

# Clinical Manifestations of Primary Hyperparathyroidism Before and After Parathyroidectomy

## A Case-Control Study

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### Background

There has been an National Institutes of Health consensus meeting concerning the management of patients with "asymptomatic" primary hyperparathyroidism, yet there is no clear definition of this condition. The authors, therefore, documented the clinical manifestations and frequencies of these manifestations in unselected patients with primary hyperparathyroidism and determined whether these clinical manifestations resolved after parathyroidectomy.

### Method

The authors studied 152 unselected consecutive patients with primary hyperparathyroidism and 132 control patients with nontoxic thyroid disorders who were treated by parathyroidectomy or thyroidectomy, respectively, between January 1986 and June 1991. All patients received a questionnaire during their initial office visits and the same questionnaire again after their operations. Patients were also questioned about their perception of the success of the operation. Eighty percent of the parathyroid patients and 70.5% of the thyroid patients completed the questionnaires, and the mean follow-up time was 20 months.

### Results

Only 7 (4.6%) patients with primary hyperparathyroidism had no symptoms, and 26 (17.1%) had no associated conditions despite 74.3% of these patients having serum calcium levels less than 12 mg/dL. Symptoms including fatigue, exhaustion, weakness, polydipsia, polyuria, nocturia, joint pain, bone pain, constipation, depression, anorexia, nausea, heartburn, and associated conditions, including nephrolithiasis, and hematuria occurred more often in patients with primary hyperparathyroidism than in the thyroid control patients ( $p < 0.05$ ). After parathyroidectomy, only eight (5.3%) patients failed to have any improvement in symptoms or associated conditions. Fifty-seven percent of the parathyroid patients versus 30% of the thyroid patients felt better overall after the operation; strength subjectively improved in 29% of parathyroid patients versus 13% in thyroid patients; thirty-seven percent of the parathyroid patients versus 13% of the thyroid patients claimed they were less depressed.

## Conclusion

When examined thoroughly, few patients with primary hyperparathyroidism were asymptomatic or without associated conditions, and most patients experienced subjective improvement after successful parathyroidectomy.

The most common cause of hypercalcemia in nonhospitalized patients is primary hyperparathyroidism.<sup>1</sup> Although once thought to be a rare disease, hyperparathyroidism occurs in 1 in every 500 women and 1 in every 2000 men older than 40 years of age.<sup>2</sup> For most patients with primary hyperparathyroidism, the condition is detected by routine screening of serum calcium, and the diagnosis is confirmed by highly sensitive two-site immunoradiometric and immunochemiluminometric assays for parathyroid hormone.<sup>3,4</sup> Experts generally agree that the treatment of choice for symptomatic patients with hyperparathyroidism or asymptomatic patients with profound hypercalcemia (>12 mg/dL) is parathyroidectomy.<sup>5,6</sup> However, there is considerable controversy regarding the definition of asymptomatic hyperparathyroidism and the proper treatment of patients with this condition.<sup>7</sup>

The recent National Institutes of Health (NIH) conference on the diagnosis and management of "asymptomatic" primary hyperparathyroidism called for case-control studies concerning the natural history of both untreated and treated patients with asymptomatic hyperparathyroidism.<sup>8</sup> It therefore seems appropriate to determine how many patients with primary hyperparathyroidism are asymptomatic. The frequency of asymptomatic hyperparathyroidism varies from 2% to greater than 80% in some series.<sup>9,10</sup> We believe this wide range is due to disagreements concerning what symptoms should be attributed to hyperparathyroidism rather than to different patient populations. For this study, we compared 152 unselected patients with primary hyperparathyroidism and 132 control patients with nontoxic thyroid disorders who underwent parathyroidectomy and thyroidectomy, respectively, during the same period. The purpose of this investigation was to determine the prevalence of symptoms and conditions associated with primary hyperparathyroidism, the frequency of asymp-

tomatic hyperparathyroidism, and whether symptoms or associated conditions resolved after parathyroidectomy.

## PATIENTS AND METHODS

We studied 152 unselected consecutive patients with primary hyperparathyroidism and 132 control patients with nontoxic thyroid disorders who had parathyroidectomies or thyroidectomies, respectively, between January 1986 and June 1991. All operations were done by one surgeon at the University of California, San Francisco. All patients were asked in an outpatient setting by a receptionist to complete a questionnaire pertaining to symptoms and associated conditions of parathyroid or thyroid disease during their initial office visit before being seen by the surgeon.<sup>9</sup> In June 1991, the same questionnaire was sent to each patient to assess any changes in his or her symptoms after the operation. Patients were also questioned about their opinion of the success of the operation. Of the 152 parathyroid patients, 121 (80%) returned the completed questionnaire, and of the 132 thyroid patients, 93 (70.5%) returned the completed questionnaire.

All patients' preoperative and postoperative symptoms; associated conditions (Table 1); available labora-

**Table 1. SYMPTOMS AND ASSOCIATED CONDITIONS IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM**

Symptom	Associated Condition
Fatigue	Neophrolithiasis
Exhaustion	Hematuria from passage of stone
Weakness	Bone fracture
Polydipsia	Gout
Polyuria	Joint swelling
Nocturia	Weight loss
Bone pain	Duodenal ulcer
Back pain	Gastric ulcer
Constipation	Pancreatitis
Increasing constipation	Hypertension
Depression	
Memory loss	
Joint pain	
Loss of appetite	
Nausea	
Heartburn	
Pruritus	

Presented at the 115th Annual Meeting of the American Surgical Association, April 6-8, 1995, Chicago, Illinois.

Supported in part by Mount Zion Health Systems and the Medical Research Service of the Veterans Affairs Medical Center, San Francisco, California.

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Accepted for publication April 10, 1995.

**Table 2. CHARACTERISTICS OF PATIENTS\***

	Parathyroid (n = 152)	Thyroid (n = 132)
Age (yr)		
Range	17.7–87.0	13.9–75.4
Median	55.8	40.3
Mean	55.7	42.1
SD	15.5	13.1
Follow-up time (mo)	n = 121	n = 93
Range	0.2–54.8	0.2–47.5
Median	20.8	16.1
Mean	21.5	17.1
SD	13.6	12.8
Gender		
Male	33 (21.7%)	29 (22.0%)
Female	119 (78.3%)	103 (78.0%)
Pathology	Single adenoma 72.8% Hyperplasia 6.0% Multiple adenomas 21.2%	MNG 28.0% Cyst 3.0% Papillary cancer 8.6% Follicular neoplasms 21.0% Medullary cancer 0.8% Hurthle cell neoplasm 7.6% Anaplastic cancer 0.8%

MNG = multinodular goiter.

\* Series is weighted as includes patients with recurrent and persistent hyperparathyroidism.

tory values for serum calcium, phosphate, parathyroid hormone, chloride, albumin, uric acid, alkaline phosphatase, and renal function; and other pertinent data were entered into "Epi Info," a data base program written by the Centers for Disease Control for epidemiologic studies.

### Patient Clinical Profile

The patients' clinical profiles, such as age, sex, disease, and follow-up time, are shown in Table 2. Overall, the parathyroid patients were about 15 years older than the patients with thyroid disorders. The male-to-female distribution, however, was similar, as was the duration of follow-up. There were more patients with multiple adenoma in this series than usual, because it included patients treated for recurrent and persistent primary hyperparathyroidism.

The classic symptoms associated with hyperparathyroidism are painful bones, renal stones, abdominal groans, psychic moans, and fatigue overtones.<sup>11</sup> The responses from the patients' symptom questionnaires were categorized into symptoms or associated conditions possibly related to hyperparathyroidism. Common symptoms that occur in patients with hyperparathyroidism are fatigue, exhaustion, weakness, polydipsia, polyuria, nocturia, bone pain, back pain, constipation, increasing

constipation, depression, memory loss, joint pain, loss of appetite, nausea, heartburn, and pruritus (Table 1). The associated conditions are nephrolithiasis, hematuria, bone fracture, gout, swollen joints, weight loss, duodenal ulcer, gastric ulcer, pancreatitis, and hypertension.

### Statistical Analysis

Differences of means for continuous variables with normal distribution were compared using Students t test. Differences in proportions were compared using chi square analysis with and without stratification. Bartlett's test was used to determine the homogeneity of variances in the samples.<sup>12</sup> For variables that were nonparametric, the Kruskal-Wallis test was used to calculate the probability value.<sup>13</sup> Unstratified and stratified analyses for linear trends were done by chi square with the Mantel-Haenszel extension.<sup>14</sup>

Because the mean age for the parathyroid group (55.7 years) was significantly greater than the mean age for the thyroid group (42.1 years), certain analyses were stratified by age. The stratification was performed by dividing the sample into two groups for certain analyses. Patients were separated into older than or younger than 50 years of age, which was the mean age for the entire group of 284 parathyroid and thyroid patients.

Stratified analysis was also done for the follow-up time after surgery. The mean follow-up time for the entire group of 284 patients was 20 months. Therefore, the patients were stratified into two groups, one with follow-up time greater than 20 months and the other with follow-up time less than 20 months.

## RESULTS

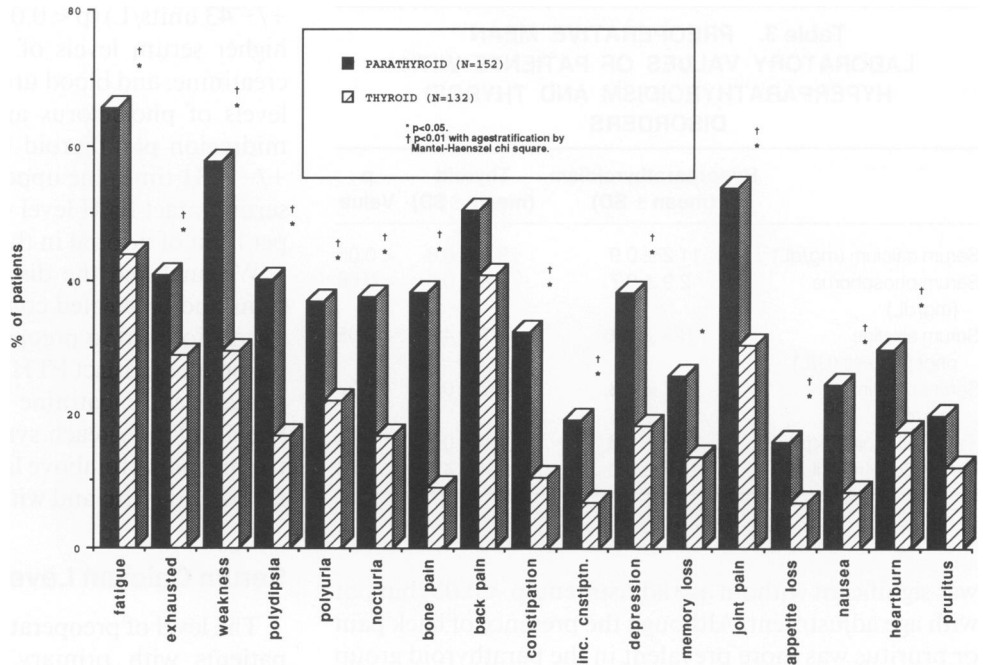
### Frequency of Asymptomatic Hyperparathyroidism

Of the 152 patients with primary hyperparathyroidism who responded to the questionnaire regarding symptoms or associated conditions before the operation, 7 patients (4.6%) had none of the above-mentioned possibly related symptoms, and 26 patients (17.1%) had no associated conditions. Only one patient (0.66%) had neither symptoms nor associated conditions and thus by strict definition had asymptomatic hyperparathyroidism. Of the 132 patients with thyroid disorders, 31 patients (23.5%) had no symptoms and 26 (19.7%) had no associated conditions before the operation. Only 17 (12.9%) patients had neither symptoms nor associated conditions.

### Profile of Symptoms and Associated Conditions in Hyperparathyroidism

For each symptom or associated condition, we compared the 152 patients with primary hyperparathyroid-

**Figure 1.** Preoperative symptoms of parathyroid and thyroid patients.

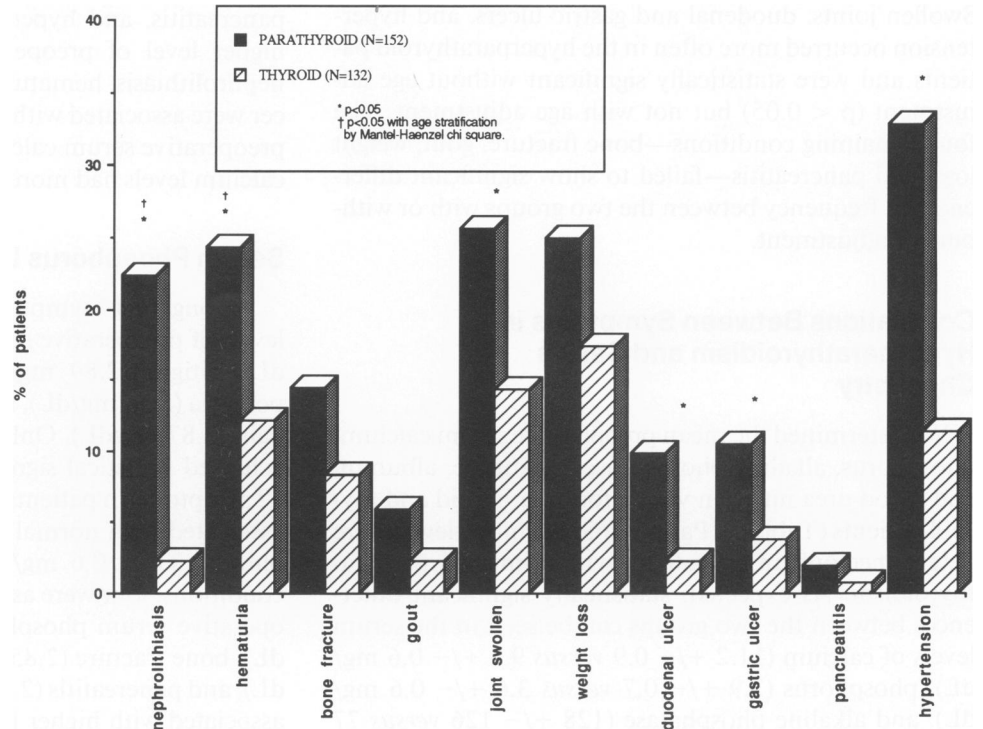


ism with the 132 patients with nontoxic thyroid disorders. We determined the frequency of each symptom and associated condition in both groups of patients (Figs. 1 and 2).

The parathyroid group had higher frequencies of all 17 symptoms listed in Table 1. Fourteen symptoms—fatigue, exhaustion, weakness, polydipsia, polyuria, noc-

turia, joint pain, bone pain, constipation, increasing constipation, depression, appetite loss, nausea, and heartburn—were more common in the hyperparathyroid patients and differed statistically with or without adjustment for age by stratification ( $p < 0.01$ ,  $p < 0.05$ ). Memory loss was more common in the parathyroid patients compared with the thyroid patients; its difference

**Figure 2.** Preoperative associated conditions of parathyroid and thyroid patients.



**Table 3. PREOPERATIVE MEAN LABORATORY VALUES OF PATIENTS WITH HYPERPARATHYROIDISM AND THYROID DISORDERS**

	Hyperparathyroidism (mean ± SD)	Thyroid (mean ± SD)	p Value
Serum calcium (mg/dL)	11.2 ± 0.9	9.3 ± 0.6	< 0.05
Serum phosphorus (mg/dL)	2.9 ± 0.7	3.6 ± 0.6	< 0.05
Serum alkaline phosphatase (U/L)	128 ± 126	77 ± 43	< 0.05
Serum creatinine (mg/dL)	1.17 ± 1.3	0.87 ± 0.2	0.27
Serum albumin (mg/dL)	4.2 ± 0.6	4.4 ± 0.5	0.24
Serum BUN (mg/dL)	15.3 ± 5.0	13.4 ± 4.2	0.26

was significant without age adjustment ( $p < 0.05$ ) but not with age adjustment. Although the presence of back pain or pruritus was more prevalent in the parathyroid group than in the thyroid group, the difference was not statistically significant with or without age adjustment.

Figure 2 shows the frequencies of the presence of the associated conditions, defined in Table 1, in the two groups of patients. All of the ten associated conditions were more prevalent in the parathyroid patients than in the thyroid patients. Two of the associated conditions, nephrolithiasis and hematuria, occurred more often in patients with primary hyperparathyroidism with or without age adjustment by stratification ( $p < 0.05$ ,  $p < 0.05$ ). Swollen joints, duodenal and gastric ulcers, and hypertension occurred more often in the hyperparathyroid patients and were statistically significant without age adjustment ( $p < 0.05$ ) but not with age adjustment. The four remaining conditions—bone fracture, gout, weight loss, and pancreatitis—failed to show significant differences in frequency between the two groups with or without age adjustment.

### Correlations Between Symptoms in Hyperparathyroidism and Serum Chemistry

We determined the mean preoperative serum calcium, phosphorus, alkaline phosphatase, creatinine, albumin, and blood urea nitrogen values for parathyroid and thyroid patients (Table 3). Parathyroid hormone levels were determined only in the patients with primary hyperparathyroidism. As expected, statistically significant differences between the two groups can be seen in the serum levels of calcium ( $11.2 \pm 0.9$  versus  $9.3 \pm 0.6$  mg/dL), phosphorus ( $2.9 \pm 0.7$  versus  $3.6 \pm 0.6$  mg/dL), and alkaline phosphatase ( $128 \pm 126$  versus  $77$

$\pm 43$  units/L) ( $p < 0.05$ ). The parathyroid patients had higher serum levels of calcium, alkaline phosphatase, creatinine, and blood urea nitrogen but had lower serum levels of phosphorus and albumin. The mean serum midregion parathyroid hormone (PTH) level was  $2.99 \pm 5.31$  times the upper limit of normal and the mean serum intact PTH level was  $3.67 \pm 3.36$  times the upper limit of normal in the parathyroid group.

We analyzed the distribution of preoperative symptoms and associated conditions of hyperparathyroidism in relationship to preoperative levels of serum calcium, phosphorus, intact PTH, midregion PTH, alkaline phosphatase, and creatinine in the 152 parathyroid patients. Specifically, for each symptom or associated condition, the means of the above laboratory values were calculated for patients with and without the symptom or condition.

### Serum Calcium Levels

The level of preoperative serum calcium was higher in patients with primary hyperparathyroidism who reported having fatigue, exhaustion, weakness, polydipsia, polyuria, back pain, constipation, increasing constipation, depression, loss of appetite, nausea, or pruritus (Tables 4 to 6). However, only fatigue ( $p = 0.047$ ) and polydipsia ( $p = 0.012$ ) had differences that were statistically significant. In contrast, patients with primary hyperparathyroidism who reported having bone pain, loss of memory, joint pain, and heartburn had lower but still elevated serum calcium levels. Among the ten associated conditions, gout, joint swelling, weight loss, duodenal ulcer, pancreatitis, and hypertension were associated with a higher level of preoperative serum calcium, whereas nephrolithiasis, hematuria, bone fracture, and gastric ulcer were associated with a lower but still elevated level of preoperative serum calcium. Patients with higher serum calcium levels had more weight loss ( $p = 0.02$ ).

### Serum Phosphorus Levels

Among the 17 symptoms, 5 were associated with lower levels of preoperative serum phosphorus ( $2.9 \pm 0.7$  mg/dL): fatigue (2.89 mg/dL), polydipsia (2.72 mg/dL), polyuria (2.76 mg/dL), nocturia (2.75 mg/dL), and back pain (2.87 mg/dL). Only the relationship for polydipsia achieved statistical significance ( $p = 0.015$ ). The other 12 symptoms in patients with hyperparathyroidism were associated with normal or higher levels of serum phosphorus ( $3.6 \pm 0.6$  mg/dL). Among the ten associated conditions, four were associated with lower levels of preoperative serum phosphorus: nephrolithiasis (2.82 mg/dL), bone fracture (2.85 mg/dL), gastric ulcer (2.82 mg/dL), and pancreatitis (2.80 mg/dL). Five conditions were associated with higher levels of serum phosphorus, and

**Table 4. RELATIONSHIP OF MEAN SERUM CALCIUM BETWEEN PATIENTS WITH AND WITHOUT THE PRESENCE OF SYMPTOMS AND ASSOCIATED CONDITIONS**

	Mean Serum Calcium (mg/dL)		p Value	
	Present	Absent		
Symptoms				
Polydipsia	11.44	11.04	0.01	
Loss of appetite	11.42	11.16		
Nausea	11.41	11.13		
Increasing constipation	11.36	11.16		
Pruritus	11.32	11.16		
Constipation	11.31	11.15		
Fatigue	11.30	10.95		0.05
Exhaustion	11.29	11.14		
Depression	11.29	11.14		
Weakness	11.24	11.13		
Back pain	11.24	11.16		
Polyuria	11.21	11.17		
Nocturia	11.20	11.20		
Memory loss	11.16	11.21		
Joint pain	11.16	11.27		
Heart burn	11.16	11.23		
Bone pain	11.14	11.24		
Associated conditions				
Gout	11.65	11.19	0.02	
Weight loss	11.50	11.10		
Duodenal ulcer	11.39	11.16		
Pancreatitis	11.30	11.19		
Hypertension	11.27	11.17		
Hematuria	11.19	11.23		
Bone fracture	11.13	11.23		
Gastric ulcer	11.05	11.23		
Joint swelling	11.00	11.22		
Nephrolithiasis	10.95	11.19		

the mean serum phosphorus levels were the same in patients with or without loss of appetite (2.91 mg/dL).

**Serum Parathyroid Hormone Levels**

Symptoms of fatigue, exhaustion, weakness, bone pain, constipation, increasing constipation, depression, joint pain, loss of appetite, nausea, heartburn, and pruritus occurred more often in patients with primary hyperparathyroidism who had higher serum-intact PTH levels. Serum-intact PTH levels were only significantly higher in patients with fatigue (p = 0.004) and pruritus (p = 0.03). Symptoms of weakness, polydipsia, nausea, heartburn, and nocturia were more common in patients with higher levels of midregional PTH values and were statistically significant for nocturia (p = 0.0004).

Among the associated conditions of primary hyperparathyroidism, hematuria, gout, weight loss, and hyper-

**Table 5. RELATIONSHIP OF MEAN SERUM INTACT PTH LEVELS BETWEEN PATIENTS WITH AND WITHOUT THE PRESENCE OF SYMPTOMS AND ASSOCIATED CONDITIONS**

Symptoms/ Associated Conditions	Ratio of PTH/Upper Limit of Normal		p Value
	Present	Absent	
Fatigue	3.64	1.54	0.004
Exhaustion	3.86	2.12	
Weakness	3.77	2.39	
Bone pain	3.77	2.39	
Constipation	3.78	2.51	
Increasing constipation	5.97	2.46	
Depression	3.98	2.15	
Joint pain	3.84	1.94	
Loss of appetite	5.72	2.01	
Nausea	4.76	2.15	
Heartburn	3.76	2.52	0.03
Pruritus	6.64	2.08	
Hematuria	4.30	2.37	
Gout	3.09	3.04	
Weight loss	4.65	2.17	
Hypertension	4.89	2.02	

PTH = parathyroid hormone.

tension were associated with higher serum-intact PTH levels, but none of these differences was statistically significant.

**Serum Alkaline Phosphatase Levels**

Among the symptoms, higher serum levels of preoperative alkaline phosphatase were seen in patients with

**Table 6. RELATIONSHIP OF MEAN SERUM MID-REGIONAL PTH LEVELS BETWEEN PATIENTS WITH AND WITHOUT THE PRESENCE OF SYMPTOMS AND ASSOCIATED CONDITIONS**

Symptoms/ Associated Conditions	Ratio of PTH/Upper Limit of Normal		p Value
	Present	Absent	
Weakness	3.90	3.40	0.0004
Polydipsia	4.12	3.31	
Nausea	3.73	3.65	
Heartburn	3.71	3.65	
Nocturia	5.35	2.15	

PTH = parathyroid hormone.

symptoms of weakness (140 units/L) and/or polydipsia (134 units/L), but these results failed to achieve statistical significance. Among the associated conditions of hyperparathyroidism, nephrolithiasis (143 units/L), hematuria (138 units/L), gout (176 units/L), weight loss (179 units/L), duodenal ulcer (129 units/L), pancreatitis (163 units/L), and hypertension (131 units/L) were seen with higher serum levels of alkaline phosphatase, but only the results associated with hypertension were statistically significant ( $p = 0.03$ ).

### Serum Creatinine Levels

Eleven symptoms—fatigue (1.24 mg/dL), exhaustion (1.31 mg/dL), weakness (1.31 mg/dL), bone pain (1.31 mg/dL), constipation (1.46 mg/dL), increasing constipation (1.66 mg/dL), depression (1.30 mg/dL), loss of appetite (1.7 mg/dL), nausea (1.63 mg/dL), heartburn (1.43 mg/dL), and pruritus (1.98 mg/dL)—were associated with higher serum levels of preoperative creatinine, but none achieved statistical significance. However, back pain (0.84 mg/dL) was associated with lower creatinine levels that were statistically significant ( $p = 0.0008$ ). Three of the ten associated conditions were associated with higher serum levels of creatinine: hematuria (1.36 mg/dL), weight loss (1.74 mg/dL,  $p = 0.039$ ), and hypertension (1.62 mg/dL,  $p = 0.04$ ). However, joint pain (1.14 mg/dL) was associated with lower serum levels of creatinine that achieved statistical significance ( $p = 0.03$ ).

### Resolution of Symptoms After Parathyroidectomy in Hyperparathyroidism Patients

The preoperative and postoperative symptoms among the 121 parathyroid patients and 93 thyroid patients were compared. In the parathyroid group, all symptoms showed a decrease in frequency after parathyroidectomy, whereas only 7 of 17 symptoms showed a decrease in frequency after thyroidectomy (Fig. 3). The parathyroid group experienced a decrease in frequency of fatigue by more than 40% after parathyroidectomy. In contrast to the dramatic improvements in symptoms after parathyroid surgery in the parathyroid group, the thyroid group experienced minimal decreases in the frequency of seven symptoms—polydipsia, polyuria, nocturia, back pain, joint pain, nausea, and heartburn—after thyroidectomy. The other symptoms showed an increase in frequency after surgery in the thyroid group. However, the changes in frequency of all 17 symptoms after thyroidectomy, regardless of the direction, were small. The largest change in percentage was less than 10% for memory loss.

Next, we selected from the 121 parathyroid and 93 thyroid patients only those who reported the presence of 1 or more of the 17 symptoms preoperatively and calculated the percentages of these patients who experienced a complete resolution of any given preoperative symptom. Parathyroid patients had higher rates of symptom resolution in 11 of the 17 symptoms. The differences in the resolution rates in fatigue, weakness, constipation, and increasing constipation between the parathyroid and the thyroid groups achieved statistical significance ( $p < 0.05$ ). The differences pertaining to weakness and constipation were also statistically significant, adjusting for age, and the differences pertaining to constipation and increasing constipation were statistically significant, adjusting for follow-up time ( $p < 0.05$ ).

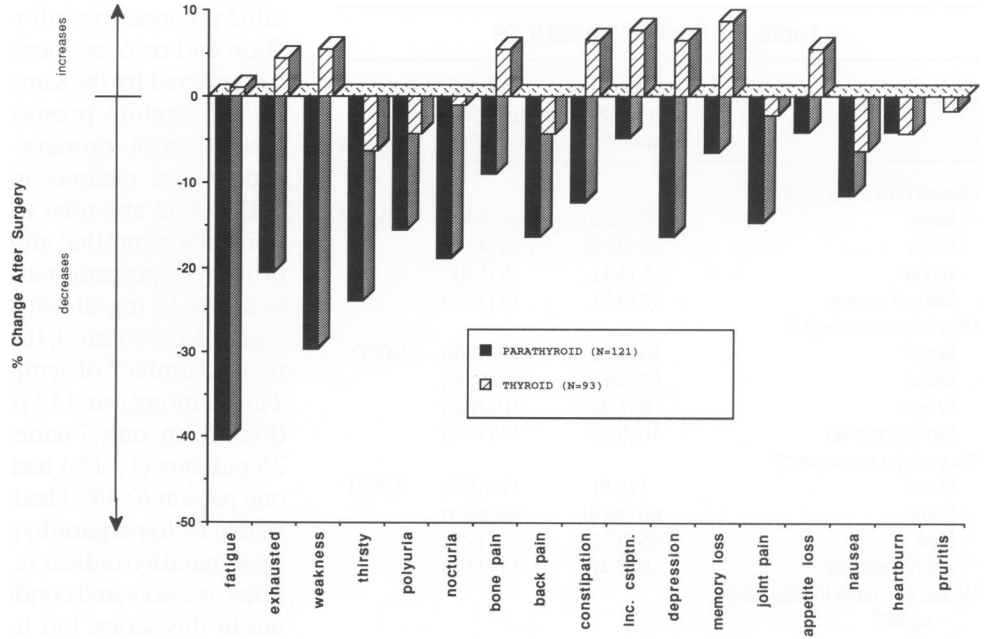
### Resolution of Associated Conditions After Parathyroidectomy in Hyperparathyroidism Patients

Similar to the analysis of the resolution of symptoms in the 121 parathyroid and 93 thyroid patients, the change in the frequency of each of the ten associated conditions after surgery was examined. Decreases in frequency were found in seven conditions (hematuria, bone fracture, joint swelling, weight loss, duodenal ulcerations, gastric ulcerations, and hypertension), whereas no changes in frequency were found in the other three conditions in the parathyroid group. In the thyroid group, only six of the ten associated conditions were found to have decreased in frequency after surgery, with the other four conditions having frequencies that were either unchanged or increased postoperatively. Figure 4 compares the magnitude and direction of the changes in frequency of the ten associated conditions between the parathyroid and thyroid groups after operation. Seven conditions (hematuria, bone fracture, joint swelling, weight loss, duodenal ulcer, gastric ulcer, hypertension) showed a greater decrease in frequency after surgery in the parathyroid group than in the thyroid group. There were little to no changes in frequency of two conditions (nephrolithiasis, pancreatitis) after surgery in the parathyroid group; however, the thyroid group had increases in frequency in these two conditions after surgery. Gout is the only condition that was associated with a larger decrease in frequency after surgery in the thyroid group compared with the parathyroid group.

### Results of Postoperative Survey

In addition to the questionnaire of symptoms that was sent to each of the 284 patients postoperatively, a survey consisting of a few questions was also sent along with the questionnaire. Table 7 summarizes the results of the

**Figure 3.** Changes in frequency of symptoms after surgery in parathyroid and thyroid patients.



survey. Approximately 80% of the patients in each of the parathyroid and thyroid groups indicated that they would have the operation again now that they knew the outcome of the surgery. Fifty-seven percent of the parathyroid patients said that they felt better overall after the parathyroidectomy, compared with 30% of the thyroid

patients who indicated that they felt better overall after the thyroidectomy. Strength was improved in 29% of the parathyroid patients but in only 13% of the thyroid patients. Finally, 37% of the parathyroid patients *versus* 13% of the thyroid patients claimed that they were less depressed after the surgery. No male patient with hyper-

**Figure 4.** Changes in frequency of associated conditions after surgery in parathyroid and thyroid patients.

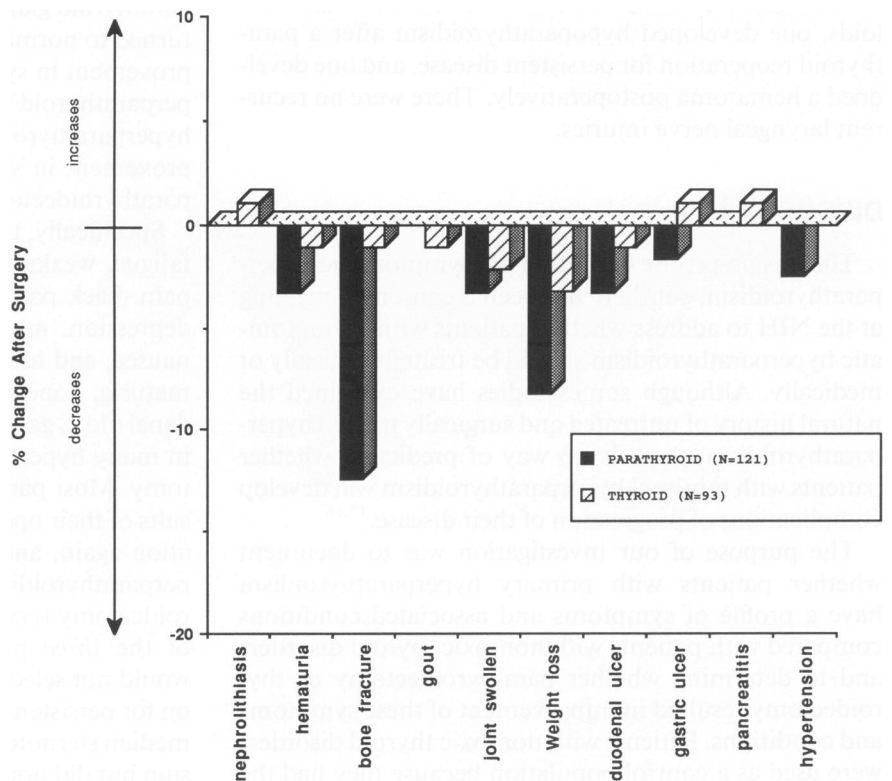




Table 7. SURVEY RESULTS

	Parathyroid (n = 121) [no. (%)]	Thyroid (n = 93) [no. (%)]	p Value
Overall how do you feel?			
Better	69 (57.0)	28 (30.1)	0.0002*
Same	35 (28.9)	46 (49.5)	
Worse	5 (4.1)	5 (5.4)	
Did not answer	12 (9.9)	14 (15.1)	
How is your strength?			
Better	35 (28.9)	12 (12.9)	0.007*
Same	67 (55.4)	60 (64.5)	
Worse	9 (7.4)	10 (10.8)	
Did not answer	10 (8.3)	11 (11.8)	
Do you get depressed?			
More	7 (5.8)	12 (12.9)	0.0001*
Same	60 (49.6)	58 (62.4)	
Less	45 (37.2)	12 (12.9)	
Did not answer	9 (7.4)	11 (11.8)	
Would you have the operation again?			
Yes	97 (80.2)	73 (78.5)	0.732
No	3 (2.5)	3 (3.2)	
Did not answer	21 (17.4)	17 (18.3)	

\* Statistically significant.

parathyroidism stated that he was more depressed, was weaker, or would not have the operation again.

Among the parathyroid patients, two developed keloids, one developed hypoparathyroidism after a parathyroid reoperation for persistent disease, and one developed a hematoma postoperatively. There were no recurrent laryngeal nerve injuries.

## DISCUSSION

There is no precise definition of asymptomatic hyperparathyroidism, yet there has been a consensus meeting at the NIH to address whether patients with asymptomatic hyperparathyroidism should be treated surgically or medically. Although some studies have examined the natural history of untreated and surgically treated hyperparathyroidism, there is no way of predicting whether patients with minimal hyperparathyroidism will develop complications of progression of their disease.<sup>15,16</sup>

The purpose of our investigation was to document whether patients with primary hyperparathyroidism have a profile of symptoms and associated conditions compared with patients with nontoxic thyroid disorders and to determine whether parathyroidectomy or thyroidectomy resulted in improvement of these symptoms and conditions. Patients with nontoxic thyroid disorders were used as a control population because they had the

same preoperative informed consent and a similar operation and recovery period and because they were generally referred by the same physicians.

We therefore prospectively studied 152 consecutive patients with primary hyperparathyroidism and 132 consecutive patients with nontoxic thyroid disorders both before and after surgical treatment. Our investigation documents that although most patients (74.3%) with primary hyperparathyroidism have serum calcium levels less than 12 mg/dL (mean serum calcium level was 11.2 mg/dL in this series), these patients have a specific "parathyroid profile" of symptoms and associated conditions. Thus, among our 152 patients with primary hyperparathyroidism, only 7 patients (4.6%) had no symptoms and 26 patients (17.1%) had no associated conditions. Only one patient (0.66%) had no clinical manifestation attributable to hyperparathyroidism, suggesting that primary hyperparathyroidism is rarely without associated symptoms or associated conditions. We did not study osteopenia in this series, but it is a common problem, even in patients with asymptomatic hyperparathyroidism.<sup>17</sup> Albright was one of the first to document that "after removal of the parathyroid tumor, these patients not only ceased to have bone symptoms, but noted that they had not felt so well in years."<sup>18</sup> Chou et al.<sup>19</sup> recently documented improvement in muscle strength and fine motor movement in patients with primary hyperparathyroidism after parathyroidectomy.

Successful parathyroidectomy (one or more abnormal parathyroid glands removed and serum calcium level returned to normal) frequently results in resolution or improvement in symptoms or associated conditions in hyperparathyroid patients. In our series, only eight (5.3%) hyperparathyroid patients did not experience any improvement in symptoms or associated conditions after parathyroidectomy.

Specifically, these studies document that symptoms of fatigue, weakness, polydipsia, polyuria, nocturia, bone pain, back pain, constipation, increasing constipation, depression, memory loss, joint pain, loss of appetite, nausea, and heartburn and associated conditions of hematuria, bone fracture, swollen joint, weight loss, duodenal ulcer, gastric ulcer, and hypertension may improve in many hyperparathyroid patients after parathyroidectomy. Most patients (about 80%), now knowing the results of their operative procedures, would have the operation again, and 57% of the patients with primary hyperparathyroidism stated they felt better after parathyroidectomy versus only 30% of the thyroid patients. Two of the three patients with hyperparathyroidism who would not select surgical treatment again were operated on for persistent hyperparathyroidism, and one required median sternotomy. The third patient had severe depression but did not improve after her parathyroidectomy.

The reason for the association of primary hyperparathyroidism with these symptoms and associated conditions is not fully understood. Joborn et al.<sup>20-23</sup> documented that neurotransmitters in the cerebrospinal fluid of patients with primary hyperparathyroidism are similar to those in patients with endogenous depression, and levels return to normal after parathyroidectomy. Although the clinical manifestations did not correlate with the serum calcium level except at very high levels ( $\text{Ca}^{+2} > 13.5 \text{ mg/dL}$ ) in our studies and in theirs, their subsequent studies documented that the psychological changes correlated best with the ionized calcium level in the cerebrospinal fluid.<sup>23,24</sup>

Whether parathyroidectomy is indicated for clinical symptoms and associated metabolic disorders probably depends on the severity of these manifestations and whether they are reversible by parathyroidectomy. A more important question is whether untreated mild or asymptomatic primary hyperparathyroidism adversely affects survival. Recent studies by Palmer et al.<sup>25-27</sup> documented that patients with mild primary hyperparathyroidism have an increased mortality rate. These findings were confirmed by Hedback et al.<sup>28-30</sup> The later investigators documented that young patients and those with less severe disease revert faster to a normal survival curve than do older patients or those with more severe hyperparathyroidism.<sup>28-31</sup> Previous investigation by Reinhoff<sup>32</sup> and by Sivula<sup>33-35</sup> have also suggested that patients with more severe hyperparathyroidism have a poorer prognosis even after successful parathyroidectomy. It appears that some associated conditions that develop in patients with hyperparathyroidism may be self-perpetuating once established.

The available information, therefore, supports parathyroidectomy for patients with primary hyperparathyroidism, because it often improves the symptoms, decreases associated conditions, and appears to improve survival. There are no long-term studies supporting a nonoperative approach to patients with mild primary hyperparathyroidism. Further studies addressing this question are needed, as called for by the NIH consensus meeting.

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## Discussion

DR. EDWIN L. KAPLAN (Chicago, Illinois): I rise to commend Dr. Clark and his associates for an important paper.

The authors have clearly shown, as many of us have believed for a long time, that most patients with primary hyperparathyroidism are symptomatic if one includes symptoms such as tiredness, weakness, depression, nocturia, and constipation in addition to the classic ones of kidney stones, hypertension, peptic ulcer, and arthritis. They showed that 95% of patients had one or more of these symptoms and that their control group of patients with a thyroid nodule had far fewer of the same symptoms. Postoperatively, virtually all of the patients exhibited benefit after parathyroidectomy, a result statistically greater than found in their thyroid controls.

This paper is a step in the right direction in clarifying this problem. There are some difficulties, however.

The patient populations were somewhat atypical, as pointed out by the authors in their manuscript. Many of the parathyroid patients had reoperations. Twenty-one percent of the patients had multiple adenomas, which is most unusual, but represents the fact that they were reoperated upon. Forty percent of the thyroid patients in the control group had cancer of the thyroid. This makes answers to some of the questions that they asked—e.g., “Do you get depressed?” or “Would you have this operation again?”—difficult to interpret.

Furthermore, the use of a patient questionnaire produced some unexplainable results. After parathyroidectomy, for example, the patients stated they had an decrease in hematuria, but no decrease in kidney stones.

I agree with the authors that a strong case can be made for

parathyroidectomy in so-called asymptomatic patients, because in fact, most patients have symptoms and the symptoms are almost always helped. Furthermore, there is no effective medical therapy for primary hyperparathyroidism. Operative mortality should be virtually nonexistent and operative morbidity, as shown in this paper, is very low when performed by expert endocrine surgeons.

I have several questions. What are your cure rates for parathyroidectomy at the first operation and at reoperations? Second, should bone densitometry be done more often before calling a postmenopausal woman with hyperparathyroidism asymptomatic? Finally, what are the benefits of parathyroidectomy in patients with osteoporosis and hyperparathyroidism?

DR. HEBER H. NEWSOME (Richmond, Virginia): This is an important paper. I think those of us who take care of any disease, in which we are convinced surgery has the best chance of cure over other treatment modalities, can certainly relate to the fact that many nonsurgeons taking care of these patients choose other modalities. In this disease, primary hyperparathyroidism, there virtually is no other treatment.

The watch-and-wait method is a treatment that has been chosen by some nonsurgeons. They watch and wait until they can detect symptoms without an understanding that symptoms are already present in, as we heard today, 95% of the cases.

I would like to point out what might be hidden symptoms and ask the authors if they have run into these sorts of things.

Out of approximately 200 cases now, we have seen maybe 10% of the people manifest the following—and I will not read you the whole list of anecdotes to illustrate a point. A faculty wife without a frank memory loss or depression is confused and cannot sequence her daily activities. After removal of a parathyroid adenoma, her mind cleared dramatically. The freelance writer who made her living writing for magazines and could no longer write. After surgery, she could write again. These are examples of subtle, but very important symptoms.

The question is, did your instrument pick that up? Was there an open question? I think some of the symptoms can be missed and might be arguably more important than obvious ones.

The other thing to point out is that the joint pain does not often disappear. I am wondering if intrinsic arthritis embedded in the same population happens to show up with primary hyperparathyroidism. I have consequently been very slow to promise them any relief of joint pains. I would appreciate a comment from you concerning this.

DR. TIMOTHY S. HARRISON (Hershey, Pennsylvania): We continually appreciate the quality of work from Orlo Clark's group about hyperparathyroidism and other conditions. This particular study is one that many of us knew should be done, but somehow could never bring ourselves to do it. It is tedious and difficult. That it has been done is important and I think has something to say about our understanding of hyperparathyroidism and what patients really do require care.

Twenty-plus years ago in the *JAMA*, there was an anecdotal case describing a woman with senile dementia, hospitalized in a mental hospital in Chicago for 18 years; the diagnosis of hyperparathyroidism was clear all of that time. The suggestion