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Surgery or Surveillance for Mild Asymptomatic Primary Hyperparathyroidism: A Prospective, Randomized Clinical Trial

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Context: It is unclear whether patients with asymptomatic primary hyperparathyroidism (PHPT) do better with parathyroidectomy (PTx) as compared with conservative medical management.

Objective: The aim of the study was to evaluate the beneficial effect of PTx *vs.* conservative management in patients with mild asymptomatic PHPT.

Design: We conducted a prospective, randomized study.

Setting: The study took place at a referral center.

Patients: We studied 50 patients who did not meet any guidelines for parathyroid surgery as recommended by the National Institutes of Health Consensus Development Conference on Asymptomatic PHPT.

Intervention: Patients were randomly assigned to PTx or no PTx and were evaluated at 6 months and at 1 yr.

Main Outcome Measures: We compared changes (percentage of basal) of lumbar spine bone mineral density (BMD) between the two groups at 1 yr.

Results: The change in BMD at lumbar spine was greater after PTx ($+4.16 \pm 1.13$ for PTx *vs.* -1.12 ± 0.71 for no PTx; $P = 0.0002$). The change in BMD at the total hip was also significantly greater in the PTx group ($+2.61 \pm 0.71$ for PTx *vs.* -1.88 ± 0.60 for no PTx; $P = 0.0001$). There was no difference in BMD after 1 yr between both groups at the one-third radius site. In comparison with those who did not undergo surgery, the PTx subjects, after 1 yr, showed significant differences in four quality of life measures as determined by the 36-item short form health survey scale: bodily pain ($P = 0.001$), general health ($P = 0.008$), vitality ($P = 0.003$), and mental health ($P = 0.017$).

Conclusions: In patients with mild asymptomatic PHPT, successful PTx is followed by an improvement in BMD and quality of life. Most patients followed without surgery did not show evidence of progression. **(*J Clin Endocrinol Metab* 92: 3114–3121, 2007)**

MOST PATIENTS WITH primary hyperparathyroidism (PHPT) are asymptomatic and discovered incidentally when the serum calcium and PTH levels are elevated (1). In this setting of asymptomatic disease, it is not clear whether parathyroidectomy (PTx) would be beneficial to these patients, even though they do not meet surgical guidelines. Long-term natural history studies indicate that most patients with asymptomatic PHPT do not develop biochemical or densitometric progression or disease-specific complications (2, 3). However, these studies have also pointed out a 25% incidence of progressive disease over a 10-yr period. Based upon these and other observations, in 1990 and again in 2002, a panel of experts set forth guidelines by which patients could be advised to have surgery or be followed conservatively (4, 5).

Despite the guidelines, it is still unclear whether all patients with asymptomatic disease should have PTx (5–7). To address this issue, we planned, in 2001, a prospective randomized study aimed at evaluating the central question: Is PTx in asymptomatic patients who do not meet surgical guidelines associated with beneficial effects compared with comparable patients who do not undergo surgery? During our study, Rao *et al.* (8) reported a measurable benefit of surgery *vs.* no surgery on bone mineral density (BMD), quality of life, and psychological function in patients with mild asymptomatic PHPT. Very recently, Bollerslev *et al.* (9) have shown a decreased quality of life and more psychological symptoms in patients with mild asymptomatic PHPT compared with normal controls but that PTx did not improve these psychological features, although BMD increased. Our results suggest that PTx may be beneficial for patients with mild asymptomatic PHPT.

Subjects and Methods

The diagnosis of PHPT was based on increased ionized (>1.32 mmol/liter) or albumin-corrected serum calcium [>10.2 mg/dl (2.55 mmol/liter)], with increased [>65 pg/ml (65 ng/liter)] or inappropriately normal intact PTH.

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Abbreviations: BMD, Bone mineral density; BSAP, bone-specific alkaline phosphatase; CTX, carboxy-terminal telopeptide of type I collagen; LV, left ventricular; 25-OHD, 25-hydroxyvitamin D; PHPT, primary hyperparathyroidism; PTx, parathyroidectomy; SCL-90R, symptom checklist revised; SF-36, 36-item short form health survey.

Patients who did not meet any of the National Institutes of Health (NIH) criteria for surgery were eligible for the study (4). Because this study was begun before the 2002 Workshop on Asymptomatic PHPT, the older guidelines formed the basis for the inclusion criteria.

Inclusion and exclusion criteria

Inclusion criteria were: 1) asymptomatic PHPT; 2) albumin-corrected serum calcium of less than 1 mg/dl above the upper limit of normal [11.2 mg/dl (2.8 mmol/liter)] on at least three occasions; 3) 24-h urine calcium excretion less than 400 mg (10 mmol); 4) creatinine clearance in the normal range or reduced by no more than 30% compared with age-matched normal people; 5) age- and sex-matched BMD at the distal third of radius more than −2.0 (Z score); and 6) age between 50 and 75 yr.

Exclusion criteria were: 1) symptomatic disease (nephrolithiasis, osteitis fibrosa cystica, prevalent fragility fractures); 2) familial PHPT; 3) menopause for less than 3 yr; 4) diseases or therapies affecting the skeleton; 5) current thyroid disease requiring surgery; and 6) contraindications to surgery and previous neck surgery.

The study was approved by the local institutional review board. Written informed consent was obtained from all patients.

Study design

The primary endpoint was a comparison of changes in lumbar spine BMD after 1 yr between patients randomly assigned to surgery (PTx group) or to no surgery (no-PTx group). Based on a previous pilot study, we expected to see a difference in mean lumbar spine BMD of at lest 5% after 1 yr between the two groups. To detect such a difference with 90% power and a significance of 0.05 using a two-sided *t* test, a minimum of 22 patients was needed in each group. By assuming a dropout rate of 10%, each group was planned to comprise 24 patients. An extension of the study for a second year was also planned.

Between January 2002 and September 2005, 412 consecutive patients with PHPT were referred to the Department of Endocrinology at the University Hospital of Pisa (Fig. 1). Of these individuals, 198 already met the NIH criteria for surgery. Of the 214 potentially eligible patients, 161 were excluded for several reasons, and the remaining 53 were asked to participate in the study. Three patients did not accept the randomization strategy; the remaining 50 (46 women and four men) agreed to be randomized to either the PTx or no-PTx group. Randomization blocks comprised six patients each. If the criteria of the 2002 Workshop on Asymptomatic PHPT were adopted, 29 of the 50 subjects would have met these newer surgical criteria. They were similarly divided between the PTx (n = 13) and the no-PTx (n = 16) groups.

The following indices were measured at baseline and 6-month intervals: serum albumin-corrected and ionized calcium, PTH, 25-hydroxyvitamin D (25-OHD), bone-specific alkaline phosphatase (BSAP), osteocalcin, serum and urinary (first void sample) carboxy-terminal telopeptide of type I collagen (CTX), BMD, and quality of life evaluation, as determined by the 36-item short form health survey (SF-36) psychometric test (10–12). Twenty-four-hour urine for calcium and creatinine clearance, abdominal ultrasound, echocardiography, and psychosocial well-being, as determined by the symptom checklist revised (SCL-90R) test (13, 14), were obtained at baseline and after 1 yr.

Two experienced parathyroid surgeons performed all surgery, using the minimally invasive approach when the abnormal gland was identified by preoperative imaging. Only four of the 24 subjects who underwent surgery required standard neck exploration because of equivocal or negative preoperative imaging studies.

Endpoints of the study

The primary endpoint of the study was a comparison of changes (percentage of basal) of lumbar spine BMD between the two groups at 1-yr follow-up. Secondary endpoints were a comparison of changes at 1 yr of total hip and forearm BMDs, bone markers, echocardiographic indices, and quality of life and psychosocial well-being. Complications of surgery and appearance of NIH criteria for PTx in the no-PTx group were also recorded.

Laboratory methods

Serum calcium, phosphorus, creatinine, and urinary calcium and creatinine clearance were measured using standard methods. Ionized calcium was measured as previously described (15). Serum PTH was measured by IRMA (DiaSorin, Saluggia, Italy), BSAP by immunoenzymatic assay (OCTEIA Ostase BAP; IDS Ltd., Boldon, Tyne and Wear, UK), and serum 25-OHD by RIA (DiaSorin). Serum osteocalcin (N-MID), and serum and urinary CTX were measured by ELISA (Nordic Bioscience Diagnostics A/S, Herlew, Denmark). Normal values are reported in Table 1.

Intraoperative PTH measurements were made using a quick PTH assay performed as previously described (16).

BMD

BMD was measured by dual-energy x-ray absorptiometry (QDR-4500; Hologic Inc., Waltham, MA) at the lumbar spine (L_1–L_4), proximal femur, and nondominant forearm. The technologist performing dual-energy x-ray absorptiometry was blinded to the patient treatment category. BMD was expressed as T scores (difference from the mean BMD value of healthy young people in SD units) or Z scores (age-matched comparison in SD units) The coefficients of variations were 1.1% at

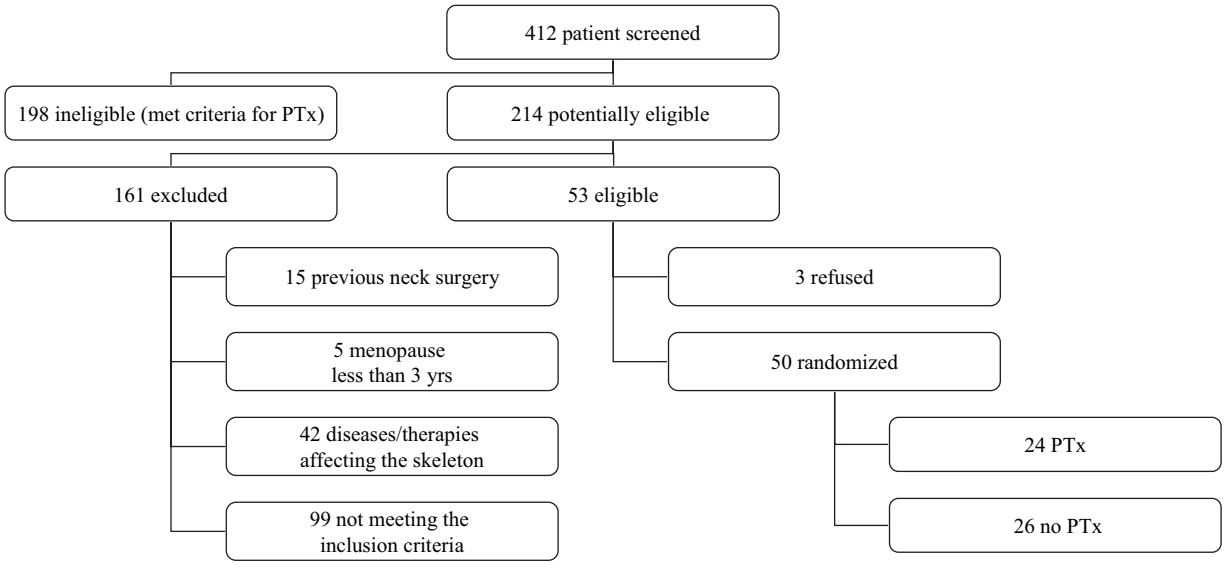

FIG. 1. Flow diagram of patient recruitment and randomization.

TABLE 1. Baseline clinical, biochemical, and densitometric (mean ± SD) data of the 50 patients enrolled in the study

	PTx (n = 24)	No PTx (n = 26)	*P* value	Normal range
Age (yr)	64 ± 6	65 ± 6	0.55	
No. of women/men	22/2	24/2		
Height (cm)	159 ± 6	160 ± 6	0.22	
Weight (kg)	71 ± 13	71 ± 13	0.97	
BMI (kg/m^2)	27 ± 5	28 ± 5	0.49	
No. of hypertensive	14	12	0.41	
Serum calcium (mg/dl)	10.2 ± 0.5	10.2 ± 0.4	0.63	8.2–10.2
Ionized calcium (mg/dl)	5.7 ± 0.2	5.7 ± 0.2	0.98	4.5–5.3
PTH (pg/ml)	109 ± 36	114 ± 48	0.47	15–75
Phosphate (mg/dl)	2.8 ± 0.4	2.8 ± 0.5	0.40	2.7–4.5
Creatinine (mg/dl)	0.7 ± 0.1	0.7 ± 0.2	0.36	0.4–1.2
24-h urinary calcium (mg)	219 ± 65	254 ± 76	0.06	<300
Creatinine clearance (ml/min)	93 ± 21	93 ± 24	0.95	65–125
BASP (μg/liter)	21.0 ± 11.0	21.8 ± 11.7	0.91	♀, 2–28; ♂, 2–15
Osteocalcin (ng/ml)	23.6 ± 12.0	26.5 ± 9.9	0.22	6.8–34
Serum CTX (pmol/liter)	5413 ± 2488	5696 ± 2013	0.49	<4520
Urine CTX (μg/nmol creatinine)	404 ± 256	403 ± 210	0.76	<407
25-OHD (ng/ml)	13.4 ± 6.7	17.5 ± 10.9	0.37	8.9–46.7
Lumbar spine BMD				
g/cm^2	0.85 ± 0.16	0.83 ± 0.12	0.74	
T score	−1.8 ± 1.4	−2.0 ± 1.1	0.72	
Z score	−0.3 ± 1.3	−0.3 ± 1.0	0.91	
Total hip BMD				
g/cm^2	0.80 ± 0.13	0.80 ± 0.11	0.75	
T score	−1.2 ± 1.0	−1.2 ± 0.8	0.81	
Z score	−0.0 ± 0.9	−0.0 ± 0.8	0.77	
Forearm BMD				
g/cm^2	0.60 ± 0.08	0.58 ± 0.08	0.36	
T score	−1.7 ± 1.1	−2.1 ± 1.1	0.29	
Z score	−0.2 ± 0.9	−0.4 ± 1.0	0.35	

BMI, Body mass index.

lumbar spine, 1.2% femoral neck, 1.5% total hip, 2.1% trochanter, and 1.4% distal third of radius.

Echocardiography

Echocardiography was performed using a digitized Philips Sonos 7500 echograph (Philips Medical Systems, Andover, MA) equipped with a broadband sector transducer. Left ventricular (LV) diastolic diameter, LV diastolic volume, LV systolic volume, ejection fraction, ventricular septum thickness, posterior wall thickness, LV mass, and LV mass index were evaluated. LV mass was derived from the Devereux formula (17).

Quality of life and psychosocial well-being

To assess quality of life and psychosocial well-being, patients were asked to fill out the SF-36 (10–12) and SCL-90R (13, 14) questionnaires, respectively. The SF-36 includes eight subscales (physical function, physical role function, bodily pain, general health, vitality, emotional role function, mental health, and social function), which are summed and transformed into a point scale ranging from zero (worst) to 100 (best). The SCL-90R measures mental health status by quantifying psychological disturbances using nine dimensions (somatization, obsessive-compulsive, sensitivity, depression, anxiety, hostility, phobic anxiety, psychoticism, and paranoid ideation). Each dimension includes multiple items, ranging from six to 13. Each item is quantified on a scale from zero (absent) to four (maximum), and the results are expressed as the sum of the scores divided by the number of items included in each dimension.

Data presentation and statistical analyses

The results observed at 6- and 12-month follow-up are reported and presented as mean ± SEM or prevalence, unless otherwise specified. Changes in BMD are expressed as percentage change *vs.* basal. Statistical analyses were performed by paired or unpaired *t* tests and Fisher exact test, as appropriate. ANOVA of repeated measures was used to analyze serial biochemical parameters. The analysis was performed using Statistical Package for the Social Sciences (version 12.01; SPSS, Inc., Chicago, IL). The data were analyzed on an intention-to-treat basis.

Basal scores of quality of life and neuropsychiatric symptoms were compared using unpaired *t* tests. A repeated measures generalized linear model was used to evaluate the follow-up data; "PTx *vs.* no PTx" is a between-subjects variable and the 6- and 12-month values are within-subject variables. In all tests, the level $\alpha = 0.05$ was assumed as a significant level.

Results

Baseline evaluation

Baseline clinical and biochemical characteristics of the study group are reported in Table 1. There was no statistically significant difference in demographic characteristics, biochemical, and densitometric data between PTx or no-PTx patients. The successful matching of subjects was sustained even if males were excluded from the analysis. Thirteen patients of the PTx group and 16 of the no-PTx group were classified as osteoporotic (T score <-2.5 at any site).

Intervention

Surgery was performed within 2 months after randomization. All but one subject had single gland disease and were cured with PTx. The patient not cured showed a decline in the intraoperative PTH level (70%), but at follow-up, serum calcium and PTH were elevated. A contralateral parathyroid tumor was found by imaging studies, and the patient is scheduled for further parathyroid surgery. No patient sustained any surgical complications, such as laryngeal nerve dysfunction.

Follow-up was completed in all patients after 1 yr. No patient was given oral calcium supplements. Blood pressure was stable during follow-up. One patient in the no-PTx group developed chronic myeloid leukemia 4 months after randomization. This patient was included only in the baseline evaluation because of chemotherapy. No clinical manifestation of PHPT occurred during the follow-up in any patient of the PTx group. Conversely, in the no-PTx group, one patient had a kidney stone and one a clinical vertebral fragility fracture. The latter was a 69-yr-old woman with untreated early menopause, and lumbar spine and forearm T scores of −3.1 and −3.2, respectively.

Biochemical data

With the exception of the patient with persistent hypercalcemia, all patients who underwent PTx showed normalization of total and ionized serum calcium, PTH, and 24-h urinary calcium. Mean values of bone markers significantly decreased 2 months after surgery and decreased further during follow-up. 25-OHD significantly increased after PTx. The improvement in 25-OH levels may be due to a reversal of the activated hepatic 24-hydroxylase pathway that is postulated to account at least in part for low levels of 25-OHD in PHPT (18).

In patients followed without PTx, all grouped measurements were stable without significant change during follow-up (Table 2). However, after 1 yr, three patients showed marked hypercalciuria [≥400 mg (10 mmol)], while one showed marked hypercalciuria along with confirmed serum calcium above 11.2 mg/dl (2.8 mmol/liter). Three of these patients had basal 24-h urinary calcium above 300 mg (7.5 mmol), which was associated in two with an increase of serum calcium compared with baseline of 1.0 and 0.7 mg/dl.

BMD

At 1 yr, the percentage change in BMD at the lumbar spine was statistically different between the two groups (+4.16 ± 1.1 for PTx *vs.* −1.12 ± 0.71 for no PTx; $P = 0.0002$), with a difference of 5.3% (Fig. 2). The change in BMD at the total hip was also significantly different between the two groups (+2.61 ± 0.71 for PTx *vs.* −1.88 ± 0.60 for no PTx; $P = 0.0001$), with a difference of 4.5%. On the other hand, there was no difference in change of BMD at the distal third of radius (−0.34 ± 0.59 for PTx *vs.* −0.55 ± 0.53 for no PTx; $P = 0.68$). A significant difference between the two groups was also observed at the femoral neck and trochanter (4.4%, $P = 0.01$; 6.8%, $P = 0.0001$, respectively). One patient in the no-PTx group had forearm Z score at 1 yr less than −2. However, on the whole, with the exception of a small but significant decrease in total hip BMD at 1 yr (−0.015 ± 0.005 g/cm^2; $P = 0.0044$), no significant changes in BMD were observed at any other site in the no-PTx group. Results did not change if males were excluded from the analysis.

To ascertain whether baseline BMD data could affect the changes during follow-up, patients were grouped according to whether they were osteoporotic or not (19). Osteoporotic patients would have been candidates for surgery according to the new 2002 criteria. As shown in Fig. 3, the changes in BMD were also significantly different between the two groups, independent of whether they were initially classified as osteoporotic (lumbar spine: +4.75 ± 2.29 for PTx *vs.* −1.47 ± 1.07 for no PTx, $P = 0.01$; total hip: +1.86 ± 1.06 for PTx *vs.* −2.03 ± 0.84 for no PTx, $P = 0.0079$) or nonosteoporotic (lumbar spine: +3.63 ± 0.77 for PTx *vs.* −0.49 ± 0.82 for no PTx, $P = 0.0018$; total hip: +3.29 ± 0.94 for PTx *vs.* −1.66 ± 0.90 for no PTx, $P = 0.0013$). There was no significant difference in the BMD gains after surgery at the lumbar spine, evaluated either as percentage change or absolute change (g/cm^2) *vs.* baseline, between patients with or without osteoporosis.

Echocardiography

All echocardiographic parameters were within the normal range and did not change during follow-up in either group. No correlation was found between echocardiographic parameters and basal serum calcium and PTH levels.

Quality of life (SF-36) and psychosocial well-being (SCL-90R)

Emotional role function score of the SF-36 questionnaire was significantly lower in the no-PTx group compared with the PTx group at baseline ($P = 0.027$). No difference was found in the remaining SF-36 and SCL-90R domains. A modest but significant beneficial effect on quality of life [bodily pain ($P = 0.001$); general health ($P = 0.008$); vitality ($P = 0.003$); and mental heath ($P = 0.017$)] was observed in patients after PTx compared with those followed without surgery (Fig. 4). No difference was found in the remaining SF-36 and SCL-90R (data not shown) domains. Results did not change if males were excluded from the analysis.

Discussion

PTx is the only cure for PHPT and should be recommended to all patients with classical symptoms or compli-

TABLE 2. Biochemical changes (mean ± SD) in the 26 patients followed without PTx

Variable	Baseline	6 months	1 yr	*P* value
Total serum calcium (mg/dl)	10.2 ± 0.4	10.4 ± 0.3	10.4 ± 0.4	0.09
Ionized calcium (mg/dl)	5.7 ± 0.2	5.7 ± 0.3	5.6 ± 0.2	0.47
PTH (pg/ml)	114 ± 48	137 ± 72	121 ± 55	0.40
BSAP (μg/liter)	21.8 ± 11.7	20.1 ± 8.9	25.6 ± 14.2	0.24
Osteocalcin (ng/ml)	26.5 ± 9.9	24.5 ± 10.6	23.4 ± 9.6	0.48
Serum CTX (pmol/liter)	5696 ± 2013	5823 ± 2130	5444 ± 2712	0.83
Urine CTX (μg/nmol creatinine)	403 ± 210	416 ± 272	527 ± 860	0.74
25-OHD (ng/ml)	17.5 ± 10.9	18.4 ± 9.3	14.5 ± 6.6	0.31
24-h urinary calcium (mg)	254 ± 76		288 ± 123	0.24
Creatinine clearance (ml/min)	93 ± 24		98 ± 3	0.48

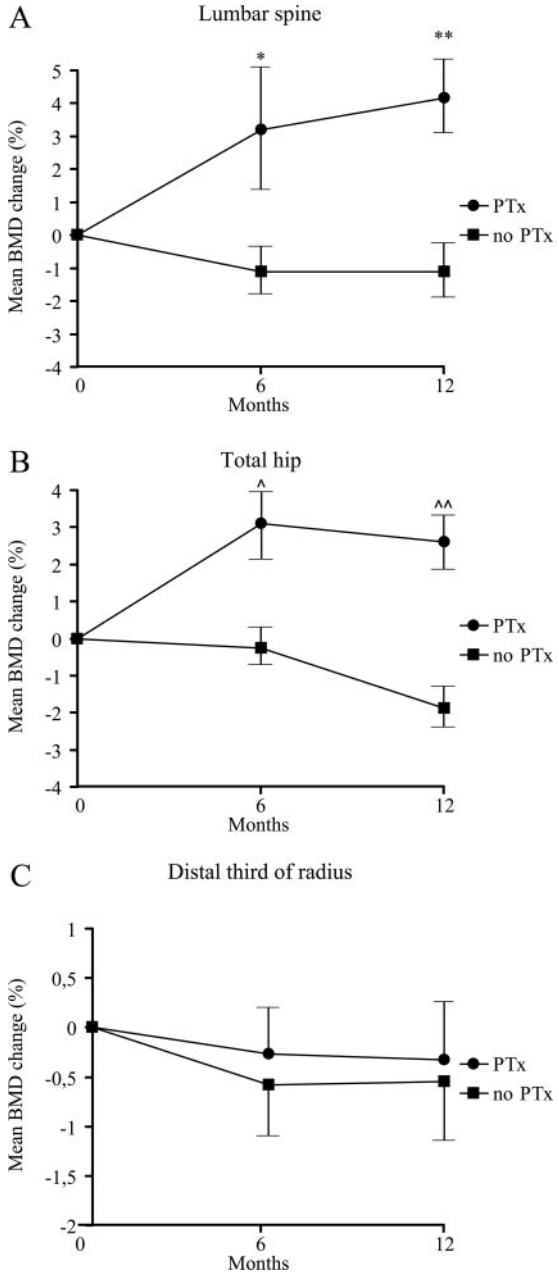

FIG. 2. Mean (±SEM) change [percentage (%) of basal] in lumbar spine (A), total hip (B), and distal third of radius (C) BMD in patients with mild asymptomatic PHPT randomized to PTx or followed without intervention (no PTx) (*, $P = 0.0005$; **, $P = 0.0002$; ^, $P = 0.003$; ^^, $P = 0.0001$). The mean BMD did not differ between the two groups of patients at 6- and 12-month evaluation ($P = 0.66$ and $P = 0.68$, respectively).

cations of the disease. Considerable controversy exists regarding the need of surgery in asymptomatic patients. In 1991, the NIH Consensus Development Conference established guidelines for the management of patients with asymptomatic PHPT (4), which were further revised in 2002 (5). According to these guidelines, approximately 60% of asymptomatic patients fulfill one or more criteria for surgery. The remaining patients can be monitored safely without intervention because untreated mild disease was usually not associated with biochemical or densitometric progression.

When asymptomatic subjects are followed without intervention for a decade, most, but not all, do not show evidence for progression (20). In asymptomatic subject who did meet criteria for surgery, improvement in BMD of the lumbar spine and hip follow. These observations raise an important question: Do patients with mild asymptomatic PHPT, who do not meet criteria for surgery, benefit from PTx? In an attempt to shed light on this central question, we designed the prospective, randomized study reported here. Rao (8) and Bollerslev (9) *et al.* have described measurable benefits of surgery on BMD, and less consistently on quality of life and psychological function in patients with mild asymptomatic PHPT. Our study confirms and extends these observations, providing even greater insights into asymptomatic PHPT.

The increase in BMD after PTx was seen at sites enriched in cancellous bone and occurred primarily during the first 6 postoperative months. The rapid improvement after PTx can be explained by rapid reduction of bone resorption and filling in of the enlarged remodeling space (21). Although the magnitude of changes of BMD is similar to that observed in osteoporotic postmenopausal women, who do not have PHPT, given oral bisphosphonates (22), it is unclear whether a benefit in terms of fracture risk reduction is likely to occur after PTx in PHPT.

In our series the average increase of lumbar spine BMD after PTx is similar to that reported by Bollerslev *et al.* (9), but greater than that observed by Rao *et al.* (8). In concert with both studies, we also found a significant increase of femur BMD. The inclusion in the study of Rao *et al.* (8) of African-American subjects could account for the difference in BMD changes at the lumbar spine. The greater number of male subjects in the reports of Rao (8) and Bollerslev (9) *et al.* could also help to account for the differences in BMD changes. This formulation is consistent with our finding that patients with the lowest T scores (*i.e.* <-2.5) showed the greatest increase in lumbar spine BMD (6.2%) compared with patients whose T scores were more than −2.5 (4.1%). Nevertheless, it should be noted that gains in bone mass were seen in these osteopenic subjects also.

Another area in which our observations are noteworthy is in the postoperative benefits on neuropsychiatric manifestations (8, 9, 23–26). The results of basal SF-36 and SCL-90 questionnaires indicated only a minimal difference when compared with healthy control, nonhyperparathyroid subjects. A modest but significant beneficial effect on quality of life was observed in our patients after PTx compared with those followed without surgery. A similar finding was also reported by Rao *et al.* (8) in social, emotional domains, but, at variance with our data, also in psychological functions. On the other hand, Bollerslev *et al.* (9) did not find any significant benefit of surgery, even though a better score compared with baseline was observed after PTx in role emotional and mental health domains. As discussed by Bollerslev *et al.*, the clinical significance of these changes is unclear. Moreover, a potential placebo effect of surgery cannot be excluded because it is reasonable to believe that patients would be expected to feel better after the operation. The finding of persistent improvement of quality of life even 2 yr after PTx makes a placebo effect of surgery unlikely (25). The true demonstra-

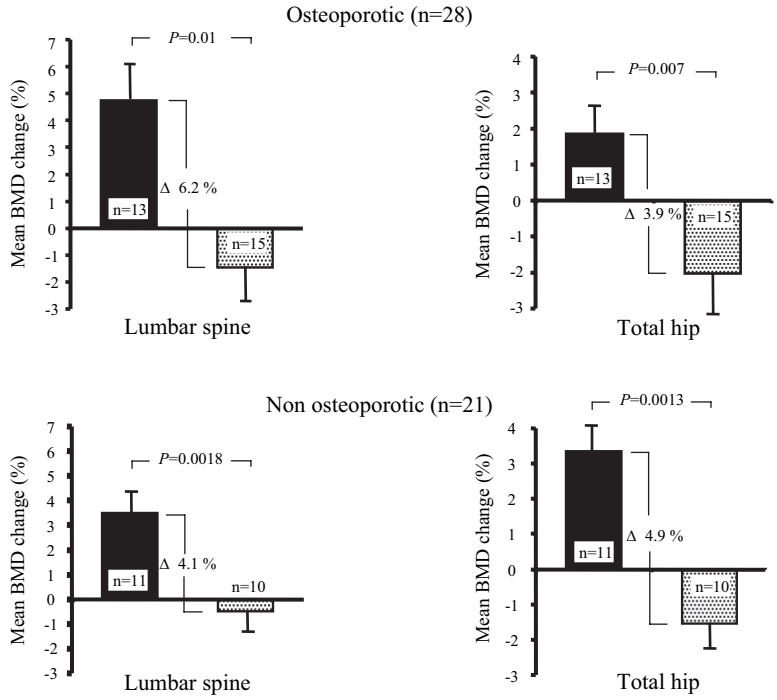

FIG. 3. Mean (±SEM) change [percentage (%) of basal] at 1 yr in lumbar spine and total hip BMD in patients classified at baseline as osteoporotic (*upper panel*) or nonosteoporotic (*lower panel*) randomized to PTx (■) or followed without intervention [no PTx (▨)].

tion that PTx improves quality of life would require a study that was more rigorously controlled.

Echocardiographic evaluation showed no signs of cardiac dysfunction at baseline and no changes during follow-up in both groups. More sophisticated techniques, evaluating endothelial and smooth muscle cell functions, have recently been applied in asymptomatic PHPT patients and should be used to investigate the potential beneficial effects of surgery in these patients (27–29).

After 1 yr, a mild but statistically significant decrease in total hip BMD was observed in the no-PTx group, whereas BMD values remained stable at the other sites. This decline in BMD is well within the least significant change of individual measurements and, thus, would not be clinically apparent during follow-up. At the same time, six of the 26 patients in the no-PTx group developed at least one NIH criterion for surgery, an unexpected finding, considering the short 1-yr follow-up. However, in four patients, the variations consisted only of small changes of serum and urinary calcium, which may merely reflect the general dynamics of these indices in PHPT and not indicate progression of the disease. The woman in the no-PTx group who had a clinical vertebral fracture also had an untreated early menopause, which might have contributed to bone fragility. To what

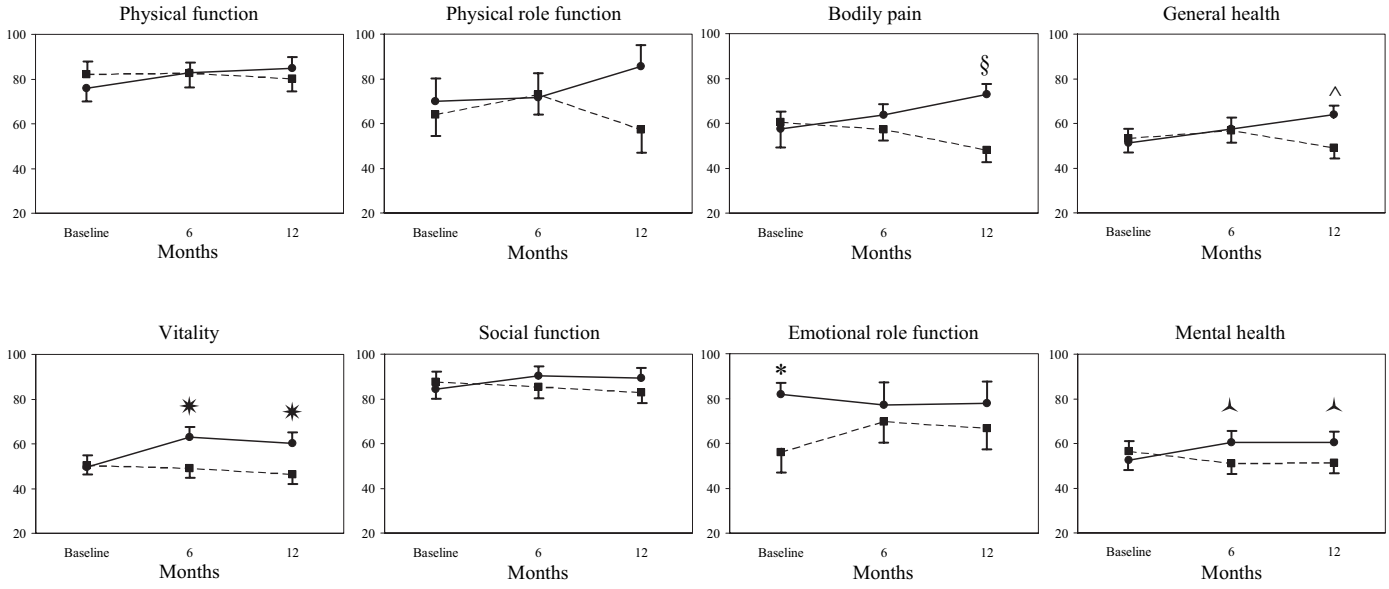

FIG. 4. Changes in SF-36 scores (on a scale 0–100) in patients with mild asymptomatic PHPT randomized to either PTx (*solid line*) or no PTx (*dashed line*). A higher score indicates better quality of life. *, $P = 0.027$. §, $P = 0.001$. ^, $P = 0.008$. ✷, $P = 0.003$. ⅄, $P = 0.017$.

extent the latter findings in patients followed without surgery, and the improvements in BMD and quality of life in patients submitted to PTx are worth the risk of surgery in such apparently healthy subjects remains to be established. In this regard, no complications of PTx were observed in our patients, but all interventions were performed by experienced parathyroid surgeons.

Bisphosphonates have been evaluated in patients with asymptomatic PHPT. BMD changes similar to those observed in our study have been reported in two double-blinded, randomized clinical trials comparing alendronate and placebo in these patients (30, 31). Chow *et al.* (30) found at 1 yr a mean increase of lumbar spine and femoral neck BMDs of 3.8 and 4.2%, respectively, in the alendronate group, which was accompanied by a reduction in the serum calcium by 0.34 mg/dl. However, 6 months after treatment, the BMD increase was maintained only at the femur. Similar BMD changes have been observed by Khan *et al.* (31), but no effect of alendronate on serum calcium was detected. A more targeted approach is the use of calcimimetics. In a multicenter, double-blind, placebo-controlled study, Peacock *et al.* (32, 33) have reported that most patients treated with cinacalcet achieved stable normocalcemia. However, only a modest reduction in PTH concentration and no clinically significant changes in BMD were observed over the 3-yr follow-up. Thus, both alendronate and cinacalcet showed partial effects on disease manifestations. Nevertheless, in asymptomatic PHPT patients who cannot or will not undergo surgery, alendronate could be considered in those with low BMD and cinacalcet in those with normal BMD in view of the possible benefits of lowering serum calcium on neuropsychological and cognitive abnormalities.

The strengths of our study are that: 1) it was a prospective and randomized study, performed in a single institution in which patients were consistently and closely evaluated; 2) the majority of eligible patients (50 out of 53) agreed to participate in the study; and 3) no patient was lost to follow-up, and only one was excluded from longitudinal evaluation. There are also some limitations: 1) the study was only powered to compare the effects of PTx *vs.* no PTx at lumbar spine BMD; 2) the follow-up period was limited to 1 yr, and, therefore, the long-term adverse events (if any) for patients followed without surgery cannot be established; 3) only a small number of men were included, and, therefore, our conclusion may not be applicable to men with PHPT; and 4) the SF-36 and SCL-90R questionnaires were not specifically designed for PHPT patients.

In conclusion, our results indicate that in patients with mild asymptomatic PHPT, successful PTx is followed by an improvement in BMD and in some parameters that reflect quality of life. These observations help to support the view that PTx may be beneficial even in asymptomatic patients who do not meet any criteria for PTx. A rigorous risk/benefit assessment of PTX remains to be established. Balancing this view, to a certain extent, is our other major observation, namely that most patients followed without surgery did not show evidence of progression over 1 yr.

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