Effect of Surgery on Cardiovascular Risk Factors in Mild Primary Hyperparathyroidism

Jens Bollerslev, Thord Rosen, Charlotte L. Mollerup, Jörgen Nordenström, Marek Baranowski, Celina Franco, Ylva Pernow, Gunhild A. Isaksen, Kristin Godang, Thor Ueland, and Svante Jansson on behalf of the SIPH Study Group

Section of Endocrinology (J.B., G.A.I., K.G., T.U.), Department of Medicine, Rikshospitalet, Oslo University Hospital, and University of Oslo, 0027 Oslo, Norway; Department of Endocrinology (T.R., C.F.), Sahlgrenska Hospital, S-41685 Gothenburg, Sweden; Department of Endocrine Surgery (C.L.M.), Copenhagen University Hospital, DK-2100 Rikshospitalet, Denmark; Department of Breast and Endocrine Surgery (J.N.), Karolinska University Hospital, SE-17176 Stockholm, Sweden; Department of Medicine (M.B.), St. Olav's Hospital, University of Trondheim, 7006 Trondheim, Norway; Department of Endocrinology (Y.P.), Karolinska University Hospital, SE-17176 Stockholm, Sweden; Research Institute for Internal Medicine (T.U.), University of Oslo, 0027 Oslo, Norway; and Department of Surgery (S.J.), Sahlgrenska Hospital, S-41685 Gothenburg, Sweden

Context: Mild primary hyperparathyroidism (pHPT) seems to have a good prognosis, and indications for active treatment (surgery) are widely discussed. The extraskeletal effects of PTH, such as insulin resistance, arterial hypertension, and cardiovascular (CV) risk, may however be reversible by operation.

Objective: Our aim was to study biochemical markers of bone turnover, indices of the metabolic syndrome, and various risk markers for CV disease in patients with mild pHPT randomized to observation without surgery or operative treatment and followed for 2 yr.

Design/Setting/Patients: A total of 116 patients (mean age, 63 $\pm$ 8 yr; 19 men and 97 women) who on May 1, 2008, had performed the 2-yr visit in a randomized study on mild pHPT (serum calcium at baseline, 2.69 $\pm$ 0.11 mmol/liter) and where frozen samples were available from baseline and follow-up participated in the study.

Results: Calcium and PTH levels were normalized after surgery, and biochemical markers of bone turnover decreased by 35%, followed by a significant increase in BMD in the spine (2.7%; $P < 0.01$) and femoral neck (1.1%; $P < 0.02$) compared with the observation group. No significant differences were observed between the groups for blood pressure, markers of insulin resistance, detailed cholesterol metabolism, adipokines, or parameters of inflammation and CV surrogate markers.

Conclusions: We observed expected effects on biochemical markers of bone turnover and bone mass after surgical treatment of mild pHPT, with stable values in the group randomized to observation. For a variety of measures of the metabolic syndrome, adipokines, and CV risk factors, no benefit of operative treatment could be demonstrated. Neither did we observe any deleterious effects of conservative management in the 2-yr perspective. **(*J Clin Endocrinol Metab* 94: 2255–2261, 2009)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-2742 Received December 16, 2008. Accepted March 30, 2009.
First Published Online April 7, 2009

Abbreviations: Apo, Apolipoprotein; BMD, bone mineral density; BMI, body mass index; Chol, cholesterol; CRP, C-reactive protein; CTX-1, C-terminal telopeptides of type I collagen; CV, cardiovascular; EIA, enzyme immunoassay; HDL, high-density lipoprotein; HOMA-B, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; MAP, mean arterial pressure; Nt-ProBNP, N-terminal pro B-type natriuretic peptide; 25(OH)Vit D, 25-hydroxyvitamin D; OPG, osteoprotegerin; pHPT, primary hyperparathyroidism; VCAM-1, vascular cell adhesion molecule 1; vWF, Von Willebrand factor.

In alignment with the marked change in incidence of primary hyperparathyroidism (pHPT) (1, 2), the clinical picture has altered, and few patients will present disease-specific symptoms when diagnosed in today's clinic (3). The so-called mild form of pHPT (3, 4) seems to have a good prognosis, and indications for active treatment (surgery) are widely discussed (4). The prevalence is higher than 2% in postmenopausal Scandinavian women (5). Unexpectedly, in these women identified through a screening program, the percentage of sick leave in a period of 5 yr before screening was markedly increased compared with normoparathyroid women from the same cohort (5). One of the most important reasons for the sick leave was cardiovascular (CV) morbidity. However, among late premenopausal women, the prevalence of the disease seems to be even higher (6), with lower scores for vitality and general health and increased mass index (BMI). Increased BMI was recently identified as a major contributor to the extraskeletal manifestations of pHPT (7).

Increased calcium levels *per se* have in case-control studies been related to increased CV mortality (8). In patients with manifest pHPT, CV morbidity and mortality were increased before operative treatment, with a normalization of risk of myocardial infarction after surgery (9, 10). However, the most recent series contributing to this case-control study found no association between mild pHPT and overall mortality (9). In accordance and indicating that patients with mild pHPT might not have increased overall mortality, a study of Rochester, Minnesota, residents showed no increase in mortality, rather a lower mortality rate (2). However, a higher maximal calcium level was an independent predictor of death.

Whereas surgery seems to improve some aspects of CV dysfunction in pHPT with higher calcium levels (11–13), controlled data for mild disease are lacking, as reviewed recently (14). Increased lipids and other proatherogenic factors have been found in mild or asymptomatic pHPT, with a likely effect of surgery (15, 16). Recently, different markers of inflammation and N-terminal pro B-type natriuretic peptide (Nt-ProBNP), an independent risk factor for heart failure and acute coronary syndrome (17, 18), were found to be increased in patients with mild pHPT, with no improvements after parathyroidectomy (19). Furthermore, arterial stiffness was increased and correlated to disease activity (PTH levels) in mild pHPT (20). However, longitudinal data are lacking, and it is an open question whether surgical treatment of mild pHPT will improve CV profile (14). On the other hand, an 18-month follow-up study of patients with mild disease found no progression in different markers of glucose and insulin metabolism (21).

The Scandinavian Study on Primary Hyperparathyroidism (SIPH) is a prospective, randomized trial based on the 1990 NIH Consensus Conference criteria for diagnosis and treatment (22), investigating the effect of operation *vs.* observation without surgery on morbidity and quality of life in mild pHPT. The first data from the cohort at the end of inclusion time point have been published (23). The aim of the present study was to investigate biochemical markers of bone turnover, indices of the metabolic syndrome, and various risk factors for CV disease in patients with mild pHPT, randomized to observation without surgery or operative treatment and followed for 2 yr.

Subjects and Methods

Subjects

The SIPH Study (ClinicalTrials.gov: NCT00522028) included a total of 191 patients (26 males) in the period 1999 to June 2005 (23). Patients were randomized to surgery (n = 96) or observation without operation (n = 95). From this cohort, 116 patients representing five centers from the three Scandinavian countries participated in the present study. This population includes all patients who on May 1, 2008, had performed the yr 2 visit and for whom frozen samples were available from the baseline visit as well as the follow-up (Table 1). The study design has been described in detail elsewhere (23). The study was approved by the local ethical committees in the respective countries and conducted according to the Declaration of Helsinki II.

Bone mineral density (BMD)

Areal BMD at the lumbar spine and femoral neck was measured by dual-energy x-ray absorptiometry. Most centers used DPX-L software (version 4.6c; Lunar Corp., Madison, WI). The center in Trondheim used

TABLE 1. Baseline demographics in 116 patients with mild pHPT randomized to observation *vs.* surgery

	Reference interval	Observation (n = 62)	Surgery (n = 54)
Age (yr)		63 ± 7	63 ± 8
Gender (no. of males)		9	10
BMI (kg/m^2)	20–25	27 ± 4	27 ± 4
S-PTH (pmol/liter)	1.6–6.9	10.5 ± 4.5	10.1 ± 4.0
S-Alb-sCa (g/liter)	2.15–2.51	2.68 ± 0.11	2.70 ± 0.11
P-Glucose (mmol/liter)	4.0–6.0	5.6 ± 1.7	5.7 ± 1.5
P-Insulin (pmol/liter)	21–210	66 ± 55	91 ± 139
S-Total Chol (mmol/liter)	3.9–7.8	5.9 ± 1.1	5.8 ± 1.3
MAP (mm Hg)		102 ± 13	104 ± 11
S-CRP (mg/liter)	<4	2.1 ± 2.5	2.7 ± 3.1
S-25(OH)Vit D (nmol/liter)	37–131	46 ± 15	41 ± 15
S-Osteocalcin (ng/ml)	5–25	8.9 ± 8.3	7.8 ± 7.6
S-CTX-1 (ng/ml)	0.12–1.35	0.57 ± 0.31	0.55 ± 0.34
LS BMD (g/cm^2)		1.074 ± 0.204	1.098 ± 0.195
FN BMD (g/cm^2)		0.834 ± 0.134	0.846 ± 0.124

Data are given as mean ± SEM. S-, Serum; P-, plasma; LS, lumbar spine; FN, femoral neck; Alb-sCa, albumin-corrected calcium.

Hologic QDR-4500 (Hologic, Waltham, MA) in dual-beam mode, and the center in Copenhagen used Norland XR 46 system 8091 (Norland Corp., Fort Atkinson, WI). BMD values were normalized as described (24).

Serum measurements

Serum calcium, albumin, creatinine, and intact PTH (1-84) were measured by standard laboratory methods at the local laboratories as previously described, and the calcium value was corrected for variation in albumin levels (23). In addition, at each visit blood samples were drawn after an overnight fast into pyrogen-free vacuum blood collection tubes without additives, allowed to coagulate, and were centrifuged (1000 × *g* at 4 C for 15 min), and serum was stored at −80 C in multiple aliquots until analyzed. All analyses for a given biochemical marker were analyzed in the same run, with paired samples run on the same immunoplate. Total cholesterol (Chol), high-density lipoprotein (HDL)-Chol, low-density lipoprotein-Chol, apolipoprotein (Apo) A-1, Apo B, and high-sensitivity C-reactive protein (CRP) assays were performed by accredited laboratories according to standard laboratory methods (Department of Medical Biochemistry, Rikshospitalet, Oslo University Hospital, Oslo) (25). Nt-proBNP was determined by an electrochemiluminescence immunoassay on a Modular platform (Roche Diagnostics, Basel, Switzerland). The bone formation marker osteocalcin was measured by immunoradiometric assay (Incstar Corporation, Stillwater, MI). Degradation products of the C-terminal telopeptides of type I collagen (CTX-1) were measured in serum by enzyme immunoassay (EIA) (Serum Crosslaps; Nordic Bioscience Diagnostics A/S, Herlev, Denmark). Serum glucose was measured by standard laboratory methods, and serum insulin was assayed by RIA (Diagnostic Products Corporation, Los Angeles, CA). Serum leptin and adiponectin, osteoprotegerin (OPG), and vascular cell adhesion molecule 1 (VCAM-1) were analyzed by EIA with matched antibodies from R&D Systems (Minneapolis, MN), according to the manufacturer's instructions. IL-1Ra was analyzed by EIA (Biosource, Camarillo, CA). Von Willebrand factor (vWF) was analyzed as previously described with antibodies from Dako Cytomation (Oslo, Norway), (25). Serum 25-hydroxyvitamin D [25(OH)Vit D] was measured using an RIA from Diasorin (Stillwater, MN) after a rapid extraction of 25(OH)Vit D and other hydroxylated metabolites from serum with acetonitrile. The International Vitamin D Quality Assessment Scheme concluded that this specific assay is accurate and reliable. All coefficients of variation were less than 10%.

Insulin sensitivity and resistance

Calculations were performed based on fasting glucose and insulin levels. The homeostatic model assessments of β-cell function (HOMA-B) and insulin resistance index (HOMA-IR) were calculated using the HOMA2 calculator (www.dtu.ox.ac.uk/homa).

Statistics

For analyzing treatment effects on paired data, univariate repeated-measures ANOVA were performed *a priori*, with time as fixed factors and subjects as random. Data not normally distributed at baseline as evaluated by the Kolmogorov-Smirnov test were logarithmically transformed before inclusion in the general linear model but are presented untransformed. Data are given as mean ± SEM unless otherwise stated. *P* values are two-sided and considered significant when <0.05.

Results

Demographics

Baseline data for the patient population are given in Table 1. As seen, data were present from 62 patients randomized to observation and 54 patients from the surgery arm. No significant differences between the groups were identified in demographics, biochemistry, or bone mass at study entry. As given, the calcium level was only mildly elevated. BMD in the two compartments, expressed as Z-scores of normative data, were not different from zero in any of the groups at baseline (data not shown).

Calcium, PTH, vitamin D, and bone mass

As expected, serum PTH was negatively correlated to 25(OH) Vit D at baseline ($r = -0.21$; $P < 0.03$). The longitudinal data on albumin-corrected serum Ca and PTH are given in Fig. 1A. Only minor changes were observed in the observation group, whereas parathyroidectomy was followed by normalization of both parameters, as expected. Significant differences in change in bone mass (δ values) were observed between the groups in the observation period. As outlined in Fig. 1B, BMD increased sig-

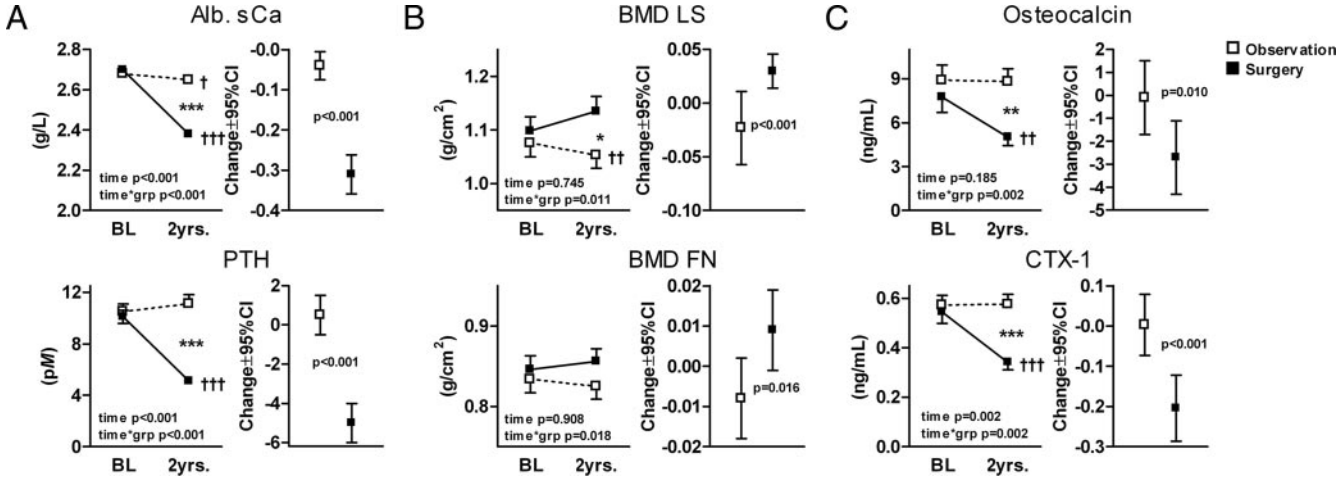

FIG. 1. Calcium and bone metabolism at baseline and during 2 yr of follow-up in 116 patients with mild pHPT randomized to observation without operation or surgical treatment. A, Changes in albumin-corrected calcium (Alb. sCA) and PTH levels. B, Changes in BMD (*left*) of the lumbar spine (*top*) and femoral neck (*bottom*). C, Biochemical markers of bone turnover (*left*). *P* value for time gives the level of significance for both groups in relation to time (ANOVA). Time*group gives the results of the effect of time and group (ANOVA). When significant, δ values were calculated (*right panels*). Data are given as mean ± SEM. BL, Baseline; LS, lumbar spine; FN, femoral neck. *Daggers* denote significance level within groups: †, $P < 0.05$; ††, $P < 0.01$; †††, $P < 0.01$. *Asterisks* denote significance level between groups: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.01$.

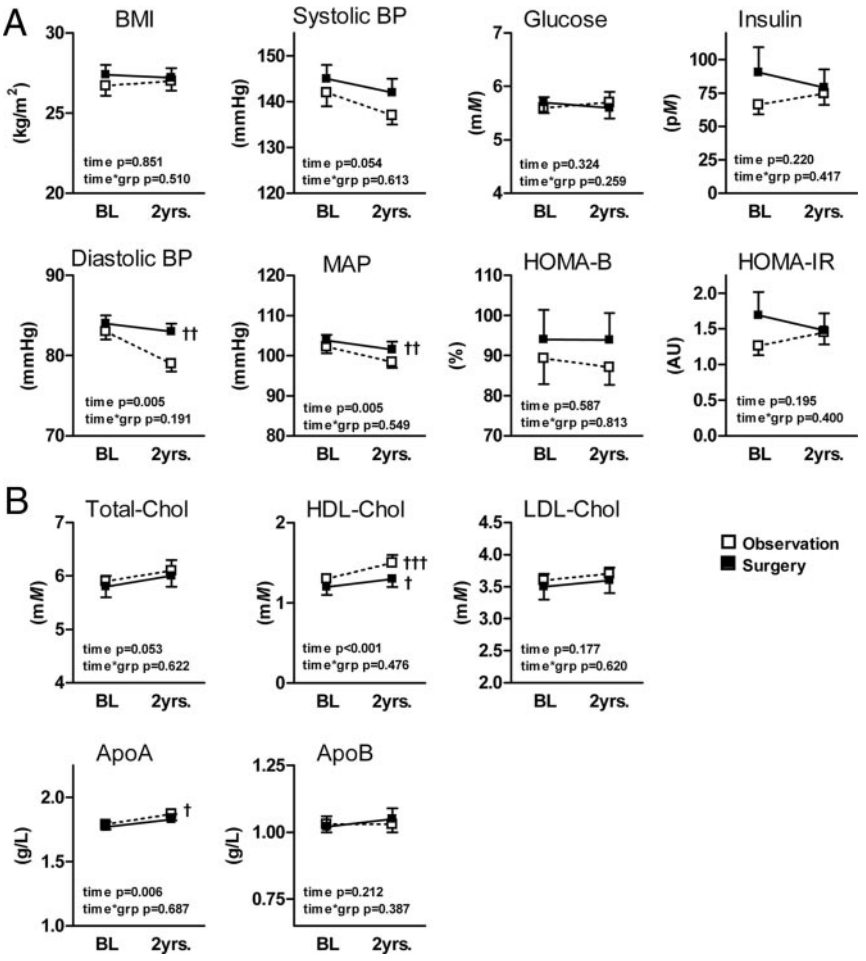

FIG. 2. Metabolic parameters at baseline and during 2 yr of follow-up in 116 patients with mild pHPT randomized to observation without operation or surgical treatment. A, Metabolic parameters. B, Cholesterol parameters. *P* value for time gives the level of significance for both groups in relation to time (ANOVA). Time*group gives the results of the effect of time and group (ANOVA). Data are given as mean ± SEM. BL, Baseline; BP, blood pressure. *Daggers* denote significance level within groups: †, $P < 0.05$; ††, $P < 0.01$; †††, $P < 0.01$. *Asterisks* denote significance level between groups: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.01$.

nificantly for both compartments in the surgery group compared with observation, due to significant declines in biochemical markers of bone turnover (Fig. 1C). Whereas BMD decreased in lumbar spine by 0.023 g/cm^2 and in femoral neck by 0.008 g/cm^2 in the observation group, the corresponding figures for the surgical arm were a gain of 0.030 g/cm^2 ($P < 0.001$) and 0.009 g/cm^2 ($P < 0.016$), respectively. The biochemical markers of bone turnover were stable in the observation group. After surgery, serum osteocalcin decreased by 35% ($P = 0.01$ for difference between the groups) and serum CTX-1 decreased by 37% ($P < 0.001$ for difference between the groups).

Metabolic parameters

No significant changes in BMI, glucose, insulin, or derivates of glucose/insulin levels (HOMA-B, HOMA-IR) were observed during the observation period. Neither could any effect of surgery on these parameters be demonstrated (Fig. 2). Evaluated as one group, significant declines were observed for mean arterial pressure (MAP) and diastolic blood pressure ($P < 0.005$ for both), without a difference between the groups (Fig. 2A). Cholesterol metabolism is given in Fig. 2B. During the observation period, significant increases were observed in the total population for serum levels of total Chol, HDL-Chol, and Apo A, with no differences between the groups.

Adipokines, inflammation, and cytokines

As given in Fig. 3A, serum adiponectin increased significantly during the observation period for both groups (~15%; $P < 0.019$); however, there was no difference between the groups. Serum levels of neither leptin nor IL1-Ra changed during the 2 yr of observation and were not influenced by surgery. As seen in Fig. 3B, high sensitivity CRP did not change in the observation period, nor was any difference between groups observed. The biochemical markers of endothelial function vWF and VCAM were unaltered in the observation period and without difference between the two treatment arms, as also seen for OPG. However, Nt-proBNP increased significantly during the period ($P < 0.005$) with a moderately different temporal pattern in the two groups ($P = 0.038$) as assessed by ANOVA. However, this was mainly due to differences at baseline because no differences were seen when comparing the degree of change ($P = 0.780$).

The risk of type 2 error for metabolic parameters

The differences between the groups for metabolic parameters were basically negative. However, as can be seen in Table 2, *a priori* and *post hoc* power calculations suggest that the study has power to detect clinically relevant differences for all negative findings.

Discussion

The present study of patients with mild pHPT, followed for 2 yr after randomization to observation or surgical treatment, demonstrated significant differences with respect to bone mass and biochemical markers of bone turnover between the groups. Whereas BMD and bone markers were stable in the observation group, a significant gain in bone mass was seen after surgery, presumably due to closure of the remodeling space (26, 27) because significant decreases were seen in biochemical markers of bone turnover. For markers of the metabolic syndrome, including cholesterol, inflammatory markers, and CV risk markers, we did not observe any differences between the two arms and could thus not demonstrate benefit of surgical treatment in this respect, for this period of time.

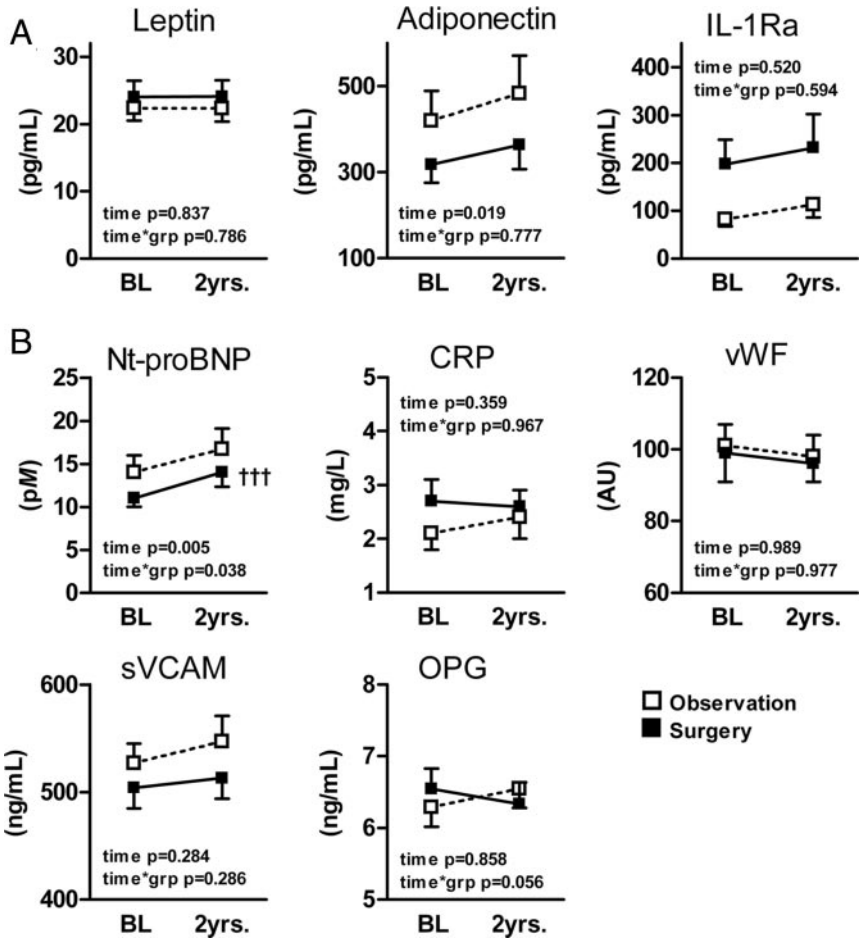

FIG. 3. Adipokines, markers of inflammation and cytokines at baseline and during 2 yr of follow-up in 116 patients with mild pHPT randomized to observation without operation or surgical treatment. A, Adipokines. B, Markers of inflammation and cytokines. *P* value for time gives the level of significance for both groups in relation to time (ANOVA). Time*group gives the results of the effect of time and group (ANOVA). Data are given as mean ± SEM. BL, Baseline. *Daggers* denote significance level within groups: †, $P < 0.05$; ††, $P < 0.01$; †††, $P < 0.01$. *Asterisks* denote significance level between groups: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.01$.

Bone mass is significantly decreased in pHPT due to increased bone resorption at the endosteal surface (28, 29) leading to cortical bone loss, also seen in mild pHPT (30–32). At the trabecular surface, however, bone mass is preserved and may even be improved (26, 28, 33, 34). At the time of inclusion, our patient population had normal bone mass as indicated by Z-scores (23). In this study, we demonstrate a decline in bone turnover markers of about 35% after surgery, leading to an increase in bone mass of 2.7% for lumbar spine and 1.1% for the femoral neck and corroborating the reversibility of the bone loss in pHPT. The latter compartment is critical because the femoral neck region consists of relatively more cortical bone than the lumbar spine. Long-term studies of patients with mild pHPT have not demonstrated significant gain of cortical bone mass after surgery (35–37), whereas cortical bone mass seems to be stable also without surgery. With prolonged observation, a recent study showed significant bone loss after more than 10 yr in mainly cortical compartments, however, based on very few observations and with methodological concerns (38). Only well-designed, long-term prospective studies can reveal whether the ultimate endpoint, fracture frequency, will be improved by active treatment of mild pHPT (4).

Vitamin D levels at baseline were relatively normal in our population, as indicated in Table 1 with the expected relation to PTH levels. Only 8.5% of our patients had 25(OH)Vit D deficiency with levels less than 25 nmol/liter; however, 69% were in the range of insufficiency (39). These figures seem to be lower than data from a recent cross-sectional study of mild pHPT from Denmark and at the level of their age- and sex-matched controls (20 and 60%, respectively) (40). Vitamin D levels in patients with mild pHPT vary geographically (41) and are of importance because low levels can mask calcium level. Although low vitamin D levels in mild pHPT were not associated with adenoma weight (40), there was an association between 25(OH)Vit D and disease activity, including measures of bone mass (40). Moreover, vitamin D deficiency may be associated with mood and neuropsychological function (42).

The various measures of extra skeletal manifestations of pHPT, including a panel of CV risk factors, did not differ significantly between the two arms in the present study. These results are in alignment with some (19, 21) but not all (15, 16) metabolic studies. Concerning cholesterol metabolism, the present study is more extensive than previous studies, and so far it is the only study based on a randomized population. The claimed benefit of surgical treatment on cholesterol metabolism from the Swedish studies (15, 16) might be questioned because no comparisons were performed on changes over time between patients and controls, and moreover, no matched group of nonoperated patients was investigated. In accordance, the recent Danish study of patients with mild pHPT followed for up to 18 months after parathyroidectomy did not reveal any benefit of operation on a variety of markers of the metabolic syndrome, inflammation markers, or echocardiography (19). They did, however, demonstrate a significant improvement in maximal workload but not in maximal oxygen uptake during bicycling exercise test. In a recent small study, biochemical markers of endothelial dysfunction including vWF, a conventional marker of endothelial cell activation also measured in our study, were increased only in patients with pHPT and established classical CV risk factors, not in patients without (43). Furthermore, vWF decreased after surgery only in the group with increased classical factors. Because increased BMI and insulin resistance are associated with pHPT (7, 10, 21), increased levels of adipokines have recently been demonstrated in pHPT (44). The question remains whether these surrogate markers of CV risk are reversible by surgical treatment, and thereby, whether the in-

TABLE 2. Power calculations for metabolic parameters

	SD at baseline	Difference (power to detect *a priori*)[a]	Difference in means between groups (*post hoc*)[b]	Difference (power to detect *post hoc*)[c]	Observed difference
BMI (kg/m^2)	4.3	2.2	1.3/1.8	0.8	0.2
SBP (mm Hg)	20.0	10	18.2/18.2	9.6	1.9
DBP (mm Hg)	8.8	4.2	9.4/9.2	4.9	2.4
MAP (mm Hg)	11.6	6.0	11.0/12.6	6.2	1.3
Glucose (mmol/liter)	1.64	0.85	0.87/1.20	0.55	0.19
Insulin (pmol/liter)	103	53	71/147	59	20
HOMA-B (%)	52	27	52/60	29	2
HOMA-IR (AU)	1.82	0.94	1.36/2.47	1.02	0.40
Total Chol (mmol/liter)	1.20	0.62	1.00/0.96	0.52	0.03
HDL-Chol (mmol/liter)	0.38	0.20	0.32/0.27	0.16	0.01
LDL-Chol (mmol/liter)	1.06	0.55	0.79/0.86	0.43	0.08
Apo A (g/liter)	0.32	0.17	0.28/0.24	0.14	0.03
Apo B (g/liter)	0.27	0.14	0.18/0.21	0.10	0.03
Leptin (pg/ml)	16	8	9/11	5	0
Adiponectin (pg/ml)	1976	1020	810/1051	524	78
IL-1 Ra (pg/ml)	860	444	160/469	179	2
Nt-ProBNP (pmol/liter)	13.3	6.9	11.7/7.5	5.3	0.7
CRP (mg/liter)	2.77	1.43	3.37/2.74	1.63	0.39
vWF (AU)	54	28	38/58	25	2
VCAM (ng/ml)	141	73	111/81	52	11
OPG (ng/ml)	2050	1058	1258/1255	662	470

$\alpha = 0.05$ and $\beta = 0.80$. SBP, Systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein.

[a] Based on 60 patients in each group and the observed SD at baseline, the column gives the difference to be detected with the α and β given.

[b] Difference in means to be detected based on SD observed in the changes within groups (*post hoc*).

[c] The study has power to detect a difference in means between groups.

creased CV morbidity and mortality indicated by epidemiological studies (9, 10) could be improved by active treatment. Our present study does not give support for improvements of these markers in mild pHPT in a 2-yr perspective.

To our knowledge, no ongoing prospective, randomized studies are powered to give data on hard CV endpoints in mild pHPT. Therefore, surrogate markers are used to evaluate CV risk. The relevance is of course questionable. Power calculations, as presented in Table 2 in the present study, revealed that overlooking a type 2 error was negligible. Moreover, the observed differences in metabolic parameters were minor and below the level of clinical relevance. Another limitation of the present study is potential selection bias. Patients included in randomized trials may be healthier than the general patient, potentially indicated by the 25(OH)Vit D level in the present study. Moreover, we had a rather high dropout rate in the beginning of the study of patients randomized to surgery (23).

In conclusion, the present study shows the expected effects on biochemical markers of bone turnover and bone mass after surgical treatment of mild pHPT, with stable values in the group randomized to observation without surgery. For a variety of measures of the metabolic syndrome, adipokines, and CV risk factors, no benefit of operative treatment could be demonstrated. Neither did we observe any deleterious effects of conservative management in a 2-yr perspective.

SIPH study group

The SIPH Study Group was established in 1994. Besides the authors of this paper, the following have contributed significantly to the project: Ewa Lundgren, M.D., Ph.D.; Göran Åkerström, M.D., Ph.D.; and Sverker Ljunghall, M.D., Ph.D., Akademiska Sjukhuset, Uppsala, Sweden; Ove Tørring, M.D., Ph.D., and Lars Ove Farnebo, M.D., Ph.D., Karolinska Institute, Stockholm, Sweden; Leif Mosekilde, M.D., Ph.D., Århus University Hospital, Århus, Denmark; Jan Falch, M.D., Ph.D., and Per Pfeffer, M.D., Ph.D., Oslo University Hospital, Oslo, Norway; and Jan-Erik Varhaug, M.D., Ph.D., and Sylvi Aanderud, M.D., Ph.D., Haugeland University Hospital, Bergen, Norway.

Acknowledgments

Catharina Sjöberg (Karolinska University Hospital, Stockholm) and Annica Alklind (Sahlgrenska Hospital, Gothenburg, Sweden) are thanked for technical assistance.

Address all correspondence and requests for reprints to: Jens Bollerslev, M.D., DMSc, Section of Endocrinology, Rikshospitalet, Oslo University Hospital, University of Oslo, N-0027 Oslo, Norway. E-mail: jens.bollerslev@medisine.uio.no.

This work received support from The Norwegian Research Council and unrestricted research grants from Biovitrum and Novo Nordisk AS Norway.

Disclosure Summary: The authors have nothing individually to declare for this study.

References

1. **Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, Melton 3rd LJ** 2006 Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. J Bone Miner Res 21:171–177

2. **Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, O'Fallon WM, Melton 3rd LJ** 1998 Survival after the diagnosis of hyperparathyroidism: a population-based study. Am J Med 104:115–122
3. **Silverberg SJ, Bilezikian JP** 2006 The diagnosis and management of asymptomatic primary hyperparathyroidism. Nat Clin Pract Endocrinol Metab 2:494–503
4. **Bilezikian JP, Potts Jr JT, Fuleihan Gel-H, Kleerekoper M, Neer R, Peacock M, Rastad J, Silverberg SJ, Udelsman R, Wells SA** 2002 Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 87:5353–5361
5. **Lundgren E, Szabo E, Ljunghall S, Bergström R, Holmberg L, Rastad J** 1998 Population based case-control study of sick leave in postmenopausal women before diagnosis of hyperparathyroidism. BMJ 317:848–851
6. **Siilin H, Rastad J, Ljunggren O, Lundgren E** 2008 Disturbances of calcium homeostasis consistent with mild primary hyperparathyroidism in premenopausal women and associated morbidity. J Clin Endocrinol Metab 93:47–53
7. **Bolland MJ, Grey AB, Gamble GD, Reid IR** 2005 Association between primary hyperparathyroidism and increased body weight: a meta-analysis. J Clin Endocrinol Metab 90:1525–1530
8. **Leifsson BG, Ahrén B** 1996 Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab 81:2149–2153
9. **Vestergaard P, Mollerup CL, Frøkjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L** 2003 Cardiovascular events before and after surgery for primary hyperparathyroidism. World J Surg 27:216–222
10. **Vestergaard P, Mosekilde L** 2003 Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. BMJ 327:530–534
11. **Nilsson IL, Aberg J, Rastad J, Lind L** 2005 Maintained normalization of cardiovascular dysfunction 5 years after parathyroidectomy in primary hyperparathyroidism. Surgery 137:632–638
12. **Lakatos P, Tátrai A, Földes J, Horváth C, Makó J, Stern PH** 1996 Endothelin concentrations are elevated in plasma of patients with primary and secondary hyperparathyroidism. Calcif Tissue Int 58:70–71
13. **Nilsson IL, Aberg J, Rastad J, Lind L** 1999 Endothelial vasodilatory dysfunction in primary hyperparathyroidism is reversed after parathyroidectomy. Surgery 126:1049–1055
14. **Fitzpatrick LA, Bilezikian JP, Silverberg SJ** 2008 Parathyroid hormone and the cardiovascular system. Curr Osteoporos Rep 6:77–83
15. **Hagstrom E, Lundgren E, Lithell H, Berglund L, Ljunghall S, Hellman P, Rastad J** 2002 Normalized dyslipidaemia after parathyroidectomy in mild primary hyperparathyroidism: population-based study over five years. Clin Endocrinol (Oxf) 56:253–260
16. **Hagström E, Lundgren E, Rastad J, Hellman P** 2006 Metabolic abnormalities in patients with normocalcemic hyperparathyroidism detected at a population-based screening. Eur J Endocrinol 155:33–39
17. **Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA** 2003 N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. Eur Heart J 24:1735–1743
18. **Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, Vasan RS** 2004 Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 350:655–663
19. **Ogard CG, Engelmann MD, Kistorp C, Nielsen SL, Vestergaard H** 2005 Increased plasma N-terminal pro-B-type natriuretic peptide and markers of inflammation related to atherosclerosis in patients with primary hyperparathyroidism. Clin Endocrinol (Oxf) 63:493–498
20. **Rubin MR, Maurer MS, McMahon DJ, Bilezikian JP, Silverberg SJ** 2005 Arterial stiffness in mild primary hyperparathyroidism. J Clin Endocrinol Metab 90:3326–3330
21. **Ayturk S, Gursoy A, Bascil Tutuncu N, Ertugrul DT, Guvener Demirag N** 2006 Changes in insulin sensitivity and glucose and bone metabolism over time in patients with asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab 91:4260–4263
22. 1991 NIH Conference. Diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. Ann Intern Med 114:593–597
23. **Bollerslev J, Jansson S, Mollerup CL, Nordenström J, Lundgren E, Tørring O, Varhaug JE, Baranowski M, Aanderud S, Franco C, Freyschuss B, Isaksen GA, Ueland T, Rosen T** 2007 Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. J Clin Endocrinol Metab 92:1687–1692
24. **Genant HK, Grampp S, Glüer CC, Faulkner KG, Jergas M, Engelke K, Hagiwara S, Van Kuijk C** 1994 Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. J Bone Miner Res 9:1503–1514
25. **Bollerslev J, Ueland T, Jørgensen AP, Fougner KJ, Wergeland R, Schreiner T, Burman P** 2006 Positive effects of a physiological dose of GH on markers of atherogenesis: a placebo-controlled study in patients with adult-onset GH deficiency. Eur J Endocrinol 154:537–543
26. **Eriksen EF, Mosekilde L, Melsen F** 1986 Trabecular bone remodeling and balance in primary hyperparathyroidism. Bone 7:213–221
27. **Mosekilde L** 2008 Primary hyperparathyroidism and the skeleton. Clin Endocrinol (Oxf) 69:1–19
28. **Christiansen P, Steiniche T, Vesterby A, Mosekilde L, Hessov I, Melsen F** 1992 Primary hyperparathyroidism: iliac crest trabecular bone volume, structure, remodeling, and balance evaluated by histomorphometric methods. Bone 13:41–49
29. **van Doorn L, Lips P, Netelenbos JC, Hackeng WH** 1993 Bone histomorphometry and serum concentrations of intact parathyroid hormone (PTH(1–84)) in patients with primary hyperparathyroidism. Bone Miner 23:233–242
30. **Charopoulos I, Tournis S, Trovas G, Raptou P, Kaldrymides P, Skarandavos G, Katsalira K, Lyritis GP** 2006 Effect of primary hyperparathyroidism on volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in postmenopausal women. J Clin Endocrinol Metab 91:1748–1753
31. **Christiansen P, Steiniche T, Brixen K, Hessov I, Melsen F, Heickendorff L, Mosekilde L** 1999 Primary hyperparathyroidism: effect of parathyroidectomy on regional bone mineral density in Danish patients: a three-year follow-up study. Bone 25:589–595
32. **Dempster DW, Parisien M, Silverberg SJ, Liang XG, Schnitzer M, Shen V, Shane E, Kimmel DB, Recker R, Lindsay R, Bilezikian JP** 1999 On the mechanism of cancellous bone preservation in postmenopausal women with mild primary hyperparathyroidism. J Clin Endocrinol Metab 84:1562–1566
33. **Dempster DW, Müller R, Zhou H, Kohler T, Shane E, Parisien M, Silverberg SJ, Bilezikian JP** 2007 Preserved three-dimensional cancellous bone structure in mild primary hyperparathyroidism. Bone 41:19–24
34. **Parisien M, Silverberg SJ, Shane E, de la Cruz L, Lindsay R, Bilezikian JP, Dempster DW** 1990 The histomorphometry of bone in primary hyperparathyroidism: preservation of cancellous bone structure. J Clin Endocrinol Metab 70:930–938
35. **Elvius M, Lagrelius A, Nygren A, Alveryd A, Christensson TA, Nordenström J** 1995 Seventeen year follow-up study of bone mass in patients with mild asymptomatic hyperparathyroidism some of whom were operated on. Eur J Surg 161:863–869
36. **Rao DS, Phillips ER, Divine GW, Talpos GB** 2004 Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab 89:5415–5422
37. **Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP** 1999 A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med 341:1249–1255
38. **Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, Udesky J, Silverberg SJ** 2008 The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab 93:3462–3470
39. **Lips P** 2001 Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 22:477–501
40. **Moosgaard B, Vestergaard P, Heickendorff L, Melsen F, Christiansen P, Mosekilde L** 2005 Vitamin D status, seasonal variations, parathyroid adenoma weight and bone mineral density in primary hyperparathyroidism. Clin Endocrinol (Oxf) 63:506–513
41. **Silverberg SJ** 2007 Vitamin D deficiency and primary hyperparathyroidism. J Bone Miner Res 22(Suppl 2):V100–V104
42. **Jorde R, Waterloo K, Saleh F, Haug E, Svartberg J** 2006 Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromso study. J Neurol 253:464–470
43. **Fallo F, Cella G, Casonato A, Ermani M, Vettor R, Zanella S, Lumachi F** 2006 Biochemical markers of endothelial activation in primary hyperparathyroidism. Horm Metab Res 38:125–129
44. **Delfini E, Petramala L, Caliumi C, Cotesta D, De Toma G, Cavallaro G, Panzironi G, Diacinti D, Minisola S, D' Erasmo E, Mazzuoli GF, Letizia C** 2007 Circulating leptin and adiponectin levels in patients with primary hyperparathyroidism. Metabolism 56:30–36