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Surgical Management of Asymptomatic Hyperparathyroidism: Long-Term Follow-Up

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Abstract

Background: Primary hyperparathyroidism (PHPT) is a frequently diagnosed endocrine disease and nowadays it is asymptomatic in the majority of patients. The management of asymptomatic PHPT is still debated in some cases, although there are evidences that asymptomatic patients may have improved outcomes after curative surgery. In this paper we show one of the longest follow-ups of surgically treated asymptomatic PHPT, focusing on skeletal long-term effects of surgery.

Methods: We included in the study 21 patients that underwent parathyroidectomy for asymptomatic PHPT at our Institution from 2006 to 2010 with a complete follow-up at 10 years. Data about age, BMI, preoperative serum and urinary calcium, vitamin D, alkaline phosphatase parathormone, bone densitometry, surgical procedure and histological examination were collected and analyzed.

Results: At follow-up we observed a normalization of PTH, serum calcium and alkaline phosphatase in all patients. Moreover, in all cases the T-score at 1 year increased significantly both at lumbar spine and femoral neck and this is maintained at long-term follow-up.

Conclusions: Parathyroidectomy can be proposed as a safe therapeutical option in the majority of cases of asymptomatic PHPT considering the good results of surgery in terms of bone demineralization reduction.

Keywords: Asymptomatic Hyperparathyroidism, Surgery, Follow-Up

Introduction

Primary hyperparathyroidism (PHPT) is an always more frequently diagnosed endocrine disease, with an incidence of 27-30/100.000 [1]. It is more frequent in advanced age and in females [2,3]. PHPT can be completely asymptomatic or it can present with symptoms. The asymptomatic PHPT is the most frequent type (85% of cases) and it has replaced the symptomatic one [4,5].

The bone is one of the main targets of this disease [4]. Nowadays however the majority of patients do not present with the classical signs and symptoms of skeletal involvement, which moved from an incidence of more than 20% to an incidence less than 2% [6]. It is important to highlight that the absence of a clear bone disease do not exclude a skeletal involvement, even in asymptomatic patients [7].

The use of bone densitometry allows to identify the bone involvement in asymptomatic patients. The Literature shows the eligibility criteria of parathyroidectomy, the timing of surgery, the biochemical and instrumental examinations during follow-up for asymptomatic PHPT [8].

The management of asymptomatic PHPT is still debated in some cases, although there are evidences that asymptomatic patients may have improved outcomes after curative surgery [9].

There are studies that evaluated the effect of parathyroidectomy on skeletal and renal manifestations of PHPT [10-14], showing that it is associated with significant improvements in bone mineral density (BMD), while without surgery BMD is stable or decreases with long-term follow-up.

In Literature there are few papers about the long-term efficacy of parathyroidectomy on bone in asymptomatic PHPT. For this reason, the aim of present study is to investigate the skeletal long-term effects of surgical treatment in patients affected by asymptomatic PHPT.

Materials And Methods

The study population is represented by postmenopausal women with diagnosis of asymptomatic hyperparathyroidism with a complete 10-year follow-up.

From 2006 to 2010, 62 asymptomatic patients were submitted to parathyroidectomy at our institution, of whom 38 were postmenopausal women. In 21 cases we have a complete follow-up at 10 years, therefore we included these patients in the present study.

We collected data about age, BMI, preoperative serum and urinary calcium, vitamin D, alkaline phosphatase and parathormone. Moreover, we collected data about bone densitometry, surgical procedure and histological examination. Data were collected retrospectively with patient's consent. Table 1 shows preoperative characteristics of the population.

Inclusion criteria	Exclusion criteria
Female patients	Male patients
Post-menopausal patients	Premature menopause (< 45 y.o.)
Age between 60-75 y.o.	BMI < 18,5 or > 30,0
T-score < -2,5	Previous osteoporotic fractures
First diagnosis of asymptomatic PHPT	Alcohol and tobacco abuse
	Ongoing steroid therapy
	Ongoing therapy with calcium or vitamin D
	History of rheumatoid arthritis
	Ongoing estrogenic-progestinal therapy
	History of neoplastic disease

Table 1: Inclusion and Exclusion Criteria

At follow-up we collected data about parathormone, serum calcium, alkaline phosphatase and bone densitometry.

We did not consider data about osteocalcin and hydroxiproline because these measurements are not available at our institution.

Statistics

Data are presented as mean and standard deviation (SD). Test results with $p < 0.05$ were considered as statistically significant. For differences between groups, the non-paired t test was used for normally distributed continuous variables, with the use of the Mann-Whitney U test if not normally distributed. Correspondingly, the paired t test was used for normally distributed within-group changes over time, and the Wilcoxon matched pairs test if the changes over time were not normally distributed. The Spearman's rank correlation coefficient was applied for all bivariate correlations analyses because of parameters not being normally distributed and/or the presence of outliers. Normal distribution of variables was tested with the Shapiro-Wilks test and equal variance was tested with the Levene test.

Results

From 2006 to 2010 62 patients were submitted to parathyroidectomy for asymptomatic hyperparathyroidism at our institution. Thirty-eight were postmenopausal women, of whom twenty-one with complete follow-up at 10 years were included in this study. The mean age at diagnoses was 61 years (56-67 years) and mean BMI was 24.5 (21.1-28.0).

The preoperative mean serum calcium was 11.5 mg/dl (10,3-12,8 mg/dl) and mean PTH value was 285 pg/ml (88-483 pg/ml). All patients also presented high levels of preoperative 24-hour urinary calcium (mean value 300 mg/24 hours; 120-480 mg/24 h) as well as high levels of alkaline phosphatase (mean value 104.5 U/L; 89-120 U/L. Vitamin D levels were normal in all cases. In Table 2 data about pre- and postoperative biochemical tests are reported.

Lab tests	Pre-operative median values ± SD	Post-operative (1 month) median values ± SD
Serum calcium (mg/dl)	11,5 ± 0,61	9,1 ± 0,35
PTH (pg/ml)	285 ± 123	36 ± 10
24-hour urinary calcium (mg/24 h)	300 ± 110	153 ± 76
Alkaline phosphatase (U/l)	104.5 ± 12	65 ± 6

Table 2: Pre-and post-operative biochemical tests

The presence of urolithiasis was excluded in all patients by means of sn abdominal ultrasound.

The preoperative bone densitometry showed in all cases low values of T-score: median lumbar spine (LS) T-score was -2.96 ± 0.48, median femoral neck (FN) T-score was -2.1 ± 0.73 and median total femoral T-score was -1.8 ± 0.54 (Table 3).

	Pre-operative median values ± SD	Post-operative (1 year) median values ± SD	p-value
Lombar Spine T-score	-2.96 ± 0.48	-2.05 ± 0.63	0,003
Femoral Neck T-score	-2.1 ± 0.73	-1.67 ± 0.50	0,039
Total Femoral T-score	-1.8 ± 0.54	-1.66 ± 0,55	0,281

Table 3: Pre-and post-operative bone densitometry values

Before surgery, all patients were submitted to radiological examination in order to localize the site or sites of pathological parathyroid. In all cases we performed a neck ultrasound and Tc-99m-sestamibi scintigraphy.

All patients received a mini-cervicotomy with monolateral cervical exploration and in all cases, we found out a single adenoma. There was no post-operative morbidity nor mortality.

At follow-up we measured serum calcium, alkaline phosphatase and PTH at 1, 6 and 12 months and then yearly until 10-year follow-up. In all cases we observed a normalization of PTH, serum calcium and alkaline phosphatase at follow-up (Table 2). At 1 month follow-up the median serum calcium was 9,1 ± 0,35 mg/dl, the median PTH value was 36 ± 10 pg/ml, the median 24-hour urinary calcium was 153 ± 76 mg/24 h and the median Alkaline phosphatase was 65 ± 6 U/l (Figure 1). In all patients these values remained stable until 10-year follow-up.

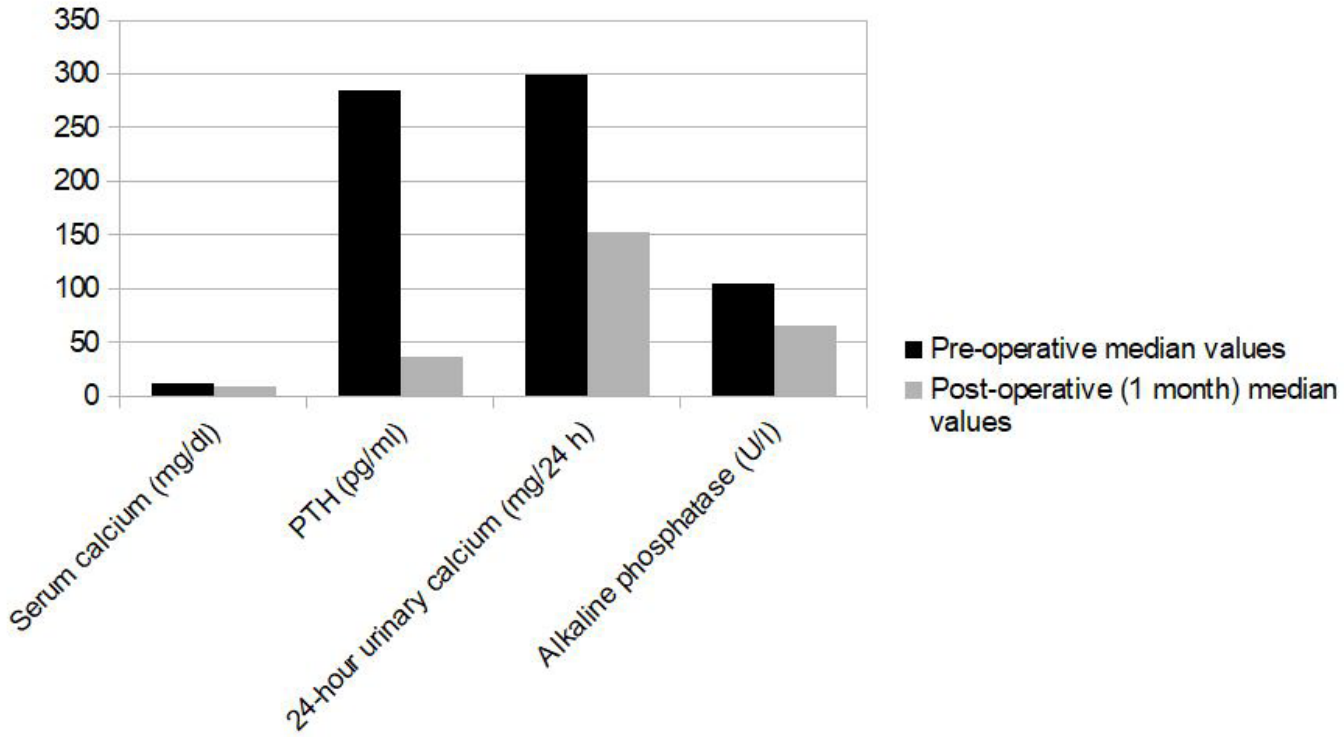

Figure 1: Pre-and post-operative biochemical testsvalues

After 1 year the median lombar spine T-score was -2.05 ± 0.63; the median femoral neck T-score was -1.67 ± 0.50 and the median total femoral T-score was -1.66 ± 0,55: in all cases the T-score at 1 year increased significantly both at lumbar spine and femoral neck compared to the preoperative values (p-value respectively 0,003 and 0,039; see table 3 and figure 2). No patients developed a disease relapse and the results at 1-year are maintained along the entire 10-year follow-up.

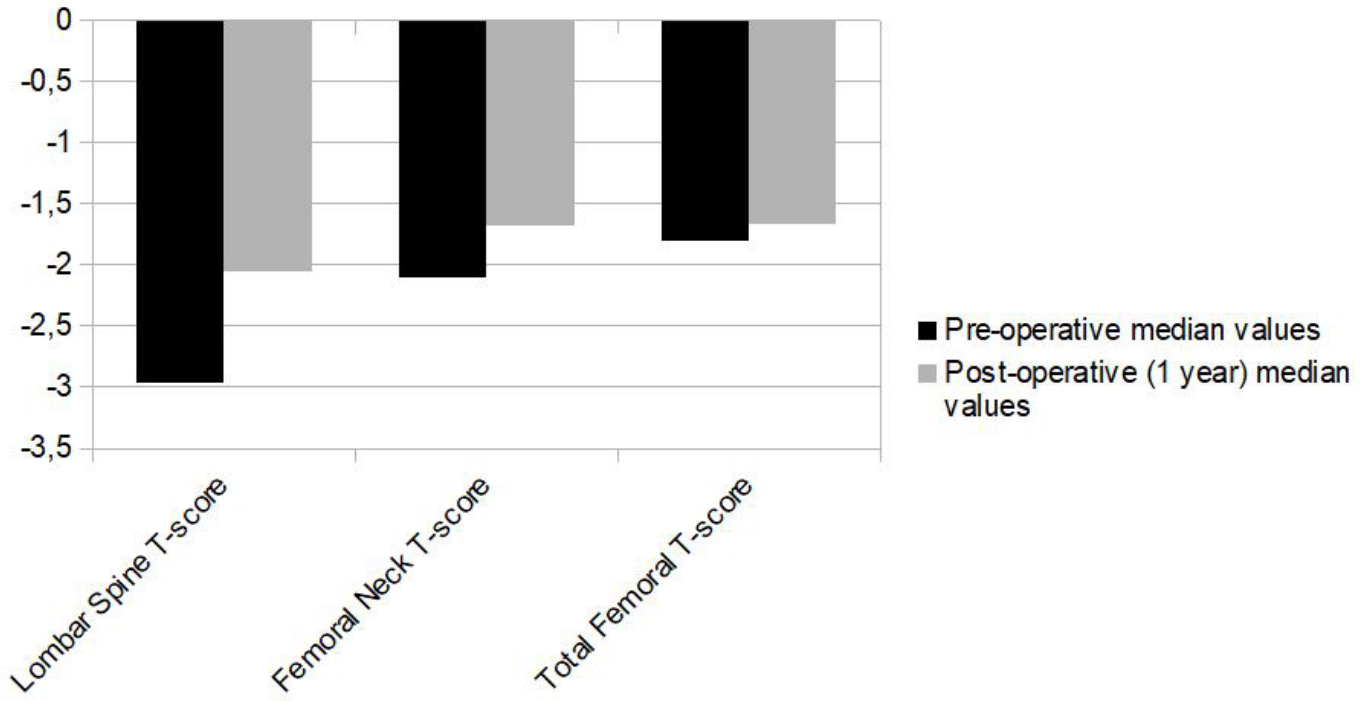

Figure 2: Pre-and post-operative bone densitometry values

Discussion

PHPT has nowadays changed its clinical profile, as about 80% of patients are asymptomatic [15]. Nevertheless, in these patients the absence of clear bone disease does not rule out a skeletal involvement, characterized by a reduction of bone mineral density (BMD) [16]. The trabecular bone is mainly involved in BMD loss [6].
Our data concern post-menopausal women with a median age of 61 years old. We excluded patients with risk factors that could interfere with bone mineral density loss (Table 1).

The eligibility criteria for surgery in case of asymptomatic PHPT are reported in the IV International Workshop [9]: serum calcium 1 mg/dL above the upper limit of normal; peri- or postmenopausal women and men age 50 y.o. or older, who have a T-score of -2.5 or less at lumbar spine, femoral neck, total hip or distal 1/3 radius; vertebral fracture; creatinine clearance <60 cc/min; renal stones.

Surgery is the only curative therapy for PHPT. Current guidelines indicates parathyroidectomy for symptomatic patients, however there are limited data on the natural history of asymptomatic disease [9,17].

The SIPH study is a randomized trial that compares surgery versus observation in patients with asymptomatic primary HPT: authors report at 5-year a reduction of BMD at all sites except at lumbar spine in the observational group and a corresponding significant treatment effect of surgery on BMD for all sites except for the radius [18]. The stability of BMD at lumbar spine during time in non-surgical group is confirmed both at short-term follow-up [10] and even after 15 years follow-up [13]; the latter study highlights also the significant reduction of BMD at femoral neck and distal radius at long-term follow-up [13].

In a meta-analysis of studies comparing parathyroidectomy to conservative management for mild PHPT, the authors concluded that, in the short-term, conservative management was safe but long-term studies are required to assess the real benefit of surgery [19].

In a study from Bolland and colleagues, a cohort of 23 post-menopausal women managed conservatively for asymptomatic PHPT was followed-up for 10 years. In these patients there was a steady increase in serum calcium and PTH and 4 patients developed fractures, 1 osteoporosis and 1 nephrolithiasis [20].

Benzon et al. analyzed a large cohort of patients correlating the direct effect of parathyroidectomy on bone mineral density (BMD): they showed a substantial effect on bone remineralization within 3 years of surgical intervention [21]. Silverberg et al. reported an increase of 12% in lumbar spine BMD and 14% in femoral neck BMD at 10 years after surgical cure [22]. The same auothors published their results at 15-year follow-up, showing BMD decline in 37% of patients in non-surgical group. Moreover, no predictive factors of bone loss were identified and even the use of antiresorptive medications did not impact upon cortical reduction [12].

A large population-based study from VanderWalde showed a 14% decrease in 10-year fracture risk in PHPT patients who underwent parathyroidectomy; the benefit was seen in all patients, regardless of age, calcium level, or PTH level [23].

Our study confirms the beneficial effect of parathyroidectomy at long-term follow-up: patients showed not only a persistent normalization of serum calcium and PTH levels, but also an improvement of T-score measured by DEXA, that is maintained at 10-year follow-up.

On the other side, the alternative to surgical management of PHPT is represented by medical therapy such as bisphosphonates and calcimimetics, or observation. Medical therapy is often costly or can lose efficacy or can present unknown side effects with continued use [24]. Moreover, long-term data on medical treatment of bone loss in PHP are lacking.

Conclusion

Our series confirms the previous data reported in literature, although it can suffer from limitations related to its retrospective nature.

In conclusion, we can state that parathyroidectomy can be proposed as a safe therapeutical option in the majority of cases of asymptomatic PHPT, considering the good results of surgery in terms of bone demineralization reduction and the absence of reliable preoperative predictive factors about bone demineralization, which raises concern regarding non-interventional monitoring of BMD.

Further study are needed to assess the role of parathyroidectomy in reducing other symptoms related to PHPT, such as neurocognitive and cardiovascular.

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