

# The Effect of Parathyroidectomy on Bone Fracture Risk in Patients With Primary Hyperparathyroidism

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**Background:** Parathyroidectomy may increase bone density in primary hyperparathyroidism (PHPT), but it is unclear whether fracture risk is decreased.

**Hypothesis:** Parathyroidectomy decreases fracture risk.

**Design:** Retrospective cohort study with median follow-up of 6.5 years.

**Setting:** Twelve regional hospitals in California.

**Patients:** One thousand five hundred sixty-nine patients with PHPT.

**Interventions:** Parathyroidectomy or observation.

**Main Outcome Measure:** Fracture-free survival.

**Results:** Mean initial calcium, parathyroid hormone, and creatinine levels were 11.2 mg/dL (2.8 mmol/L), 123.0 pg/mL, and 0.9 mg/dL (79.6  $\mu$ mol/L), respectively. Parathyroidectomy was performed in 452 (28.8%) patients, and 1117 (71.2%) were observed. The 10-year fracture-free survival after PHPT diagnosis was 73% in patients treated with parathyroidectomy compared with 59% in

those observed (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.38-0.73;  $P < .001$ ). Parathyroidectomy decreased the 10-year hip fracture rate by 8% ( $P = .001$ ) and the upper extremity fracture rate by 3% ( $P = .02$ ). Parathyroidectomy was independently associated with a decreased fracture risk (HR, 0.68; 95% CI, 0.47-0.98), whereas female sex (HR, 1.82; 95% CI, 1.19-2.80) and increased creatinine level (HR per 1-mg/dL [88.4- $\mu$ mol/L] increment, 2.05; 95% CI, 1.22-3.46) remained independently associated with an increased fracture risk. Age of 50 years or older (HR, 1.62; 95% CI, 0.99-2.66), initial parathyroid hormone level (HR, 1.00; 95% CI, 0.99-1.02), and calcium level (HR, 1.02; 95% CI, 0.75-1.37) were not independently associated with fracture risk after adjusting for all other variables.

**Conclusions:** Parathyroidectomy is associated with a decreased risk of fracture in PHPT. The largest decrease was in hip fractures. Parathyroidectomy should be considered for all patients with PHPT to reduce fracture risk, regardless of age or calcium or parathyroid hormone levels.

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**A**S MORE PATIENTS ARE DIAGNOSSED as having primary hyperparathyroidism (PHPT) following routine laboratory tests, severe bone disease such as osteitis fibrosa cystica is rarely seen. However, milder PHPT continues to carry significant consequences to bone health. Bone mineral density is significantly decreased,<sup>1,2</sup> and fracture rates in patients with PHPT are estimated to be 1.5-fold greater than those of the general population.<sup>3</sup>

Although parathyroidectomy has been shown to increase bone mineral density in patients with PHPT,<sup>2,4-6</sup> there is ongoing debate as to whether fracture risk is re-

duced.<sup>7-12</sup> Population-based evidence from Europe shows that patients who undergo parathyroidectomy have an approximately 30% decrease in fracture incidence.<sup>13,14</sup> On the other hand, a smaller cohort study<sup>15</sup> has shown that many patients with mild asymptomatic PHPT who do not undergo parathyroid surgery do not necessarily have progressive bone mineral loss or subsequent fracture.

The objective of our study was to use a large population database to determine the effect of parathyroidectomy on fracture risk in patients with PHPT. We hypothesized that parathyroidectomy would decrease the risk of fracture.

**Table 1. Characteristics of Patients Diagnosed as Having PHPT in Kaiser Permanente Southern California Hospitals, 1995-2000\***

Characteristic	Data
Age, y	
<50	252 (16.1)
≥50	1317 (83.9)
Sex	
Female	1218 (77.6)
Male	351 (22.4)
Charlson comorbidity index	
0	1263 (80.5)
1	122 (7.8)
≥2	72 (4.6)
Unknown	112 (7.1)
Initial calcium level, mg/dL, mean ± SD	11.2 ± 0.5
Initial PTH level, pg/mL, mean ± SD	123.0 ± 78.7
Initial creatinine level, mg/dL, mean ± SD	0.9 ± 0.3
Parathyroidectomy	
Yes	452 (28.8)
No	1117 (71.2)

Abbreviations: PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; creatinine to micromoles per liter, multiply by 88.4.

\*Unless otherwise indicated, data are expressed as number (percentage) of patients.

## METHODS

### DATA SOURCES AND STUDY SUBJECTS

We used the Southern California Kaiser Permanente Laboratory Management System database to identify all southern California Kaiser Permanente members with an intact parathyroid hormone (PTH) level greater than 65 pg/mL, a calcium level greater than 10.5 mg/dL (>2.6 mmol/L), and a creatinine level less than 2.5 mg/dL (<221.0 μmol/L) between January 1, 1995, and December 31, 2000. Any patient who had these laboratory levels was defined as having PHPT and was included in the study cohort, and they were followed up until the study completion date of May 31, 2004.

To ensure that no patient was included who had tertiary HPT, any patient who had at least 2 separate blood samples drawn for measurement of cyclosporine (laboratory procedure code 8718671), tacrolimus (FK 506; laboratory procedure code 8203004), or sirolimus (laboratory procedure code 8718652) levels was considered to be a probable kidney transplant recipient and excluded. A second database, the Southern California Kaiser Permanente Discharge Abstract Database, was used to exclude patients with any history of chronic renal failure requiring dialysis (*International Classification of Diseases, Ninth Revision [ICD-9] code 585.6*). Patients who were younger than 20 years were also excluded. This study was approved by the institutional review board of Kaiser Permanente Southern California.

### DEFINITION OF FRACTURE

We used the Southern California Kaiser Permanente Discharge Abstract Database to identify patients who were hospitalized with the outcome variable of fracture (hip fracture [ICD-9 code 820], spine fracture [ICD-9 codes 805 and 806], pelvis fracture [ICD-9 code 808], upper extremity fracture [ICD-9 codes

812 and 813], and lower extremity fracture [ICD-9 codes 821 and 823]) that occurred at least 1 day after the diagnosis of PHPT until the study completion date of May 31, 2004.

## STATISTICAL ANALYSIS

The data were exported to SAS, version 8, statistical software (SAS Institute, Cary, NC) for all analyses. Associations between predictor variables and fractures were assessed using Cox proportional hazards modeling. Variables analyzed for their influence on fractures were age (<50 and ≥50 years); sex; Charlson comorbidity index<sup>16</sup> (CCI); levels of calcium, PTH, and creatinine; and whether parathyroidectomy was performed. The strength of associations was expressed as hazard ratios (HRs) and 95% confidence intervals (CIs) for having a fracture. The independent effect of potential predictor variables was assessed using multivariable Cox regression modeling for fractures, adjusting for the same variables used in the univariate analysis. Fracture-free survival time was calculated as the time from the diagnosis of PHPT until a fracture, last follow-up, or May 31, 2004, whichever came first. Fracture-free survival was estimated using the Kaplan-Meier method and survival curves were compared using the log-rank test. Estimates were considered statistically significant if the 95% CI did not overlap 1.00 and if  $P < .05$ . The  $\chi^2$  test was used to compare differences in categorical variables, and the Wilcoxon signed rank test was used to compare differences in means between continuous variables. All  $P$  values reported were 2-tailed.

## RESULTS

### PATIENT DEMOGRAPHICS

There were 1569 patients diagnosed as having PHPT. Most of the patients were women and older than 50 years (**Table 1**). Overall, most patients were healthy as measured by the CCI. The mean initial calcium and PTH levels were 11.2 mg/dL (2.8 mmol/L) and 123.0 pg/mL, respectively. Most of the patients (78.3%) had calcium levels less than 11.4 mg/dL (<2.9 mmol/L) (<1 mg/dL [<0.3 mmol/L] above the reference range). Seventeen patients had fractures before the diagnosis of PHPT.

### PARATHYROIDECTOMY VS OBSERVATION

Parathyroidectomy was performed in 452 patients (28.8%), and 1117 (71.2%) were observed. Patients who were treated operatively were more likely to be younger ( $P < .001$ ) and male ( $P = .02$ ) and to have a lower CCI ( $P < .001$ ). Patients who had parathyroidectomy had a lower mean initial creatinine level ( $P = .003$ ) and higher mean initial calcium and PTH levels ( $P < .001$ ) (**Table 2**).

### FRACTURES

Patients were followed up for an average of 6.5 years, with a range of 1 day to 10.4 years. There were a total of 215 fractures during the study period, including 56 hip fractures, 23 spine fractures, 9 pelvic fractures, 82 non-hip lower extremity fractures, and 45 upper extremity fractures. The 10-year fracture-free survival after the diagnosis of PHPT was 73% in patients treated with parathy-

**Table 2. Characteristics of Patients Treated With Parathyroidectomy Compared With Those Observed\***

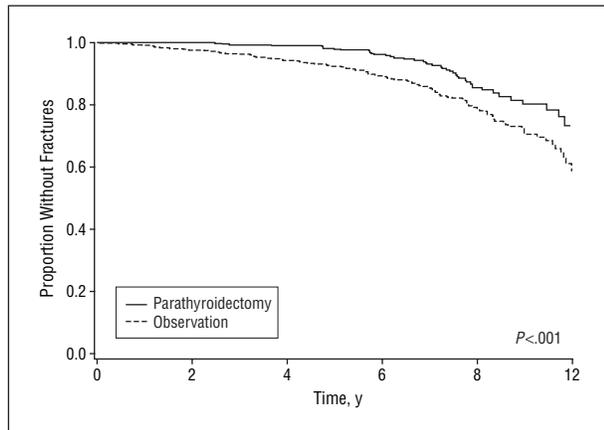
Characteristic	Parathyroidectomy (n = 452)	Observation (n = 1117)	P Value
Age, y			
<50	117 (25.9)	135 (12.1)	<.001
≥50	335 (74.1)	982 (87.9)	
Sex			
Female	333 (73.7)	885 (79.2)	.02
Male	119 (26.3)	232 (20.8)	
Charlson comorbidity index			
0	377 (83.4)	886 (79.3)	
1	14 (3.1)	108 (9.7)	<.001†
≥2	5 (1.1)	67 (6.0)	<.001†
Unknown	56 (12.4)	56 (5.0)	
Initial calcium level, mg/dL, mean ± SD	11.33 ± 0.56	11.09 ± 0.49	<.001
Initial PTH level, pg/mL, mean ± SD	140.52 ± 97.92	116.28 ± 68.26	<.001
Initial creatinine level, mg/dL, mean ± SD	0.87 ± 0.25	0.93 ± 0.29	.003

Abbreviation: PTH, parathyroid hormone.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; creatinine to micromoles per liter, multiply by 88.4.

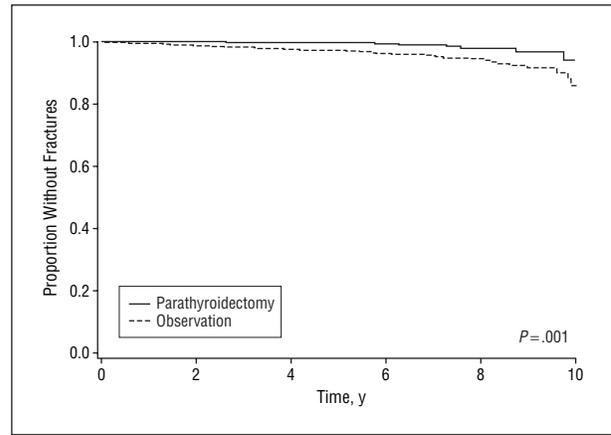
\*Unless otherwise indicated, data are expressed as number (percentage) of patients.

†Compared with a Charlson comorbidity index of 0.

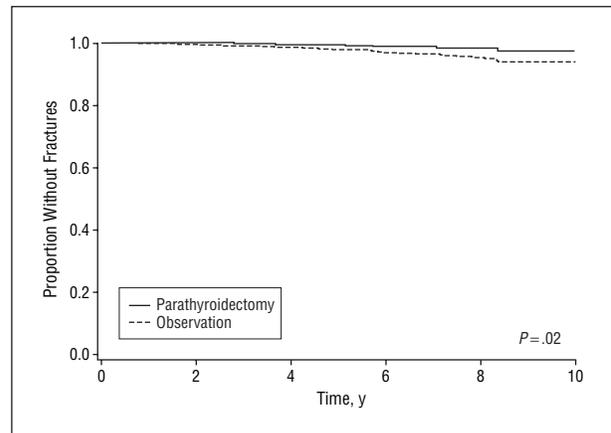


**Figure 1.** Fracture-free survival of 1569 patients with primary hyperparathyroidism in those who have had parathyroidectomy compared with those who have been observed. Parathyroidectomy reduced the risk of fracture. The 10-year fracture-free survival was 73% in those who underwent parathyroidectomy compared with 59% in those who did not ( $P<.001$ ).

roidectomy compared with 59% in those observed (HR, 0.53; 95% CI, 0.38-0.73;  $P<.001$ ) (**Figure 1**). Parathyroidectomy was associated with a decreased 10-year fracture rate in the hip by 8% ( $P=.001$ ) (**Figure 2**) and in the upper extremity by 3% ( $P=.02$ ) (**Figure 3**); rates of spine, pelvis, and nonhip lower extremity fractures were not decreased. In addition, older age (HR age ≥50 years, 2.06; 95% CI, 1.30-3.26), female sex (HR, 1.51; 95% CI, 1.04-2.20), and increased creatinine level (HR per 1-mg/dL [88.4-μmol/L] increment, 1.66; 95% CI, 1.02-2.70) were associated with increased fracture risk, but calcium and PTH levels were not (**Table 3**).



**Figure 2.** Proportion of patients free from hip fracture in those who have had parathyroidectomy compared with those observed. Parathyroidectomy reduced the risk of hip fracture. The 10-year hip fracture-free survival was 94% in those who underwent parathyroidectomy compared with 86% in those who did not ( $P=.001$ ).



**Figure 3.** Proportion of patients free from upper extremity fracture in those who have had parathyroidectomy compared with those observed. Parathyroidectomy reduced the risk of upper extremity fracture. The 10-year upper extremity fracture-free survival was 97% in those who underwent parathyroidectomy compared with 94% in those who did not ( $P=.02$ ).

Multivariable analysis revealed that parathyroidectomy was independently associated with a decreased fracture risk (HR, 0.68; 95% CI, 0.47-0.98), whereas female sex (HR, 1.82; 95% CI, 1.19-2.80) and increased creatinine level (HR per 1-mg/dL [88.4-μmol/L] increment, 2.05; 95% CI, 1.22-3.46) remained independently associated with an increased fracture risk. Age of 50 years or older (HR, 1.62; 95% CI, 0.99-2.66), CCI, initial PTH level (HR, 1.00; 95% CI, 0.99-1.02), and calcium level (HR, 1.02; 95% CI, 0.75-1.37) were not independently associated with fracture risk after adjusting for all other variables.

#### COMMENT

In this large population-based study, patients with PHPT who underwent parathyroidectomy had a decrease in 10-year fracture risk of 14%. The largest decrease in 10-year fracture risk was in the hip, with a reduction of 8%. A benefit was seen in all patients, regardless of age, calcium level, or PTH level.

**Table 3. Analysis of the Likelihood of Fracture in the Patients Treated With Observation or Parathyroidectomy**

Variable	Univariate Analysis		Multivariable Analysis	
	HR* (95% CI)	P Value	HR* (95% CI)	P Value
Age, y				
<50†	1.00		1.00	
≥50	2.06 (1.30-3.26)	.002	1.62 (0.99-2.66)	.05
Sex				
Male†	1.00		1.00	
Female	1.51 (1.04-2.20)	.03	1.82 (1.19-2.80)	.006
CCI				
0†	1.00		1.00	
1	1.40 (0.87-2.25)	.17	1.21 (0.75-1.96)	.44
Initial calcium level	0.84 (0.64-1.10)	.20	1.02 (0.75-1.37)	.93
Initial PTH level	1.00 (0.997-1.001)	.26	1.00 (0.99-1.02)	.80
Initial creatinine level	1.66 (1.02-2.70)	.04	2.05 (1.22-3.46)	.007
Parathyroidectomy				
No†	1.00		1.00	
Yes	0.53 (0.38-0.73)	<.001	0.68 (0.47-0.98)	.04

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; PTH, parathyroid hormone.

\*An HR of 1.00 indicates no difference compared with the referent group; an HR of greater than 1 indicates a higher likelihood of fracture compared with the referent group; and an HR of less than 1 indicates a lower likelihood of fracture compared with the referent group.

†Indicates referent group.

As with all retrospective studies, our study has some limitations. Only patients who were hospitalized for fracture were included; fractures of the extremity, usually treated on an outpatient basis, and fractures of the spine, often only diagnosed with spine radiographs, were therefore likely to be underrepresented. However, we think that very few clinically significant fractures would be missed because all patients were admitted to the hospital. In addition, our database did not have sufficient clinical detail to determine other risk factors for fracture or to analyze variables such as preoperative bone mineral density or whether patients were symptomatic, although such variables are often used in deciding between parathyroidectomy and observation. It is therefore possible that these unmeasured risk factors for fracture were not balanced in each group.

Other studies have also suggested a benefit from parathyroidectomy in preventing fractures. Vestergaard et al<sup>12</sup> reported that fracture risk for patients who have parathyroidectomy returns to that expected of age-matched controls following surgery, indicating that parathyroidectomy has a significant role in decreasing fractures among patients with PHPT. This was further supported by recent studies demonstrating a significant reduction in fractures of the hip and upper arm following parathyroidectomy.<sup>14,15</sup> Our study parallels these results, illustrating a decreased fracture risk at the hip and upper extremity in patients with PHPT treated with parathyroidectomy.

Reducing hip fractures is an important goal in patients with osteoporosis or PHPT. Hip fractures have been shown to shorten life expectancy,<sup>17,18</sup> and only half of patients who experience this injury will return to their previous level of functionality and independence.<sup>19</sup> Because parathyroidectomy is a safe operation, with current morbidity estimated at 1% to 3%,<sup>20,21</sup> it is an extremely attractive therapeutic modality for patients with PHPT

to reduce hip fracture risk and the significant health burden associated with hip fracture.

We believe that the results of our study support recommending parathyroidectomy for all patients with a biochemical diagnosis of PHPT, regardless of the presence or absence of symptoms. The threshold for surgical intervention in asymptomatic patients continues to be debated, but current National Institutes of Health (NIH) guidelines include age younger than 50 years and a calcium level greater than 1 mg/dL (0.3 mmol/L) above the reference range as factors to recommend parathyroidectomy.<sup>22</sup> Although in our study we could not determine who was asymptomatic, age and calcium level were not independently associated with fracture risk. In fact, most of the patients in our study were older than 50 years and had mild biochemical disease with calcium levels less than 1 mg/dL (<0.3 mmol/L) above the reference range, and they benefited from parathyroidectomy. We therefore argue, as others have,<sup>23,24</sup> that the current NIH recommendations are too narrow, and suggest that all patients with PHPT be offered parathyroidectomy.

Recognizing that some patients are medically unfit to undergo the operation, bisphosphonate therapy may be an alternative, but it is not curative.<sup>25</sup> A recent randomized controlled trial demonstrated the efficacy of alendronate sodium in increasing bone mineral density in patients with PHPT.<sup>26</sup> However, Horiuchi et al<sup>27</sup> found that parathyroidectomy had an effect on increasing bone mineral density than did bisphosphonate therapy. Therefore, parathyroidectomy should continue to be the primary therapeutic modality for PHPT.

In conclusion, parathyroidectomy in patients with PHPT was associated with a substantial reduction in fracture risk compared with observation. Parathyroidectomy should be considered for all patients with PHPT to reduce fracture risk, regardless of age or calcium or PTH levels.

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## DISCUSSION

Orlo Clark, MD, San Francisco, Calif: This important and clearly written paper provides helpful new information regarding the management of patients with PHPT. According to the NIH consensus meeting and guidelines (1990 and 2002), most of the patients treated surgically in this investigation did not have criteria warranting parathyroidectomy, since 65% were older than 50 years of age, blood calcium levels were less than 11.5 mg/dL, and renal function was normal.

Other experts have also documented that:

- Patients with PHPT are more likely to have osteopenia and osteoporosis. Leppla et al (*Invest Radiol*. 1982;17:604-606) noted that postmenopausal women with PHPT lose about 6% of their bone mass per year.
- Silverberg et al<sup>15</sup> have reported a significant gain in bone density in the hip, lumbar spine, and forearm after parathyroidectomy, even in patients with mild HPT.
- Vestergaard et al<sup>9,12</sup> reported in a study of 1201 Danish patients that the bone fracture rate is increased up to 10 years prior to parathyroidectomy and returns to that expected of age-matched controls following parathyroidectomy.
- Parathyroidectomy also has a greater impact on increasing bone mineral density than bisphosphonate therapy (Horiuchi et al<sup>27</sup>).
- It has also been clearly documented that hip fractures decrease functionality and shorten life expectancy (Braithwaite et al<sup>18</sup>).

I have several questions for the authors:

1. When did the fractures occur in patients post parathyroidectomy? Vestergaard et al<sup>9,12</sup> reported an increased risk for fractures during the first year following parathyroidectomy, then a decreased risk after this time, returning to the same rate as in the control population.
2. Were there any racial differences among the patients included in this report, since African Americans are less prone to osteoporosis and fractures?
3. Are the differences in fracture rate smaller than what might actually be present, since osteoporosis is usually an indication for operation and thus more fracture-prone patients would probably have been included in the surgically treated group?
4. Have the authors presented their observations to the administrative leadership at Kaiser so that the 1117 patients who have been observed can now be treated surgically? This should be good for the patients and also be cost-effective.

I would also be interested in the death rate in the 2 groups, since several investigations from Sweden suggest that patients with PHPT die prematurely. Thus, patients with PHPT have a form of progeria. I again congratulate Phil Haigh and colleagues on presenting this important information. Their observations add additional information suggesting that almost all patients with PHPT benefit from being treated surgically.

**Quan-Yang Duh, MD, San Francisco:** Dr Haigh, this is a wonderful paper. Obviously it is our own bias, too, that most patients with PHPT should be operated on. I have 2 questions for you, related to what Dr Clark just mentioned, regarding the NIH criteria. One is regarding the younger patients. Twelve percent of the patients who were not operated on were younger than 50. Do you know why those patients were not operated on? The NIH criteria, which include young age, are quite conservative.

The second question relates to the diagnosis of osteoporosis and osteopenia. Nowadays, if you are going to follow a patient, you should have dual-energy x-ray absorptiometry (a DEXA scan) to know what the bone density is. In what proportion of your patients did you have a DEXA scan? Do you now routinely, if you were going to follow the patient, get a DEXA scan to make sure that the T-score is not low?

**Sean J. Mulvihill, MD, Salt Lake City, Utah:** This was an interesting data set and a beautifully presented paper, but I think it suffers from an important error in that the data do not support the conclusion presented by the authors. The simple declarative conclusion that parathyroidectomy reduces the risk of fracture is not borne out by the data. This is not a randomized study. It is observational. Although the patients who were selected for parathyroidectomy had a lower rate of fracture, they were also younger and they also had less comorbid illness. So one cannot conclude in a declarative way that it was the parathyroidectomy that was the cause of the improved outcome.

**David R. Byrd, MD, Seattle, Wash:** I want to expand a little bit on the DEXA scan question that Dr Duh just mentioned. Many of these patients now come to us already having had a DEXA scan, which demonstrates either mild osteopenia or osteoporosis, or a percentage decrement over time. In follow-up to his question, if you have a patient with a normal DEXA scan, either an initial normal scan or sequential normal scans, will you still make the same conclusion that they all need parathyroidectomy for that reason?

Second, after they get their parathyroidectomy, I frequently hear questions from patients about future calcium intake and the role of bisphosphonates or other medications to improve bone calcium repletion. How do you address that with your patients?

**John A. Ryan, MD, Seattle:** I would like to congratulate the authors on a wonderful paper. A fabulous amount of research went into it. I would like to see a control group, age and sex matched, of patients who didn't have HPT to see what their 10-year fracture-free survival was.

**Ronald G. Latimer, MD, Santa Barbara, Calif:** Obviously this paper has precipitated many questions. I have a problem with the conclusion. I think it is very interesting, but we don't really know how these patients were treated post parathyroidectomy. Were they given Fosamax? Were they given vitamin D? Were they given other medications post parathyroidectomy that would explain the difference in the fracture rate? We don't have bone density studies of comparative groups. We don't have 24-hour urine tests for calcium, so we don't know really what the metabolism of calcium is in these 2 groups, and, furthermore, we don't have vitamin D levels in these groups, which would affect the outcome.

**Bruce E. Stabile, MD, Torrance, Calif:** Obviously this paper addresses a very complicated issue, and I think the discussants have brought out many confounding factors. Perhaps we can shed a little light on this if we know whether there was a correlation between biochemical cure of patients and reduction of risk of fracture. Was there a correlation established between biochemical cure and decreased fracture risk? Second, were the results any different in patients with single-gland vs multiple-gland disease?

**Dr O'Connell:** Many years ago, we knew when to operate on parathyroid patients because they came in with terrible complications, either bone disease or significant renal abnormalities. However, with the use of routine chemical panels, many more people with elevated calcium levels were identified who were otherwise asymptomatic. The question became whether to operate on them or not. Certainly the indications for operations by the NIH Panel, as has been mentioned before, are very conservative. They need to be young, under 50, and have at least 1-mg/dL elevation in their calciums or have significant complications from their HPT. So the question remains, what should be done with the large group of other patients, about 70% of the total? Would they benefit from intervention with parathyroidectomy?

Going back to the individual questions, Dr Clark wanted to know when these fractures occurred. If you look at the graphs, you can see the fractures were accumulative over time. We didn't see any marked increased difference between the 2 groups in the first year, but that probably means they would either fracture or not in the first year anyway, and probably the positive effect of the parathyroidectomy was not seen yet. So we didn't see the increased fracture rate in the first year as reported by Vestergaard et al.<sup>12</sup> Many of these patients could have had fractures before they had their parathyroidectomy, but this was not captured in our data. The measurement commenced after the intervention of parathyroidectomy.

The next question from Dr Clark was the influence of race. We didn't look at the data for race, but we could certainly do that and report on that in the future.

The next question was, what was the bone density in these patients, and that question was echoed in many of the questions of the other discussants. We didn't have any data on bone density. In our files there were no data regarding bone density or DEXA scan. We would need to review the individual charts to get this information. But we presume the patients had parathyroidectomy for a reason, and one of those reasons may be that they had bone density scan abnormalities, which would make them highest risk for fractures. It goes back to Dr Mulvihill's question whether the healthiest patients with the lowest CCIs had parathyroidectomy. Yes, but it is also likely that the patients with bone density abnormalities, a T-score of -2.5 or less, were operated on for that specific indication.

The next question is, what do we do with the other 1200 patients who were not operated on? We believe in an evidence-based and data-driven approach and, hopefully, by collecting these data and giving it to primary care doctors and endocrinologists, they will reassess their evaluation of these patients and indications for referral for operation. Surgeons don't have control of the vast majority of these patients, and nobody in your own practice knows how many patients with HPT are out there and haven't been referred for surgery. By our data it is a large number. Hopefully, the data presented here will change the indications and increase the referrals for surgery.

Dr Quan Duh's questions: As far as the 12% of younger patients with a calcium level greater than 1 mg/dL above normal who were not operated on, we don't know from our data set why these patients have not been referred for parathyroidectomy simply because they were not operated on. Often, as surgeons we eventually see patients with various diseases and we ask why these patients were not referred earlier so that they could be taken care of. We simply don't know the answer for that.

Again, there were no data on DEXA scans. We would like to go back now that we have the data and look through specific individual charts. This information was not in our database, but it is important and needs to be assessed in the individual patient chart rather than from the administrative database.

Dr Mulvihill is correct that this is not a randomized prospective study. But the data are still here. In population out-

come studies, it is accepted that a multivariate analysis of a large population database produces statistically accurate evidence-based results. The large numbers and the use of multivariate analysis diminish the effect of possible bias or selection and validate the results to approximate randomized prospective studies. To do a randomized prospective study would be very difficult. It would take a very large number of patients followed for many years to get the results. It would also be very difficult to get through an institutional review board because this study shows that unoperated patients have increased fractures, especially hip fractures. Therefore, it would be unethical to have an untreated control with the end point of fracture. Perhaps you could convince them to have a control group of medically treated patients, ie, treated with bisphosphonates, etc.

Again, Dr Byrd's question: We don't really have the information at this point of the DEXA scans being normal or abnormal and what was done medically for those individual patients, either before or after the diagnosis of HPT. Again, this is a population analysis.

To Dr Ryan's question: There is no doubt that HPT disease increases the rate of fractures. Data from the literature show that patients with HPT have 1.5 times the rate of fractures of

the normal population. We didn't have a normal control group without parathyroid disease, since those data are already known. Patients with HPT have an increased number of fractures, and that's why you see so many fractures in both of our groups. What we did see is a statistically significant decrease in the number of fractures in patients with parathyroidectomy, and this is supported in the multivariate analysis as an independent predictor of decreased fracture rate.

Again, Dr Latimer had a lot of good questions, but we don't have any of this information from our database. These types of tests and treatments were done in the outpatient offices of the individual physicians and so were not available in this administrative database.

Dr Stabile's question: How many patients are biochemically cured by parathyroidectomy, and what is the rate of fracture in the group? In our database, over 95% of the patients who had parathyroidectomy were biochemically cured of their disease and, therefore, represent the overwhelming majority of the treated patients. Therefore, parathyroidectomy equates with biochemical cure and that is what produces the observed beneficial outcome.