0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(11):5415–5422

doi: 10.1210/jc.2004-0028

Randomized Controlled Clinical Trial of Surgery *Versus* No Surgery in Patients with Mild Asymptomatic Primary Hyperparathyroidism

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Parathyroidectomy is the definitive therapy for patients with symptomatic primary hyperparathyroidism. However, the role of surgery in mild asymptomatic primary hyperparathyroidism remains controversial. Accordingly, we conducted a prospective, randomized, controlled clinical trial of parathyroidectomy to determine the benefits of surgery *vs.* adverse effects of no surgery.

Fifty-three patients were randomly assigned to either parathyroidectomy (n = 25) or regular follow-up (n = 28). Bone mineral density (BMD), biochemical indices of the disease, quality of life, and psychological function were measured at 6- or 12-month intervals for at least 24 months.

Twenty-three of the 25 patients randomized to parathyroidectomy had surgery within the specified time of the protocol and three of the 28 patients randomized to regular follow-up had parathyroidectomy during follow-up. After parathyroidectomy, there was an increase in BMD of the spine (1.2%/yr, $P < 0.001$), femoral neck (0.4%/yr, $P = 0.031$), total hip (0.3%/yr, $P = 0.07$), and forearm (0.4%/yr, $P < 0.001$) and an expected fall in serum total and ionized calcium, serum PTH, and urine calcium ($P < 0.001$ for all). In contrast, patients followed up without surgery lost BMD at the femoral neck (−0.4%/yr, $P = 0.117$) and total hip (−0.6%/yr, $P = 0.007$) but gained at the spine (0.5%/yr; P = ns) and forearm (0.2%/yr, $P = 0.047$), with no significant changes in biochemical indices of disease. Consequently, a significant effect of parathyroidectomy on BMD was evident only at the femoral neck (a group difference of 0.8%/yr; $P = 0.01$) and total hip (a group difference of 1.0%/yr; $P = 0.001$) but not at the spine (a group difference of 0.6%/yr) or forearm (a group difference of 0.2%/yr).

Quality-of-life scores as measured by a 36-item short-form health survey showed significant declines in five of the nine domains (social functioning, physical problem, emotional problem, energy, and health perception) in patients followed up without surgery but in only one of the nine domains (physical function) in the patients who had parathyroidectomy. Consequently, a modest measurable benefit of parathyroidectomy was evident in social and emotional role function ($P =$ 0.007 and 0.012, respectively). Psychological function as assessed by the symptom checklist revised did not change significantly in either group, except for a significant decline in anxiety ($P = 0.003$) and phobia ($P = 0.024$) in patients who had surgery in comparison with those who did not.

We conclude that it is feasible to conduct a randomized, controlled clinical trial of parathyroidectomy in patients with mild asymptomatic primary hyperparathyroidism, and measurable benefits of surgery on BMD, quality of life, and psychological function can be demonstrated. However, the small but significant benefits of parathyroidectomy must be weighed against the risks of surgery in these otherwise healthy individuals. (*J Clin Endocrinol Metab* 89: 5415–5422, 2004)

PARATHYROIDECTOMY IS THE treatment of choice for patients with symptomatic primary hyperparathyroidism, significant hypercalcemia (>12 mg/dl) even in the absence of symptoms, and bone or active stone disease. Despite the National Institutes of Health consensus guidelines a decade ago (1), the role of surgery in mild asymptomatic primary hyperparathyroidism remains controversial (2–6). The guidelines were developed after some studies had demonstrated that untreated mild primary hyperparathyroidism was not associated with biochemical or densitometric progression or disease-specific complications (7–9). Two prospective observational studies in the United States (10, 11) confirmed the results of earlier reports (7–9, 12, 13), whereas others have reported on the long-term results in treated (both medical and surgical) and untreated cohorts of patients with primary hyperparathyroidism (13–24). However, except for one study (18), none were randomized, controlled clinical trials.

With the changing patterns of presentation, a vast majority of patients with contemporary primary hyperparathyroidism in the United States do not manifest the symptoms traditionally attributed to this disease (25). Consequently, the role of parathyroidectomy, the only definitive therapy for the condition, has been called into question (2, 6, 9, 26) and is a subject of considerable debate (3–6). As a result, some patients and clinicians are reluctant to consider parathyroidectomy because of the uncertainty of its benefits. Several guidelines and algorithms have since been suggested (1, 7, 13, 27) and modified (28–30), and many divergent opinions have been expressed (3–6). However, none are based on randomized, controlled clinical trials of parathyroidectomy. Accordingly, we undertook the first such trial in patients with mild asymptomatic primary hyperparathyroidism to address two specific questions: is it feasible to conduct a randomized clinical trial in which an invasive therapy is recommended to apparently healthy subjects in whom the

Abbreviations: AP, Alkaline phosphatase; BMD, bone mineral density; Cr, creatinine; SF-36, 36-item short-form health survey; SCL-90R, symptom checklist revised.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

disease-specific complications (such as kidney stones and skeletal fractures) are not always serious or inevitable, and are there any measurable benefits from parathyroidectomy or conversely, are there any adverse health effects if left untreated?

Patients and Methods

Patients

Patients were recruited between June 1994 and March 1997 from within the Henry Ford Health System by either physician referral or centralized laboratory computer tracking of all patients with hypercalcemia. Entry criteria for the study were similar to those previously published (7, 8, 11, 24) but differed in important ways from the two long-term observational studies from the United States (10, 12). The patients in this study were asymptomatic, had milder disease, and were generally representative of the vast majority of patients with contemporary primary hyperparathyroidism. Briefly, the inclusion criteria were age between 50 and 75 yr regardless of gender or ethnicity; mean of at least three albumin-adjusted (31) serum calcium (Ca) levels between 10.1 and 11.5 mg/dl (2.52–2.87 mmol/liter); intact PTH level greater than 20 pg/ml (>20 ng/liter); normal renal function, defined as serum creatinine (Cr) less than 1.5 mg/dl (<133 μmol/liter); forearm bone mineral density within 2 SD adjusted for age, sex, and race (Z-scores); absence of relevant symptoms and complications directly attributable to either hypercalcemia or excess PTH secretion; willingness to participate and ability to give informed consent for a randomized trial of parathyroidectomy; and living within a 150-mile radius of the Henry Ford Hospital.

Patients were excluded if they had familial hyperparathyroidism, previous neck surgery or current thyroid disease requiring surgical intervention, nontraumatic vertebral or hip fractures, or nephrolithiasis within the past 2 yr. Also excluded were women within 5 yr of menopause, patients taking medications known to affect bone and mineral metabolism (glucocorticoids, anticonvulsants, and bisphosphonates), and those with unexpected echocardiographic findings that precluded surgery. Each eligible subject gave informed consent before randomization, and the study was approved by the Institutional Review Board on Human Rights.

Of approximately 283 potentially eligible patients, 53 patients who gave informed consent were block randomized, stratified on gender and ethnicity. Each patient was seen every 6 months for at least 24 months (median 42 months; range 24–64 months). We assessed each patient for symptoms of hypercalcemia and complications of the disease such as skeletal fractures and kidney stones. Bone mineral density (BMD) and indices of disease, such as serum total and ionized Ca, PTH, and total and bone-specific alkaline phosphatase (AP) were measured at 6-month intervals. Renal function by endogenous Cr clearance, renal tubular function by the urine to serum ratio of β2-microglobulin (32), biochemical markers of bone turnover, and 24-h urine Ca were measured yearly. X-rays of the thoracic and lumbar spine, anteroposterior view of both hands, and tomograms of the abdomen were performed at baseline to exclude patients with prevalent vertebral deformities, subperiosteal resorption of phalanges or nephrolithiasis, and nephrocalcinosis, respectively. The x-ray studies were repeated at the end of the study to ascertain incident vertebral fractures and kidney stones.

Quality of life and psychosocial well-being were assessed with two standardized, validated questionnaires: health-related quality of life was assessed every 6 months with the 36-item short-form health survey (SF-36) (33, 34). This widely used instrument contains eight subscales: physical function, physical role function, bodily pain, general health perception, energy, social function, emotional role function, and mental health as well as overall change in health status (33, 34). Summed data from the subscales are transformed into 0- (worst) to 100 (best)-point scales. Psychological disturbances were assessed yearly with the symptom checklist revised (SCL-90R) (35), another validated instrument for measuring mental health status, which quantifies psychological distress in nine dimensions of somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, aggression, phobia, paranoid ideation, and psychoticism in addition to three global scales: the Global Severity Index, the Positive Symptom Distress Index, and the Positive Symptom Total.

Fasting lipid profile, echocardiograms, and bone histomorphometry (in a small subset of women) were also performed at baseline and at 1 yr to assess the effect of parathyroidectomy. The preliminary results of these studies were reported as abstracts (36, 37), and the detailed results will be reported separately.

Study safety and data monitoring

An independent committee consisting of an endocrinologist, parathyroid surgeon, cardiologist, biostatistician, and psychiatrist met twice a year to monitor the study progress and patient safety. None of the members were involved in the care of the patients.

Laboratory methods

Serum levels of total Ca, phosphate, AP, and Cr were measured in the hospital laboratory by standard methods using a Hitachi-747 autoanalyzer. Serum-ionized Ca was measured by Nova-6 ion-specific electrode. Serum PTH was measured by immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). Serum bone-specific AP was measured by slight modification of the method of Farley *et al.* (38). Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were measured by RIA and radioreceptor assay, respectively, using Nichols Institute kits. Urine hydroxyproline was measured by HPLC. BMD of the lumbar spine, proximal femur, and nondominant forearm was measured by QDR-2000 bone densitometer (Hologic, Inc., Waltham, MA); the same instrument was used throughout the study and a single technician performed all BMD measurements.

Statistical methods

Unpaired Student's *t* test was used to compare the two groups at baseline. The primary analysis was based on the intention-to-treat principle (39). However, because results were similar, analyses excluding observations after cross-over from nonsurgery to surgery have been omitted in the main analyses presented. Average annual change for each variable of interest was estimated for and compared between treatment groups using varying intercept models (40) with separate slopes fit for each group. In these models the slopes were treated as fixed effects, but separate intercepts (random effects) were used for each patient. The SAS procedure PROC MIXED (41) was used for these models. For plotting of serial data, adjusted means and SEs were computed to minimize the impact of patients without data at all specified follow-up times. Adverse event rates were compared by Fisher's exact test. Unadjusted nominal significance level was set at $P < 0.05$.

Results

A total of 1201 patients between the ages of 50 and 75 yr with hypercalcemia (serum Ca > 10.1 mg/dl or > 2.52 mmol/liter) were identified during the 33-month recruitment period. However, a great majority of these patients (918 or 76%) either had non-PTH mediated hypercalcemia or did not meet one or more of the entry criteria (Fig. 1). Of the remaining 283 potentially eligible patients, 95 (33%) refused parathyroidectomy (a requirement for randomization) because they felt well and, therefore, did not think they needed surgery. In 105 (37%) cases, the primary care physicians did not respond to our request for recruitment, and another 30 (11%) patients could not participate because of either incomplete information or recruitment and follow-up window constraints. The remaining 53, or 19% of the 283 potentially eligible patients, were enrolled in the study: 22 patients (42%) through laboratory computer tracking method and 31 (58%) from physician referral.

Except for the older mean age of the surgery group ($P = 0.03$), the baseline characteristics of the two groups were similar (Table 1). There were no significant differences in demographic or relevant biochemical features between the

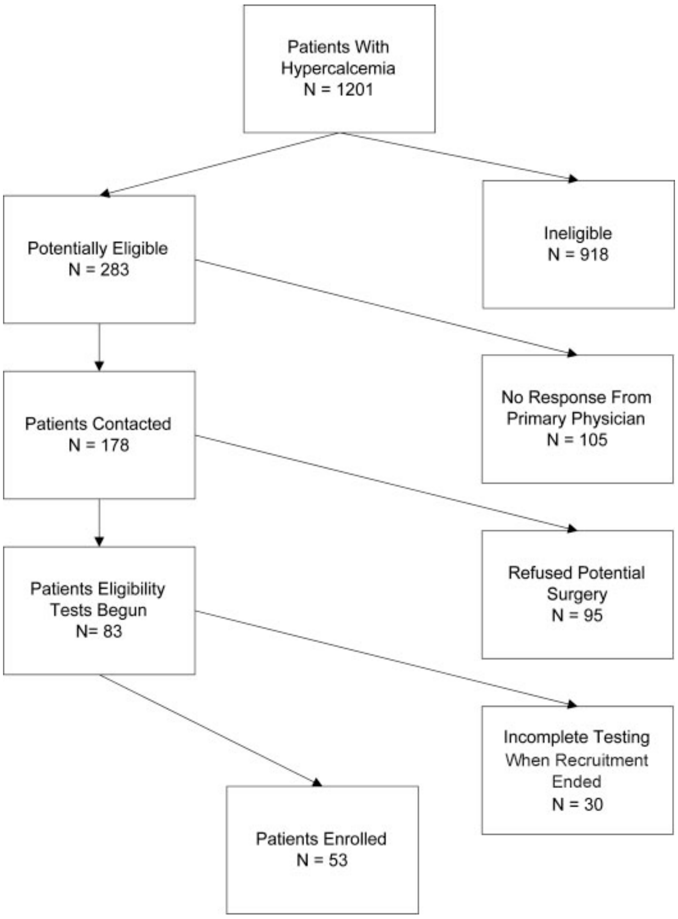

FIG. 1. Flow diagram of patient recruitment and randomization process.

TABLE 1. Baseline characteristics of the study subjects

Variable	Patients randomized to parathyroidectomy	Patients randomized to regular follow-up
n	25	28
Age (yr)	67 ± 7	63 ± 7
Women/men	21/4	21/7
Black/White	11/14	14/14
Height (cm)	166.5 ± 9.3	164.0 ± 9.5
Weight (kg)	83.3 ± 17.3	91.3 ± 21.3
BMI (kg/m^2)	30.1 ± 6.2	34.2 ± 9.4
Systolic BP (mm Hg)	143 ± 20	145 ± 18
Diastolic BP (mm Hg)	84 ± 9.4	83 ± 8.8

Except for older mean, the age of the patients was randomized to parathyroidectomy ($P = 0.03$); none of the differences is significant. BMI, Body mass index; BP, blood pressure.

53 enrolled patients and the 230 patients who were not (data not shown). The proportion of women and blacks, baseline height, weight, body mass index, blood pressure (Table 1), BMD at relevant sites (Table 2), biochemical indices of disease (Table 2), and quality-of-life (by SF-36) and psychological function (by SCL-90R) scores were similar in the two randomized groups.

An experienced parathyroid surgeon (G.B.T.) performed the surgery; he attempted to identify four parathyroid glands in each patient and resected only the grossly abnormal parathyroid gland(s). Consistent with our prevailing practice at the time, no localizing imaging study was performed. Twenty-three of the 25 patients (92%) randomized to surgery had parathyroidectomy within 3 months of randomization, and at least one abnormal parathyroid gland (median weight 550 mg; range 80–9600 mg) was found in each patient (42). One patient refused surgery after randomization but had successful parathyroidectomy a year later, and the other did not have surgery; both were included in the surgery group with intention-to-treat analysis (39). Details of surgical outcomes, parathyroid pathology, peri- and postoperative course, and other surgery-related aspects have been reported previously (42).

Biochemical indices of disease

After parathyroidectomy there was the expected fall in serum total and ionized Ca, PTH, total and bone-specific AP, and 24-h urine Ca and a rise in serum phosphate (Table 3). The small changes in serum Cr and fasting urine Ca/Cr and hydroxyproline/Cr ratios were not significant (Table 3). Glomerular function as assessed by endogenous creatinine clearance and renal tubular function as assessed by urine to serum ratio of β2-microglobulin (32) did not change in either group (data not shown). After parathyroidectomy, the mean serum 1,25-dihydroxyvitamin D levels declined, and the mean serum 25-hydroxyvitamin D levels rose significantly ($P < 0.0001$ for both; Table 3), most likely the result of a decrease in PTH secretion and metabolic clearance rate of 25-hydroxyvitamin D, respectively (43).

No significant changes were seen in any of the biochemical indices of the disease or biochemical markers of bone turnover in patients followed up without surgery (data not shown).

BMD

A significant effect of parathyroidectomy on BMD was evident only at the femoral neck (a group difference of 0.8%/yr; $P = 0.01$) and total hip (a group difference of 1.0%/yr; $P = 0.001$) but not at the spine (a group difference of 0.6%/yr) or forearm (a group difference of 0.2%/yr). In the 25 patients randomized to surgery, BMD increased significantly at the spine (1.2%/yr, $P < 0.001$), femoral neck (0.4%/yr, $P = 0.031$), total hip (0.3%/yr, $P = 0.07$), and forearm (0.4%/yr, $P < 0.001$) (Fig. 2). In the 28 patients followed up without surgery, BMD increased slightly at the lumbar spine (0.5%/yr, $P = 0.087$) and forearm (0.2%/yr, $P = 0.047$) but declined at the femoral neck (−0.4%/yr, $P = 0.117$) and total hip (−0.6%/yr, $P = 0.007$).

Quality of life

In comparison with the patients who did not have surgery, a statistically significant beneficial effect of parathyroidectomy was seen in two of the nine domains (social function, group difference $P = 0.007$; and emotional role function, group difference, $P = 0.012$; Fig. 3). The mean baseline SF-36 scores were similar to those published for patients without primary hyperparathyroidism (34). In the patients followed up without surgery, a significant worsening occurred in five of the nine domains (social functioning, physical problem,

TABLE 2. Baseline BMD and biochemical findings

Variable	PTX group	No-PTX group	Reference range[a]
BMD			
Forearm arm (g/cm^2)	0.66 ± 0.11	0.68 ± 0.11	0.596 and 0.667
Lumbar spine (g/cm^2)	1.09 ± 0.24	1.11 ± 0.17	0.939 and 1.052
Femoral neck (g/cm^2)	0.76 ± 0.14	0.79 ± 0.15	0.691 and 0.816
Total hip (g/cm^2)	0.92 ± 0.16	1.00 ± 0.16	NA
Biochemical data			
Calcium (mg/dl)	10.37 ± 0.56	10.37 ± 0.54	8.2–10.0
Ionized Ca (mmol/liter)	1.37 ± 0.09	1.37 ± 0.08	1.0–1.35
Phosphate (mg/dl)	2.98 ± 0.38	2.94 ± 0.48	2.5–4.5
Cr (mg/dl)	0.90 ± 0.29	0.93 ± 0.20	0.6–1.5
PTH (pg/ml)	88 ± 27	76 ± 33	10–55
AP (IU/liter)	87 ± 34	98 ± 28	<140
Bone-specific AP (IU/liter)	58.5 ± 26.0	52.5 ± 23.7	3–59
25-Hydroxyvitamin D (ng/ml)	20.2 ± 9.5	20.6 ± 10.8	10–55
Fasting urine Ca/Cr (mg/g)	0.14 ± 0.08	0.16 ± 0.15	<0.15
Hydroxyproline/Cr (mg/g)	20.7 ± 8.9	22.4 ± 10.4	7–21
Urine calcium (mg/d)	245 ± 133	235 ± 139	<300

None of the differences between the two groups are significant. PTX, Parathyroidectomy.

[a] For BMD reference range only, the means for whites and blacks, respectively, are given (62). Other values are shown as means ± SD or as ranges. To convert values for Ca and P to mmol/liter, multiply by 0.2495 and 0.3229, respectively. To convert values for Cr to μmol/liter, multiply by 88.4. To convert values for PTH to pmol/liter, multiply by 0.105. To convert values for total and bone-specific AP to microkatals per liter, multiply by 0.0167. To convert values for 25-hydroxyvitamin D to nmol/liter, multiply by 2.496.

TABLE 3. Relevant biochemical indices of disease before and after parathyroidectomy in 23 patients randomized to surgery

Variable	Before parathyroidectomy	After parathyroidectomy
Calcium (mg/dl)	10.41 ± 0.51	9.33 ± 0.42
Ionized calcium (mmol/liter)	1.37 ± 0.09	1.22 ± 0.06
Phosphate (mg/dl)	3.03 ± 0.37	3.5 ± 0.35
Cr (mg/dl)	0.87 ± 0.26	0.93 ± 0.21
PTH (pg/ml)	87 ± 27	39 ± 28
1,25-Dihydroxyvitamin D (pg/ml)	52.8 ± 21.7	39.7 ± 9.4
25-Hydroxyvitamin D (ng/ml)	20.6 ± 8.9	24.9 ± 8.8
Total AP (IU/liter)	95 ± 34	74 ± 16
Bone-specific AP (IU/liter)	55 ± 28	33 ± 11
Urine Ca/Cr (mg/mg)	0.15 ± 0.08	0.11 ± 0.14
Urine hydroxyproline/Cr (mg/g)	21.0 ± 9.1	18.9 ± 6.5
Urine calcium (mg/d)	252 ± 135	147 ± 86

Except for serum Cr and urine Ca/Cr and hydroxyproline/Cr ratios, all other differences are highly significant (all P values < 0.001). Values are shown as means ± SD. To convert values for Ca and P to mmol/liter, multiply by 0.2495 and 0.3229, respectively. To convert values for Cr to μmol/liter, multiply by 88.4. To convert values for PTH to pmol/liter, multiply by 0.105. To convert values for AP to microkatals per liter, multiply by 0.0167. To convert values for 1,25-dihydroxyvitamin D to pmol/liter, multiply by 2.4. To convert values for 25-hydroxyvitamin D to nmol/liter, multiply by 2.496.

emotional problem, energy, and health perception, $P = 0.013$ to < 0.0001; Fig. 3). Although a small decline was also seen in six of the nine SF-36 domains in patients who had parathyroidectomy, only the decline in physical function score was significant ($P = 0.022$). Nevertheless, in comparison with the patients without surgery, a statistically significant beneficial effect of parathyroidectomy was still evident in two of the nine domains.

A favorable effect of surgery was seen in two of the nine dimensions of the SCL-90R psychological scores (Fig. 4). There was less anxiety and phobia in comparison with the patients who had not had surgery (group difference $P =$ 0.003 and 0.024, respectively). In the remaining seven dimensions, there was a trend in favor of surgery, but no significant change was noted in the three composite scores (Fig. 4). No significant worsening was observed in patients followed up without surgery in either the nine individual or the three composite SCL-90R scores (Fig. 4).

Adverse events

In the surgery group, one patient required an overnight postoperative drain in the neck most likely related to the removal of an occult substernal goiter; another patient was not satisfied with parathyroidectomy after she was told that her surgery was somewhat atypical because of an intrathyroidal adenoma, and three patients developed recurrent hyperparathyroidism (42). Among the 28 patients followed up without surgery, one patient developed a small kidney stone 2 yr after randomization (she had hypercalciuria both at baseline and during follow-up); another patient developed pancreatitis; and a third patient developed fatigue, irritability, and depression. All three patients underwent parathyroidectomy. None of the remaining patients in either group developed subperiosteal bone resorption in phalanges, skeletal fractures, nephrolithiasis, or renal dysfunction. All patients randomized to regular follow-up without surgery ful-

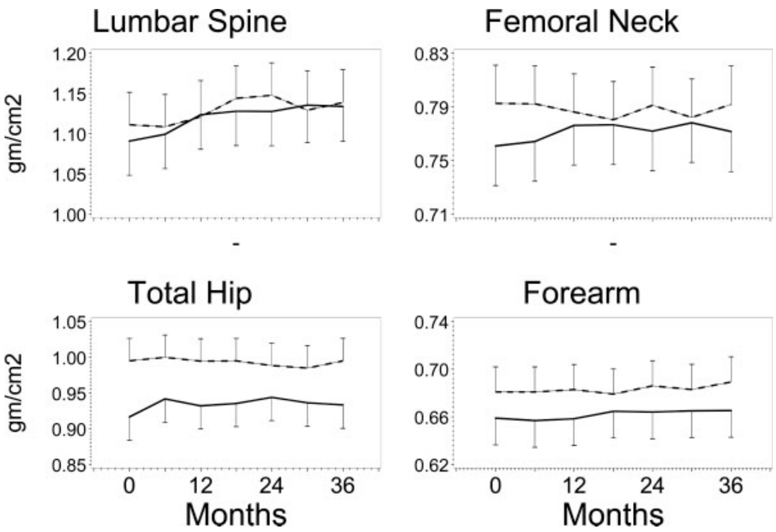

FIG. 2. Annual estimated changes in BMD (grams per square centimeter) of the lumbar spine, femoral neck, total hip, and nondominant forearm in patients with mild asymptomatic primary hyperparathyroidism. The *solid line* represents mean and SEM for patients randomized to parathyroidectomy, and the *dashed line* represents mean and SEM for patients followed up regularly without surgery. The means at each time point are adjusted to account for missing observations. The estimated annual rates of change in BMD were different between the treatment groups for femoral neck ($P = 0.01$) and total hip ($P = 0.001$).

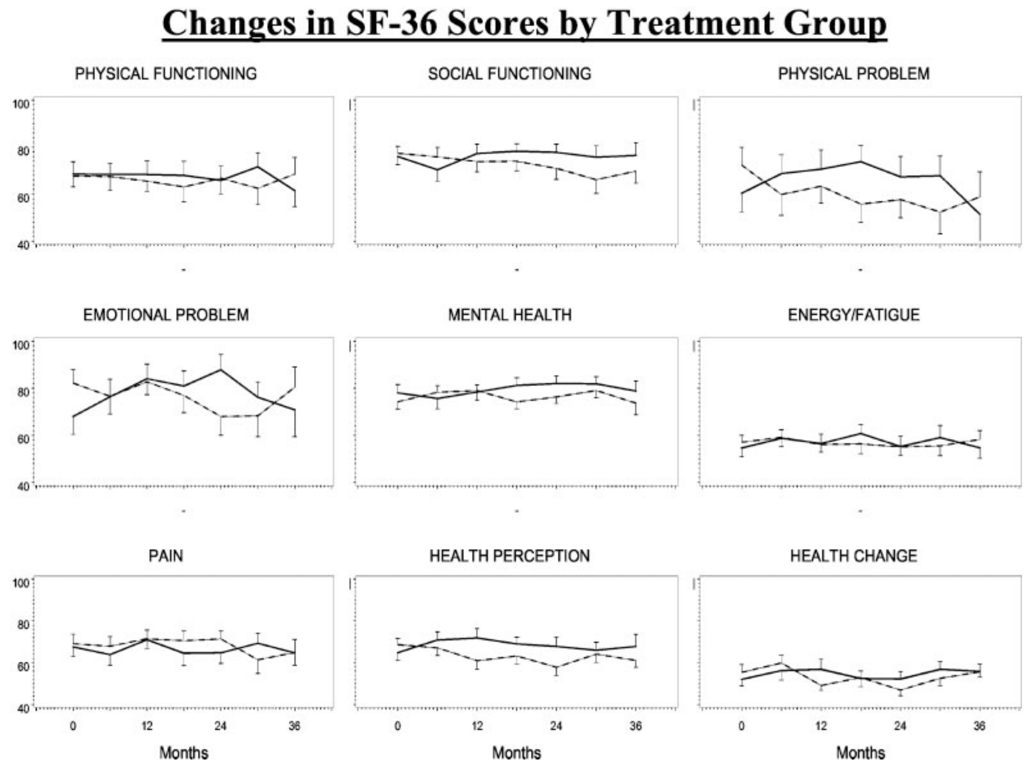

FIG. 3. Estimated annual changes in SF-36 scores (on a scale of 0–100) in patients with mild asymptomatic primary hyperparathyroidism randomized to either parathyroidectomy (*solid line*; mean and SEM) or regular follow-up without surgery (*dashed lines*). A higher score indicates better quality of life. The estimated annual rates of change were different between the treatment groups for social function ($P = 0.007$) and emotional problem ($P = 0.012$).

filled the criteria for continued observation throughout the study. The proportion of patients developing any adverse event was not significantly different between the two groups (8.0% in the surgery group *vs.* 11% in the no-surgery group, $P = 0.67$ by Fisher's exact test). Follow-up was complete in all patients until the time of the closure of the study.

Discussion

We demonstrate, for the first time, that despite the invasive nature of the only available treatment, it is feasible to conduct a randomized, controlled clinical trial of surgery in patients with mild asymptomatic primary hyperparathyroidism, provided an experienced parathyroid surgeon is available. In addition, the results from this study affirm our earlier findings (7, 8, 11, 24), now in a randomized, controlled clinical trial setting. The results of this trial and our previous studies (7, 8, 11, 24) are in agreement with the only two other prospective observational studies from the United States (10, 12) that in the absence of parathyroidectomy neither disease-specific complications nor accelerated rate of bone loss occur uniformly.

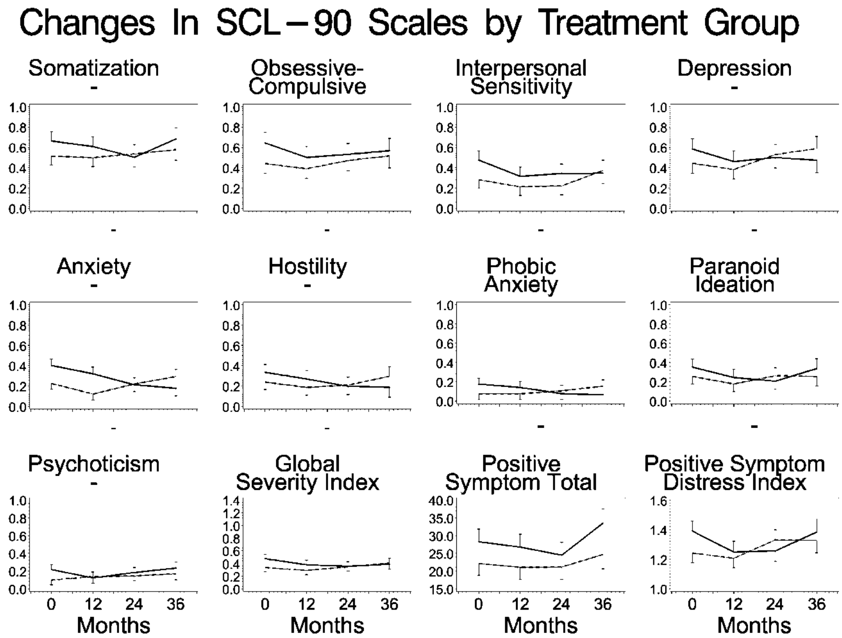

FIG. 4. Estimated annual changes in SCL-90R scales (on a scale of 0–1) in patients with mild asymptomatic primary hyperparathyroidism randomized to either parathyroidectomy (*solid line*; mean and SEM) or regular follow-up without surgery (*dashed lines*). A higher score indicates better quality of life. The estimated annual rates of change were different between the treatment groups for anxiety ($P = 0.003$) and phobia ($P = 0.024$).

Even in these carefully selected asymptomatic patients with mild primary hyperparathyroidism, demonstrable benefits of surgery were seen in bone density, quality of life, and psychological function. Despite predictable increases in BMD after surgery, most likely the result of contraction of remodeling space (44), the differences between the groups was significantly in favor of surgery only at the femoral neck and total hip but not at the spine or forearm. Lack of an effect of parathyroidectomy on the spine and forearm BMD was due to a gain in BMD in both groups, most likely due to an anabolic effect of modestly elevated serum PTH levels not only in the patients without surgery but also due to continued mildly elevated levels (albeit within the reference range) in patients who had parathyroidectomy (45). Another potential reason for a lack of difference in BMD changes between the groups could be due to inclusion of blacks, although our previous data suggest that the rates of change in BMD are similar both in blacks and whites (7, 24), and black subjects were equally distributed between the two groups. Therefore, it is unlikely that inclusion of blacks obscured any potential benefit of surgery or deleterious effect of no surgery. In any case the overall magnitude of gains in BMD were quite small (<1%) within each group.

With the changing clinical presentation of primary hyperparathyroidism in the past two decades (25), increasing attention is directed toward nontraditional manifestation of the disease (2). Several recent studies have emphasized the benefits of parathyroidectomy on neuromuscular and neuropsychiatric manifestations, physical activity and endurance, work performance, and quality of life (46–49). Although we could not exclude an independent effect of age, a modest but significant beneficial effect in quality of life and psychological function was seen after surgery. The type and scope of subtle beneficial effects of surgery on quality of life and psychological function may indeed reflect a broader impact of hyperparathyroidism on activities of daily living. However, because the benefits of surgery were limited to social, emotional, and psychological functions, we cannot exclude a potential placebo effect of surgery, and ethical considerations would preclude a sham surgery group. With the advent of minimally invasive parathyroidectomy, a more liberal approach to surgery is advocated (25), but it is unclear whether small improvements in BMD, quality of life, and psychological function are worth the risk of an invasive procedure in such seemingly healthy subjects (6, 25).

There are important differences between the results of this unique randomized clinical trial and those of the other observational studies. First, we studied only patients with mild form of primary hyperparathyroidism; the mean serum levels of Ca and PTH in our study were significantly lower than in other similar studies (10, 12, 13), and the PTH levels were within the reference range in more than one third of the patients (19 of the 53, or 36%). This might explain a smaller magnitude of increases in BMD after surgery in this trial, compared with other observational studies (10, 13, 28). Second, many previous reports included patients with more severe disease and/or patients with complications traditionally associated with this disease such as osteoporosis or nephrolithiasis (9, 10, 12, 14, 16, 23, 50–56). Third, unlike one study (19) but similar to our previous reports and others (7, 8, 10, 11, 24), we did not observe continued accelerated rate of bone loss in the untreated patients. Fourth, the incidence of disease-specific complications in this trial was lower than in other studies (10, 12), most likely a reflection of our careful selection. We did not include, for instance, patients younger than 50 yr, a group known to have higher prevalence of kidney stones and greater likelihood of bone loss during menopausal transition. Nevertheless, we believe that the patients included in this trial are generally representative of the vast majority of contemporary patients with this disease (25).

Although we were pleased to have successfully completed the first and only randomized trial of surgery in patients with mild asymptomatic primary hyperparathyroidism, there were limitations to our study. Only 53 of the 100 originally planned patients were enrolled, and recruitment took 15 months longer than the anticipated 18 months. Both of these problems reflect a growing perception among clinicians that untreated primary hyperparathyroidism is usually not associated with classic disease-specific complications (24, 57–59). The lower-than-predicted recruitment rate is not surprising because a few reports, including our own studies, were published during the active recruitment phase of this study (7, 8, 16, 56) and also considering the invasive nature of the treatment for patients who feel generally healthy. Many patients refused parathyroidectomy, a requirement for the trial participation, believing that they were well and did not need intervention. This implies that a different randomization strategy would be needed for any future such trials. Many clinicians did not respond to our request for recruitment, as has been observed in other surgical trials involving even lethal disease such as breast cancer (60). Finally, although not the primary objectives of this study, the sample size was too small and follow-up period was too short (<3 yr) to assess the effect of parathyroidectomy on other outcome variables of interest such as nephrolithiasis, fractures, morbidity, and mortality. A larger trial with a longer follow-up may uncover disease-specific complications in the untreated patients not seen in our smaller feasibility study. All of these issues should be taken into consideration in planning any such future trials.

In summary, we believe that it is feasible to conduct a randomized, controlled clinical trial of parathyroidectomy in patients with mild asymptomatic primary hyperparathyroidism because very few diseases-specific complications occurred in the absence of definitive treatment. Despite the mild disease and asymptomatic status, there appeared to be measurable effects of surgery on BMD, quality of life, and psychological function. With the advent of minimally invasive surgery, a more liberal approach to surgery is recommended, but these potential small benefits of parathyroidectomy must be tempered by the possibility of unmet patient expectations and/or complications from surgery (6, 9, 42, 61). The ultimate balance of the risks and benefits of parathyroidectomy in such patients, however, can be determined only by a larger, longer-term, multicenter study as has been emphasized in a recent follow-up NIH-sponsored workshop on the management of asymptomatic primary hyperparathyroidism (30).

Acknowledgments

We acknowledge the help of former colleagues Drs. H. Bone, M. Kleerekoper, and A. M. Parfitt during the design phase of this study; Dr. M. Honasoge, for her help during recruitment of patients; Dr. M. Lee for interpretation of parathyroid pathology; Ms. Doris Monace for BMD measurements; and Nayana Parikh for PTH and other biochemical markers of bone turnover. We also thank the Study Safety Monitoring Committee: Drs. M. Wisgerhof (Chairman), J. Abrams, M. R. Ansari, G. Brown, and H. Rosman. Finally, we thank Dr. Ron Margolis (National Institute of Diabetes and Digestive and Kidney Diseases) for his continued support during the conduct of the study.

Received January 7, 2004. Accepted July 30, 2004.

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This work was supported by NIH Grant DK 43858.

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