33 (0.63–2.82)	1.63 (0.77–3.45)	1.70 (0.80–3.61)	1.77 (0.83–3.77)
Successful PTX	0.29 (0.18–0.46)	0.43 (0.27–0.68)	0.44 (0.28–0.69)	0.45 (0.29–0.72)
Non-hip fracture				
	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)	Adjusted HR‡ (95% CI)
Observation	1	1	1	1
Failed PTX	1.21 (0.79–1.85)	1.29 (0.84–1.97)	1.31 (0.86–1.99)	1.37 (0.90–2.09)
Successful PTX	0.62 (0.52–0.74)	0.74 (0.62–0.89)	0.74 (0.62–0.89)	0.78 (0.65–0.93)

* Adjusted for age, sex, and race/ethnicity.
† Adjusted for age, sex, race/ethnicity, and bisphosphonate use.
‡ Adjusted for age, sex, race/ethnicity, bisphosphonate use, and Charlson Comorbidity Index.

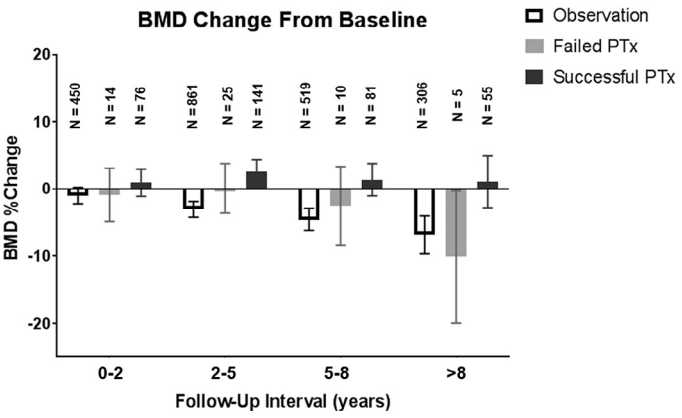

Fig 2. Bone mineral density changes over baseline. Error bars represent 95% confidence intervals.

differences were found between the BMD changes in any period of time ($P = .9$, .09, .5, and .5 for 0–2 years, 2–5 years, 5–8 years and >8 years, respectively). In the SPTx group, the trajectory of BMD was better than that of observed patients for 0 to 2 years, 2 to 5 years, 5 to 8 years, and >8 years ($P < .0001$ each).

Discussion

We previously reported that patients with PHPT who undergo PTx have a decreased risk for fracture. These findings persist in this updated cohort. Our new finding that patients who undergo FPx carry a risk for fracture that is similar to that of observed patients may be intuitive; however, to our knowledge these are the first published data that support this hypothesis. Our findings indicate that the cohort of patients who have undergone FPTx have been subjected to the risks for PTx without accruing any durable benefit with respect to their skeletal outcomes.

KPSC is a vertically integrated health care system serving 4.2 million people, within which we reported previously a success rate of 92% for initial PTx. This rate is less than reported success rates from expert centers staffed by high-volume surgeons.[5-8] In KPSC, >120 surgeons perform PTx with presumably different techniques and outcomes. This overall success rate is likely reflective of those found in general community practice.[9] As enrollees in an integrated medical system, Kaiser patients stay predominantly within Kaiser facilities for all of their health care needs and referral outside of the system is rare. As an alternative strategy, it may be beneficial to identify high-volume parathyroid surgeons within the Kaiser network. Additionally, reoperation should be offered to patients with well-localized persistent or recurrent disease because cure rates in specialized centers are as high as 95%.[14]

Limitations of this study include its retrospective, nonrandomized design. Additionally, the transition from ICD-9 to ICD-10 during the study period may have led to differential capture of fractures as a result of changes in the coding. A small number of patients was excluded from the study due to lack of biochemical follow-up data. This study is strengthened the racial, ethnic, and socioeconomic profile of the KPSC population, which closely mirrors that of the state of California. Furthermore, long-term follow-up was possible in a large fraction of patients because two-thirds of subscribers maintain membership for ≥5 years.[9]

Osteoporotic fractures, especially hip fractures, constitute a serious public health burden and are associated with increased delayed mortality in the elderly.[15,16] It has been estimated that 10 parathyroidectomies must be performed to prevent 1 major fracture.[17] The recommendation that PTx is the preferred treatment for patients with PHPT is predicated on high cure rates for PTx. The recent finding that bisphosphonates are ineffective in decreasing the risk for fracture in patients with PHPT further underscores the importance of maintaining high quality in endocrine surgical care.[3]

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Discussion

Dr Haggi Mazeh (Jerusalem, Israel): Great study. Thank you very much. I wanted to ask you if you looked at a subgroup analysis of patients who had osteoporosis because they're the ones who are at risk for developing fractures and if they have a higher rate of fractures compared with the successful parathyroidectomy group?

Dr Feibi Zheng: We did not specifically perform a subgroup analysis in this cohort of patients, but I believe that in our previous work, when comparing surgery to bisphosphonates, we had found that in the patients with primary hyperparathyroidism with osteoporosis, bisphosphonates did not significantly improve bone mineral density.

Dr Mira Milas (Phoenix, AZ): I would like to congratulate your collaborative group in Los Angeles for continuing to contribute to this literature consistently enriching it over time, because it changes practices. I have one observation and one question. The observation is that you had nearly 5,000 patients in the observation group and only about 1,000 to 2,000 in the surgery group. And with this information, how do you plan to shift the dial and encourage or convince endocrinologists that this is a meaningful intervention?

And the second question is, with the age difference in older patients in your observation group, was your data able to say at which point of duration of hyperparathyroidism does the risk for fractures really significantly change? In other words, how long could they wait to possibly get the operation, failed or not, without incurring negative side effects?

Thank you.

Dr Feibi Zheng: So, absolutely, we have found previously in our work, both within the Kaiser system and at UCLA, that approximately only 30% of patients who could potentially meet criteria based on the guidelines for parathyroidectomy actually get referred to a surgeon. And I think that was actually going to be one of our posters. And this is definitely an area of ongoing effort in health care to get people the appropriate care.

I'm a little bit surprised, since it's an integrated health system and they're both the payer and the provider, that Kaiser has not implemented more stringent guidelines for this. I'm certain in our academic centers as tertiary referral centers, we have much less control over this. So really I think where the push is going to come from is from the payers.

Dr Collin J. Weber (Atlanta, GA): I agree with your findings. Our recently published paper with the smaller N found the same thing: The increase in bone density is stable over time and actually can increase even out at 5 years, which is, I think, pretty remarkable.

Mira stole some of my thunder. But I agree with what she asked you about why aren't all these patients being referred for parathyroidectomy. But 2 specific questions: What is the percent of hyperparathyroidism in the Kaiser group? You told us there were 57,000 patients in your study with hyperpara. What's the bottom line? What's the denominator?

And the second thing is that a 10% failure rate in your operations wouldn't pass muster with most of the people in this audience.

Dr Feibi Zheng: Thank you very much for those questions. To answer your second question about the failure rate, that is absolutely true. Many people in this room have reported a successful parathyroidectomy rate of 95% to 98%. However, we believe that this is what is happening in the community practices around the country, and this is sort of where we need to meet people where they're at.

In terms of consolidating care into high-volume centers, we think it's probably a better strategy to consolidate care into high-volume surgeons within each individual health system, as that's probably more practical. As you're probably well aware, most patients are not that willing to travel very far for care and would rather receive care near their own homes.

Dr Scott Wilhelm (Cleveland, OH): Just a quick question. Did you do any additional breakdown on your actual DEXA bone density by site? Obviously we know that the distal third of the radius is an important area and probably the most affected by hyperparathyroidism. Do you have any idea what percentage of your patients actually had that included in their DEXA and if you saw more decline there?

Thank you.

Dr Feibi Zheng: Yes. So we actually only looked at the hip sites, as that's the site that previously has been reported to cause the most morbidity. That was also fortunately the area where we had the most complete data, and that's what we chose to report.

Dr Michael Yeh (Los Angeles, CA): One of the questions was the prevalence of disease in our cohort. So Kaiser is about 4 million individuals in southern California; prevalence of the disease, 1 in 400 women; 1 in 1,200 men. Mira asked a question concerning the time to develop a risk for fracture, how long do you have to be sick before you might be at risk? I'll tell you in a year.