

Quality of Life is Modestly Improved in Older Patients with Mild Primary Hyperparathyroidism Postoperatively: Results of a Prospective Multicenter Study

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ABSTRACT

Background. The objectives of this study were to evaluate, in mild primary hyperparathyroidism (pHPT) patients, the quality of life (QoL) using the SF-36 questionnaire before and after parathyroidectomy and to detect preoperatively patients who benefit the most from surgery. Most pHPT patients present a mild pHPT defined by calcemia ≤ 11.4 mg/dL. For these patients, there is debate about whether they should be managed with surveillance, medical therapy, or surgery.

Methods. A prospective multicenter study investigated QoL (SF-36) in patients with mild pHPT before and after parathyroidectomy in four university hospitals. Laboratory results and SF-36 scores were obtained preoperatively and postoperatively (3, 6, and 12 months).

Results. One hundred sixteen patients were included. After surgery, the biochemical cure rate was 98%. Preoperatively, the mental component summary and the physical component summary (PCS) were 38.69 of 100 and 39.53 of 100, respectively. At 1 year, the MCS and the PCS were 41.29 of

100 and 42.03 of 100. The subgroup analysis showed a more significant improvement in patients < 70 years and with calcemia ≥ 10.4 mg/dL. Postoperative PCS was correlated with age and preoperative PCS: variation = $32.11 - 0.21 \times \text{age} - 0.4 \times \text{preoperative PCS}$. Men did not improve their MCS postoperatively. Only women with a preoperative MCS < 43.6 of 100 showed postoperative improvement.

Conclusions. This study showed, in patients with mild pHPT, an improvement of QoL 1 year after parathyroidectomy. Patients < 70 years and with calcemia ≥ 10.4 mg/dL had a more significant improvement.

Most patients (80 % of cases) with primary hyperparathyroidism (pHPT) present a mild pHPT defined by moderate hypercalcemia (≤ 11.4 mg/dL). Patients with mild pHPT are typically defined as asymptomatic.^{1,2} When pHPT is symptomatic, there is a consensus in favor of parathyroidectomy. Most patients with mild pHPT experience subtle fatigue, abdominal pain, and depression.³⁻⁵ These symptoms alter quality of life (QoL).⁶⁻⁹ However, for asymptomatic or minimally symptomatic patients, there is debate about whether they should be managed with surveillance, medical therapy, or surgery. The consensus conferences on surgery for pHPT established guidelines for

surgery, which currently form the basis for therapeutic decisions.^{1,10,11} Among patients with pHPT, these criteria are serum calcium level >11.4 mg/dL, creatinine clearance decreased by ≥ 10 % of normal level, bone mineral density reduced by >2.5 T-score, and age ≤ 50 years. The effect of pHPT on QoL is not a criterion for recommending surgery. In fact, it is difficult to know exactly who would benefit from surgery.

The aims of this study were to evaluate QoL using SF-36 questionnaires before and after parathyroidectomy in patients with mild pHPT and to predict, using the results from the preoperative SF-36 score, the effect of surgery on QoL.

METHODS

Between December 2007 and June 2010, patients were prospectively enrolled in a multicentric study in 4 French departments of endocrine surgery at university hospitals in Angers, Limoges, Marseille, and Nantes. All patients had pHPT defined by a serum calcium level between 10.4 and 11.4 mg/dL (normal levels are 9.2–10.4 mg/dL) with a parathyroid hormone (PTH) level ≥ 25 ng/L and a serum creatinine level <160 $\mu\text{mol/L}$ or a serum calcium level between 10.0 and 10.4 mg/dL and a PTH level ≥ 35 ng/L. Exclusion criteria were calcemia >11.4 mg/dL, calciuria >400 mg/day (according to French consensus), creatinine clearance decreased by >10 %, age ≤ 50 years, benign familial hypocalciuric hypercalcemia, multiple endocrine neoplasia, serum creatinine level >160 $\mu\text{mol/L}$ (to exclude patients with secondary hyperparathyroidism), and patients taking medication containing lithium or thiazide diuretics.¹²

Biological cure was defined as a normal calcemia 6 months after surgery, regardless of the PTH level. All patients were asked to fill in the SF-36 questionnaire (SF-36 Health Survey; SF-36 Medical Outcomes Trust, Waltham, MA, USA) preoperatively and 3, 6, and 12 months after surgery. The SF-36 survey was self-administered. The survey consists of 36 questions that evaluate 8 discrete areas: physical functioning, social functioning, bodily pain, general health perceptions, vitality, role limitations due to emotional problems (role-emotional), role limitations due to physical health problems (role-physical), and mental health. The number of questions pertaining to each domain varies from 2 to 10. Two summary outcomes are obtained: a physical component summary (PCS) and a mental component summary (MCS). The results range from 0 (poorest health status) to 100 (best health status). Demographic, clinical, and biological data (calcemia, PTH, 25-OH vitamin D, and creatinine levels) were prospectively collected during the preoperative period and 3, 6, and 12 months after parathyroidectomy. The

normal range of PTH levels was 25–65 ng/L. Vitamin D was normal when >35 $\mu\text{g/L}$. The types of anesthesia and cervical approach (bilateral, unilateral, or videoscopic) were at the surgeon's discretion.

All patients received a written explanation of the study protocol and gave their signed informed consent. Morbidity and the operative mortality were specified.

The study was approved by an institutional local review board committee (University Hospital of Angers, France, No. 2012/45) and was registered at clinicaltrials.gov (Registration No. NCT01776502).

Statistical Analysis

Biological data were expressed as a median with range values. Analysis and scoring of SF-36 data were carried out according to guidelines.¹³ SF-36 results were expressed as mean \pm SD. The comparisons of values of the variables among times of measurements was performed by using Wilcoxon signed-rank tests.

To determine characteristics of the individuals having an improvement of QoL, linear models were developed to determine the variation of the two summary scores (PCS and MCS) between the preoperative measurement and 1 year after surgery as a function of the age of patients, of the calcemia, and of the value of preoperative PCS and MCS. These two models have been used to determinate the maximal preoperative PCS and MCS values, which can lead to increased values 1 year after surgery of >0 points or ≥ 5 points (a clinically significant increase according to Strand and Singh).¹⁴ Analyses were performed using the Stata 12 software (Stata Corp., College Station, TX, USA). Statistical significance was determined as $p < 0.05$ for all tests.

RESULTS

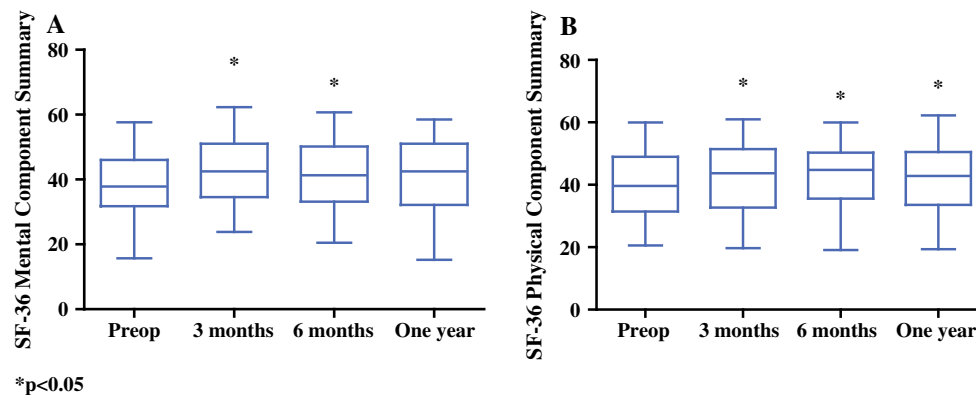
Between December 2007 and June 2010, 392 patients were operated on for pHPT. One hundred ninety-six patients fit criteria for mild pHPT, and 116 met inclusion criteria. The median age was 68 years (range 51–87 years). There were 90 females (78 %) and 26 males. The preoperative data are shown in Table 1. Ninety patients (78 %) had a vitamin D deficiency. Twenty-nine patients (33 %) had a normal calcemia associated with increased PTH concentration. Preoperative MCS and PCS were respectively 38.69 (SD 9.16) and 39.53 (SD 10.28; Fig. 1).

There was no mortality, and postoperative morbidity was 3 %: 1 patient developed a superficial hematoma that required reoperation, and 3 patients had transitory recurrent laryngeal nerve palsy. There was no postoperative hypocalcemia (calcium <8.0 mg/dL).

TABLE 1 Evolution of biological data

Variable	Preoperative	3 months	6 months	1 year
Calcemia (mg/dL)	10.68 [10–11.4]	9.6* [7.72–11.0]	9.48* [8.2–10.88]	9.48* [8.0–11.8]
Phosphoremia (mg/dL)	2.54 [1.05–8.89]	3.41* [1.98–5.17]	3.31* [1.58–4.86]	3.53* [1.98–5.30]
PTH (ng/L)	92.70 [38.10–310.00]	34.30* [0.90–278.00]	48.50* [27.00–102.10]	44.00* [0.50–164.00]
Creatinine ($\mu\text{mol/L}$)	69.00 [35.00–125.00]	NA	NA	83.65 [70.00–97.30]
25 OH-hydroxyvitamin D ($\mu\text{g/L}$)	18.80 [2.46–73.60]	27.05* [6.82–80.00]	NA	25.20* [8.00–74.00]

Data are median (range)

* $p < 0.05$ **FIG. 1** Evolution of MCS (a) and PCS (b) before and after parathyroidectomy (mean \pm SD)

Evolution of Biology After Surgery

The median serum calcium level was normalized after surgery and remained normal at 3 months (Table 1). Calcium and PTH levels normalized in 96 patients (83 %). High PTH levels (>60 ng/L) with normocalcemia were observed in 16 patients (13 %). Three patients had a persistent hypercalcemia at 3 months with normal PTH levels (3 %). The median serum phosphorus level was also normalized at 3 months. Sixty-three patients (54 %) had persistent vitamin D deficiency despite postoperative supplementation. At 6 months, the biochemical cure rate was 98 %. The median serum calcium and PTH levels were normalized at 6 months. Five patients had hypercalcemia at 6 months. At 1 year, the same five patients had hypercalcemia. Among the 16 patients with a high PTH level and normocalcemia at 3 months, 2 still had an elevated PTH level with normocalcemia 1 year postoperatively. These patients had a median preoperative PTH level above the median of the preoperative overall analysis (127 vs. 92.7 ng/L). The median serum phosphorus level was normalized at 1 year. Concerning the vitamin D, 37 patients (32 %) had vitamin D deficiency, and 33 (28 %) had a normal vitamin D level (missing data for 46).

Evolution of SF-36

At 3 months, 97 % of questionnaires were completed (Figs. 1, 2). Patients' QoL improved significantly. These improvements were observed for both MCS (42.68; SD 9.74; $p < 0.0001$) and PCS (41.93; SD 10.84; $p = 0.013$).

At 6 months (88 % of questionnaires completed), significant improvement (compared with the preoperative period) persisted in 5 dimensions: role physical, bodily pain, vitality, social functioning, and mental health. The MCS (41.48; SD 9.91) and PCS (43.18; SD 9.61) were significantly improved ($p = 0.042$ and $p = 0.0004$, respectively).

At 1 year (89 % of questionnaires completed), the MCS and PCS were 41.29 (SD 10.58) and 42.03 (SD 10.01; Fig. 2). Six domains improved significantly (compared with the preoperative period): role physical, bodily pain, vitality, social functioning, role emotional, and mental health. The PCS improved significantly ($p = 0.015$) but not the MCS ($p = 0.109$). PCS and MCS were not statistically different between patients with normocalcemia and a normal PTH level and those with normocalcemia and an elevated PTH level. Similarly, PCS and MCS were not statistically different between patients with a normal vitamin D level and those

with deficiency. PCS and MCS were not statistically different between patients with hypercalcemia and those with normocalcemia at 1 year (PCS 44.6 ± 9.8 vs. 42.0 ± 9.4 , $p = 0.551$; MCS 45.6 ± 13.1 vs. 40.7 ± 10.7 , $p = 0.292$).

Patients were classified using an age cutoff (<70 or ≥ 70 years; Fig. 3). It was the most relevant cutoff of improvement based on age. Sixty-seven patients were under 70 years before surgery, and 49 patients were 70 years or older. Preoperatively, there was a significant difference concerning the domain physical functioning between the two groups. At 1 year, all biological parameters were significantly improved regardless of the patient's age. Improvement of SF-36 at 1 year was greater in patients <70 years for PCS: in these patients, improvement was seen in 6 domains (role physical, bodily pain, general health, role emotional, social functioning, and vitality),

whereas only 1 domain significantly improved in patients ≥ 70 years (role physical).

Patients were classified using calcemia cutoff criteria (<10.4 or ≥ 10.4 mg/dL; Fig. 4). This cutoff was used because it was the upper normal limit. Twenty-nine patients had serum calcium levels <10.4 mg/dL before surgery, and 87 patients had calcium levels ≥ 10.4 mg/dL. Preoperatively, there was no significant difference between the 2 groups concerning SF-36 score. At 1 year, calcium, phosphorus and PTH levels were significantly improved in all patients. Improvement of SF-36 at 1 year was more significant in patients with calcemia ≥ 10.4 mg/dL. Indeed, for these patients, 5 domains were significantly improved (role physical, general health, mental health, role emotional, and vitality), whereas in patients <10.4 mg/dL, 2 domains were significantly improved (role physical and bodily pain).

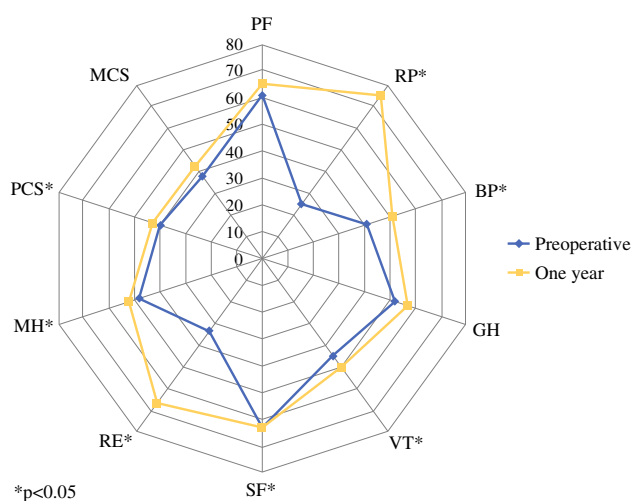


FIG. 2 Preoperative and 1-year SF-36 scores (mean)

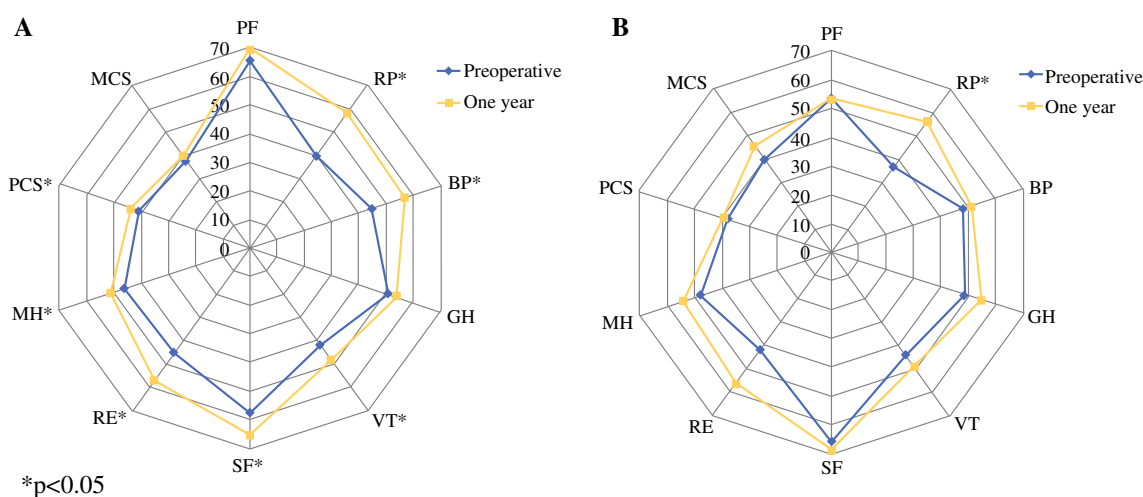


FIG. 3 Preoperative and 1-year SF-36 scores for patients <70 years (a) and ≥ 70 years (b) (mean)

Prediction of Postoperative QoL

The next step was to detect the patients who improved their QoL postoperatively the most. PCS and MCS were separated for the computation. An equation explaining the variation of the score based on age and the maximum preoperative PCS result was estimated. The result was PCS variation = $32.11 - 0.21 \times \text{age} - 0.4 \times \text{preoperative PCS}$.

These results show that the older the patient, the more the preoperative PCS score must be altered to benefit from surgery. In this study, 66.7 and 31.6 % of the patients respectively improved their PCS >0 points and ≥ 5 points. Concerning the MCS, no improvement was observed in men, regardless of age and the preoperative value of MCS. In women, progress was not based on age but only on the preoperative score: MCS variation = $24.39 - 0.56 \times \text{preoperative MCS}$.

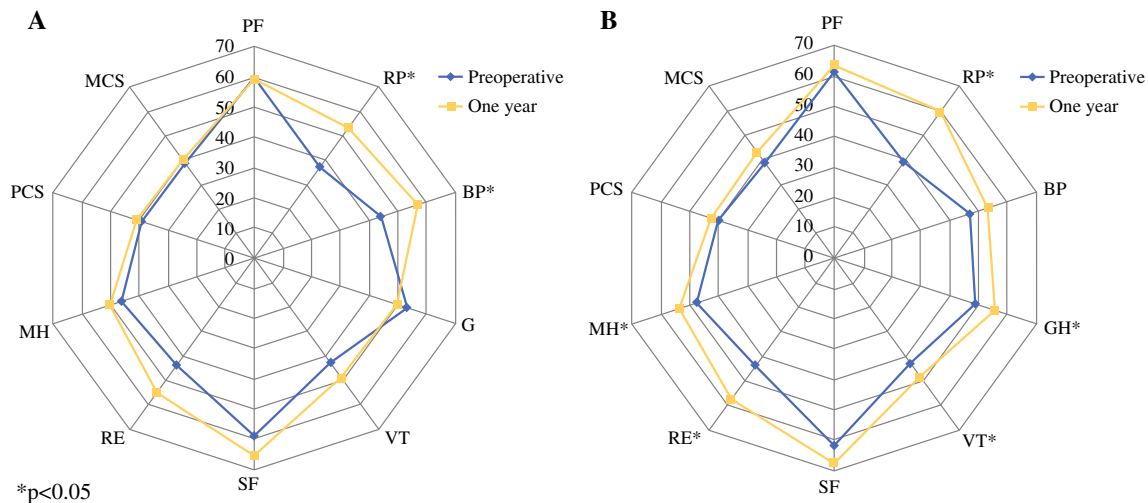


FIG. 4 Preoperative and 1-year SF-36 scores for patients <10.4 mg/dL (a) and ≥ 10.4 mg/dL (b) (mean)

Women who improved their MCS >0 points had a maximum preoperative MCS <43.6 (69.4 % of women in the series). Women who improved their MCS ≥ 5 points had a maximum preoperative MCS ≤ 34.6 (42.4 % of women in the series).

DISCUSSION

The aim of this multicenter and prospective study was to evaluate the evolution of the QoL before and 3, 6, and 12 months after parathyroidectomy for mild pHPT. This study also calculated, for the first time, the level of maximal preoperative PCS and MCS to expect with postoperative QoL improvement.

This study showed a significant improvement of QoL by 3 months, measured by the SF-36. This significant improvement was noticed in all 8 domains. 6 months after parathyroidectomy, a significant improvement persisted in 5 domains. There was still a significant improvement in the MCS and PCS. 1 year after surgery, the MCS and PCS were respectively 41.29 and 42.03, compared with 38.69 and 39.53 preoperatively. There was a significant improvement in 6 domains: role physical, bodily pain, vitality, social functioning, role emotional, and mental health. Improvement was significant for the PCS but not for the MCS. Some studies show that MCS can be altered by age, body mass index, and comorbidities.^{15,16} In this study, the whole population was over 50 years, which could explain the nonsignificant improvement of MCS.

To more accurately predict patients' surgical outcome, a correlation between preoperative and postoperative scores was computed. This shows the maximal preoperative PCS and MCS results required to expect QoL improvement after parathyroidectomy. This is feasible in consultation when preoperative PCS and MCS are known. Results show that

the older the patient, the lower the PCS score must be to benefit from surgery. Regarding the MCS, no improvement was observed in men. In women, evolution of the MCS depended only on the preoperative score (<43.6).

Many investigators agree that most patients with mild pHPT have a constellation of nonspecific symptoms that alter QoL. Results of the present study are consistent with the literature. Few studies included solely mild pHPT patients.^{7,17,18}

Furthermore, the subgroup analysis showed a greater improvement in QoL at 1 year in patients ≤ 70 years (6 domains vs. 1 domain). Egan et al. showed, in 50 patients aged over 80 years with pHPT, that QoL was maintained, not improved. The study included only 10 completed questionnaires.¹⁶ Kebebew et al. published a series of 54 octogenarian and nonagenarian patients. Postoperatively, all patients showed clinical improvement, but none had mild asymptomatic pHPT.¹⁹ Morris et al. showed, in 18 mild pHPT patients >50 years, that surgery only increased the 6-min walk distance.²⁰ This study, which included 49 patients >70 years, is the largest one with older mild pHPT patients. One can conclude that the improvement of QoL in older patients seems to be less than in younger ones. However, older patients, although they have clinical improvement after parathyroidectomy, have a moderate benefit. Only those with a very low preoperative PCS and MCS results may expect a significant clinical improvement.

In addition, this study demonstrated that a preoperative serum calcium level ≥ 10.4 mg/dL was associated with a greater improvement of QoL at 1 year compared with patients with a preoperative serum calcium level <10.4 mg/dL (5 vs. 2 domains). Symptoms probably appear throughout the course of the disease, and patients with a calcium level ≥ 10.4 mg/dL have a more advanced disease. As for >70 -year-old patients, normocalcemic

patients do benefit from parathyroidectomy, but improvement is low.

Many scores or questionnaires have been used to evaluate the clinical consequences of pHPT on patients.^{3,6,21} These various questionnaires evaluated different effects of pHPT on patients. SF-36 has been widely used in pHPT literature.⁶⁻⁸ In this study, SF-36 was chosen because it allows a more comprehensive evaluation of patients and has been established as the “gold standard” of QoL. Although SF-36 is a standard tool for QoL evaluation, it may pick up certain subtleties in mild pHPT. Furthermore, the results of all these preoperative scores could not predict postoperative QoL, contrary to this study.^{3,5,21}

There were some limitations to this study. First, this study did not compare surgery versus medical treatment. However, other studies have shown that control of pHPT using medication is not as effective as surgery.²² In mild pHPT, these effects need to be better evaluated. Second, there is no control nonsurgical group. This nonsurgical group (especially >70 years with mild pHPT) could potentially show a greater deterioration than in the normal population that would make the moderate improvement or stabilization significant for operated patients. The strengths of this study are its prospective, multicentric nature; the number of mild pHPT patients (>100), all above 50 years; and the first description of preoperative PCS and MCS that can predict postoperative outcome.

CONCLUSIONS

This study showed, in patients with mild pHPT, an improvement in QoL that remains 1 year after parathyroidectomy. The subgroup analysis demonstrated that patients under 70 years and with a serum calcium level ≥ 10.4 mg/dL showed a significantly better improvement than other groups. This should be taken into consideration when discussing management of these patients. Further studies are warranted to establish benefits in mild pHPT groups with limited QoL deterioration.

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