

CLINICAL STUDY

Surgery for ‘asymptomatic’ mild primary hyperparathyroidism improves some clinical symptoms postoperatively

Claire Blanchard, Muriel Mathonnet¹, Frédéric Sebag², Cécile Caillard, Antoine Hamy³, Christelle Volteau⁴, Marie-Françoise Heymann⁵, Vincent Wyart, Delphine Druil⁶, Malanie Roy, Bertrand Cariou⁶, Françoise Archambeaud⁷, Patrice Rodien⁸, Jean-François Henry², Rasa Zarnegar⁹, Jean-Benoît Hardouin^{4,10} and Eric Mirallié

Clinique de Chirurgie Digestive et Endocrinienne (CCDE), Institut des Maladies de l'Appareil Digestive (IMAD), Centre Hospitalier Universitaire (CHU) Nantes-Hôtel Dieu, Place Alexis Ricordeau, 44093 Nantes, France, ¹Service de Chirurgie Digestive, Hôpital Dupuytren, 87042, Limoges, France, ²Service de Chirurgie Générale et Endocrinienne, Hôpital de la Timone, 13385 Marseille Cedex, France, ³Service de Chirurgie Digestive, CHU Angers, 49933 Angers Cedex 9, France, ⁴Plateforme de Biométrie, CHU Nantes, 44093 Nantes, France, ⁵Service d'Anatomie Pathologique, CHU Nantes, 44093 Nantes, France, ⁶Service d'Endocrinologie, CHU Nantes, 44093 Nantes, France, ⁷Service de Médecine Interne, Endocrinologie et Maladies Métaboliques, CHU Limoges, Limoges, France, ⁸Service d'Endocrinologie, CHU d'Angers, 49000 Angers, France, ⁹Department of Surgery, Weill Cornell Medical College, New-York Presbyterian Hospital, New York, New York, USA and ¹⁰EA 4275-SPHERE, Faculté de Médecine et Pharmacie, 44035 Nantes Cedex 1, France

(Correspondence should be addressed to E Mirallié; Email: eric.mirallie@chu-nantes.fr)

Abstract

Objective and background: Most primary hyperparathyroidism (pHPT) patients do not conform to the guidelines for parathyroidectomy established by an international panel of specialists and have a mild pHPT. This group is typically defined as ‘asymptomatic’. The primary aim of this study was to determine symptom improvement in this ‘asymptomatic’ group after parathyroidectomy. Secondly, we aimed to create a preoperative clinical score predicting postoperative symptom resolution.

Design: A prospective nonrandomized study included patients with mild pHPT.

Methods: A questionnaire (22 items) was given to ‘asymptomatic’ patients preoperatively and at 3, 6, and 12 postoperative months. A logistic regression was performed to create a preoperative clinical score.

Results: One hundred and sixteen patients were included. Postoperatively, HPT was resolved in 98% of patients. Twelve of 22 nonspecific symptoms were improved at 1 year. Subgroups analysis showed a greater improvement in patients <70 years and those with a serum calcium level ≥ 2.6 mmol/l preoperatively. A clinical score, based on age and five symptoms, was established to predict the clinical improvement after surgery in mild pHPT patients with a positive predictive value of 81%.

Conclusion: Patients with asymptomatic pHPT have clinical improvement of their symptoms postoperatively even after 1 year. Younger patients and those with higher preoperative calcium levels show the best improvement.

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Introduction

Primary hyperparathyroidism (pHPT) is due to an inappropriate secretion of parathyroid hormone (PTH) by one or more pathological parathyroid glands, which causes hypercalcemia associated with hypercalciuria and hypophosphatemia. Currently, most pHPT patients (80% of cases) present with mild pHPT, defined by moderate hypercalcemia (≤ 2.85 mmol/l) and a 24-h urine calcium level ≤ 10 mmol. Most patients with mild pHPT are considered to be asymptomatic (1, 2). Following the consensus statement of an international workshop, guidelines have been established concerning indication for surgery (3, 4, 5). Indication for parathyroidectomy comprises the following criteria: serum calcium level ≥ 2.85 mmol/l, calciuria > 10 mmol/24 h, creatinine clearance decreased by

$\geq 10\%$ of normal level, bone mineral density (BMD) reduced by > 2.5 T-score, and age ≤ 50 years. Patients who do not meet these criteria can either undergo surgery or be managed medically (6, 7).

Over the last few years, knowledge about mild pHPT has dramatically increased. Some studies have shown the benefit of surgery for patients with mild pHPT. Our group conducted a prospective, multicentric study, in patients with pHPT, evaluating some nonspecific symptoms and quality of life criteria using the SF-36v2 (8). The results showed that the surgical cure of pHPT significantly improved the quality of life and decreased the number of nonspecific symptoms (appetite loss, thirst, headache, and nausea) 1 year after surgical cure. Other studies drew the same conclusions and a French consensus suggested surgery for all patients with pHPT (9). Randomized studies often showed a

moderate improvement of quality of life in operated patients, but none have evaluated nonspecific symptoms (10, 11). Surgery is followed by the normalization of calcium and PTH levels, a decrease in bone turnover, and an increase in BMD in lumbar spine and femoral neck (7, 10, 11).

Patients with mild pHPT often have nonspecific symptoms: fatigue, mood disorders, anxiety, depression, irritability, headache, constipation, and abdominal pain, among others (12, 13). These symptoms are never cited in the consensus conferences and therefore are not used as indications for surgery in mild pHPT patients. Consequently, subjective symptoms and their presumable effects on patients' quality of life are not indications for parathyroidectomy.

The question remains unanswered whether all patients with mild pHPT should undergo surgery and which clinical symptoms should be taken into account before surgery. The purposes of this study were i) to evaluate nonspecific symptoms in patients with mild pHPT preoperatively and 3, 6, and 12 months postoperatively and ii) to create a new preoperative clinical score to predict clinical improvement after surgery.

Subjects and methods

Between December 2007 and June 2010, patients from four French Departments of Endocrine Surgery, Hospitals of Angers, Limoges, Marseille, and Nantes, were prospectively enrolled in a multicentric study. Departments of Endocrine Surgery of Marseille and Angers only included patients between October 2009 and June 2010. During this period, all patients with mild pHPT scheduled for parathyroidectomy were evaluated for inclusion. Inclusion criteria included calcium level between 2.6 and 2.85 mmol/l (normal: 2.3–2.6 mmol/l) with a PTH level ≥ 25 ng/l and a serum creatinine level < 160 $\mu\text{mol/l}$, or a serum calcium level between 2.5 and 2.6 mmol/l and a PTH level ≥ 35 ng/l. To measure calcemia, blood samples were collected and centrifuged at 2000 *g* for 10 min at 4 °C within 1 h after venipuncture. Total calcium on heparinized plasma was determined using the method according to Schwarzenbach with *o*-cresolphthalein complexone on cobas c6000 Roche system with intra-assay coefficients of variation below or equal to 0.7%. Calcemia was not albumin-corrected, because the total calcium is used in clinical practice. In addition, the difference between the total calcium and corrected calcium is not major, concerning the healthy subjects.

Exclusion criteria included all patients with pHPT who met NIH criteria for parathyroidectomy (calcium level > 2.85 mmol/l, calciuria > 10 mmol/24 h, creatinine clearance decreased by $> 10\%$, and age < 50 years). Other exclusion criteria include benign familial hypocalciuric hypercalcemia, multiple endocrine neoplasia, serum creatinine level > 160 $\mu\text{mol/l}$ (to exclude

patients with secondary HPT), and patients under medication containing lithium or thiazide diuretics, as well as comorbidities which could be responsible for some evaluated symptoms. Patients could not participate in another study over a period of 1 year after inclusion. The study was approved by the Institutional Local Review Board Committee (University Hospital of Angers, France. #2012/45).

Biological cure was defined by a normal serum calcium level 3 months after surgery. All patients were asked to fill in a questionnaire about nonspecific symptoms preoperatively and 3, 6, and 12 months postoperatively. The questionnaire of nonspecific symptoms was created using previously published data (8, 13, 14, 15). This questionnaire evaluated the presence and severity of 22 symptoms frequently observed in patients with pHPT (Table 1). Demographic, clinical, and biological data (serum calcium, PTH, 25-OH vitamin D, and creatinine levels) were collected prospectively during the preoperative period, and 3, 6, and 12 months after parathyroidectomy. The normal range of PTH level was 25–65 ng/l. Vitamin D was normal when above 35 ng/l. The types of anesthesia (local or general) and cervical approach (bilateral, unilateral, or videoscopic) were left to surgeons' discretion.

All patients received a written explanation of the study protocol and gave their signed, informed consent. The morbidity (hypoparathyroidism, recurrent nerve palsy, and postoperative hematoma) and the operative mortality were specified.

Statistical analysis

Median values of biological markers were compared between a baseline and each of the follow-up visits

Table 1 Twenty-two nonspecific symptoms.

No.	22 Nonspecific symptoms
1	Appetite loss
2	Weight loss
3	Thirst
4	Polyuria
5	Headaches
6	Itchy skin
7	Bone pain
8	Joint pain
9	Muscular pain
10	Muscular weakness
11	Mobility difficulties
12	Nausea
13	Abdominal pain
14	Abdominal distension
15	Constipation
16	Ulcer
17	Fatigue
18	Depression
19	Mood swings
20	Irritability
21	Anxiety
22	Forgetfulness

(3, 6, and 12 months) using Wilcoxon's signed-rank test. The prevalence of each nonspecific symptom was compared between a baseline and each of the follow-up visit using McNemar's test.

A score of prediction of clinical improvement was then established using a logistic regression. Clinical improvement was evaluated by using questions addressing the subjective improvement of overall health at the 1-year visit. We divided the study population into two groups: i) patients who did not feel better (felt the same or worse compared with before surgery) 1 year after surgery in terms of their perception of their overall health; and ii) patients who felt better 1 year after surgery in terms of their perception of their overall health.

In order to build a score predicting the postoperative belonging to one of these two groups, we introduced in the logistic regression the presence or absence at baseline of nonspecific symptoms, age of the patients (<70 vs \geq 70 years), calcium level (<2.6 vs \geq 2.6 mmol/l), and vitamin D levels (< vs \geq 35 ng/l). Variables were selected using a step-by-step backward selection procedure with type-I error established at 10% in order to keep in the score variables that could be at the limit of the significance (between 5 and 10%), but that was important to improve the predictive properties of the score. This analysis highlighted the most relevant preoperative symptoms to predict the improvement of health after surgical cure of mild pHPT. Visual inspection of the Receiver Operating Characteristic (ROC) curve associated with this logistic regression enabled determination of a threshold value on the obtained score in order to divide the patients into two groups (improvement and nonimprovement) so as to achieve the lowest possible rate of misclassified patients. To choose the value, the specificity of the score was favored in order to detect a maximal number of patients presenting an improvement of their overall vision health. The score obtained by the logistic regression was composed of decimal weights associated with each retained variable. In order to create a simpler score, for an easy use in a clinical context, these weights have been proportionally transformed in obtain weights among the first integers (1, 2, or 3).

Results

Preoperative data

One hundred and sixteen patients were enrolled in this study. Median age was 68 years old (range 51–87). There were 90 females (78%) and 26 males (22%). Median preoperative serum calcium value was 2.67 mmol/l (range 2.50–2.85) and median PTH level was 92 pg/l (range 38–310) (Table 2). Ninety patients (78%) had a vitamin D deficiency and 13 (11%) had normal vitamin D level (missing data in 25 patients). Twenty-nine patients (33%) had a normal serum calcium level (\leq 2.6 mmol/l) associated with increased PTH concentration.

Preoperatively, the most commonly reported nonspecific symptoms included the following: fatigue (53%), anxiety (50%) and bone pain (44%) (Table 3).

Surgery and pathology

The types of surgical procedure were classic Kocher (78%), lateral cervicotomy (17%), or focal approach using cervicoscopy (5%). A total of 94 (81%) parathyroidectomies were performed under general anesthesia and 22 (19%) under local anesthesia (five under hypnosis). There was no perioperative mortality, and postoperative morbidity was 3%: one patient developed a superficial hematoma that required reoperation and three patients had transitory recurrent laryngeal nerve palsy. There was no postoperative (transient or permanent) hypocalcemia (defined by calcium level below 2.00 mmol/l).

Histologic examination revealed 107 solitary adenomas (92%) and nine cases of multiglandular disease (hyperplasia or multiple adenomas) (8%). There was no parathyroid carcinoma.

Evolution of biology after surgery

Three months after surgery The median serum calcium level was normalized after surgery and remained normal at 3 months. Median serum calcium and PTH levels are indicated in Table 2. Calcium and PTH levels normalized in 96 patients (83%). High

Table 2 Significant decrease over time of biological data (median (min–max)).

	Preoperative (%)	3 months	6 months	1 year
Calcemia (median (min–max)) (mmol/l)	2.67 (2.50–2.85)	2.40* (1.93–2.75)	2.37* (2.05–2.72)	2.37* (2.00–2.95)
Phosphoremia (median (min–max)) (mmol/l)	0.82 (0.34–2.87)	1.10* (0.64–1.67)	1.07* (0.51–1.57)	1.14* (0.64–1.71)
PTH (median (min–max)) (pg/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 (median (min–max)) (μ mol/l)	69.00 (35.00–125.00)	NA	NA	83.65 (70.00–97.30)
25 OH-hydroxyvitamin D (median (min–max)) (μ g/l)	18.80 (2.46–73.60)	27.05* (6.82–80.00)	NA	25.20* (8.00–74.00)

* $P < 0.05$ (statistical data relative to preoperative).

PTH levels (>60 pg/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 (>0.8 mmol/l). Sixty-three (54%) patients had persistent vitamin D deficiency albeit they all had postoperative vitamin D supplementation.

Six months after surgery Median serum calcium and PTH levels are indicated in Table 2. The median serum calcium level and PTH levels were normalized at 6 months. Only five patients had hypercalcemia.

Twelve months after surgery Median serum calcium and PTH levels are indicated in Table 2. Only five patients had hypercalcemia. Among the 16 patients with high PTH level and normocalcemia at 3 months, two still had an elevated PTH level with normocalcemia 12 months postoperatively. These were considered as persistent hypercalcemia (HPT). These patients had a median preoperative PTH level above the median of the preoperative overall analysis (127 vs 92.70 pg/l). The median serum phosphorus level was normalized at 1 year. Concerning the vitamin D, 37 patients (32%) were considered as vitamin D replete, 33 (28%) as vitamin D deplete, and data were missing for 46 (40%).

Evolution of nonspecific symptoms

Three months after surgery At 3 months, 97% of questionnaires were completed. Nineteen out of 22 nonspecific symptoms decreased after surgery (Table 3).

This decrease was statistically significant for 12 items: appetite loss, weight loss, thirst, polyuria, bone pain, muscular weakness, nausea, constipation, fatigue, depression, mood swings, and anxiety.

Six months after surgery At 6 months (88% of questionnaires completed), only six symptoms were significantly improved (appetite loss, thirst, bone pain, constipation, fatigue, and mood swings).

Twelve months after surgery At 1 year (89% of questionnaires completed), 15 of the 22 symptoms decreased and 11 symptoms were significantly improved (appetite loss, weight loss, thirst, polyuria, bone pain, constipation, fatigue, depression, mood swings, irritability, and anxiety). The level of vitamin D did not influence the nonspecific symptoms improvement.

Nonspecific symptoms according to age (<70 or ≥70 years)

Patients were classified according to an age cut-off (<70 or ≥70 years). It was the most relevant cut-off of improvement based on age. Sixty-seven patients were under 70 years before surgery and 49 patients were older. Preoperatively, there was no significant difference between the two age groups concerning nonspecific symptoms. At 1 year, all biological parameters were significantly improved regardless of the patients' age. Improvement of nonspecific symptoms at 1 year was greater in patients <70 years in whom nine symptoms significantly improved, while only four symptoms significantly improved in patients ≥70 years (Table 4).

Table 3 Nonspecific symptoms in all patients at preoperative period, 3, 6, and 12 months.

Symptoms	Preoperative (%)	3 months (%)	6 months (%)	12 months (%)
Appetite loss	22	6*	11*	6*
Weight loss	24	11*	15	13*
Thirst	29	12*	8*	5*
Polyuria	26	18*	15	12*
Headaches	22	14	13	14
Itchy skin	13	10	15	13
Bone pain	44	28*	27*	33*
Joint pain	38	38	36	39
Muscular pain	25	20	25	25
Muscular weakness	37	27*	26	23
Mobility difficulties	18	17	16	16
Nausea	8	2*	6	5
Abdominal pain	15	17	18	15
Abdominal distension	37	33	36	35
Constipation	28	17*	15*	17*
Ulcer	12	15	15	14
Fatigue	53	31*	32*	28*
Depression	27	18*	15	14*
Mood swings	27	17*	15*	16*
Irritability	27	21	24	18*
Anxiety	50	34*	44	34*
Forgetfulness	25	21	28	25

* $P < 0.05$ (statistical data relative to preoperative).

Table 4 Nonspecific symptoms significantly improved at 1 year according to age (<70 or ≥70 years).

Nonspecific symptoms significantly improved at 1 year	
<70 years	≥70 years
Appetite loss	Appetite loss
Thirst	Thirst
Headaches	Headaches
Bone pain	Fatigue
Muscular weakness	
Constipation	
Fatigue	
Mood swings	
Anxiety	

Nonspecific symptoms according to serum calcium level (<2.6 or ≥2.6 mmol/l)

We classified patients using calcemia cut-off criteria (<2.6 or ≥2.6 mmol/l). This cut-off was used because it was the upper normal limit. Twenty-nine patients had serum calcium levels <2.6 mmol/l before surgery and 87 patients had serum calcium levels ≥2.6 mmol/l. At 1 year, calcium, phosphorus, and PTH levels were significantly improved in all patients. Preoperatively, there was a significant difference in the prevalence of thirst and constipation, 7 and 13% in patients with calcium level <2.6 mmol/l vs 30 and 32% for patients with calcium level ≥2.6 mmol/l respectively. Improvement of nonspecific symptoms at 1 year was better in patients with serum calcium levels ≥2.6 mmol/l. Indeed, at 1 year, for these patients 12 symptoms remained significantly improved (Table 5), whereas in patients with serum calcium levels <2.6 mmol/l, two symptoms remained significantly improved (Table 5).

Preoperative clinical score

The purpose of the preoperative score was to detect the patients who will be clinically benefited from the surgery. A logistic regression enabled to create a score describing clinical improvement at 1 year as a function of age ($P=0.03$), and five nonspecific symptoms (weight loss ($P=0.01$), abdominal pain ($P=0.03$), abdominal distension ($P=0.06$), fatigue ($P=0.002$), and depressive symptoms ($P=0.03$)). The vitamin D level had no influence on the score preoperatively ($P=0.74$) and at 1 year ($P=0.27$). The parameters obtained from the logistic regression were then standardized to obtain a score between 0 and 12 (Table 6). The higher the score correlated with greatest improvement.

A cut-off at 3 allowed a specificity of 91% and sensitivity of 54% to be obtained for failure of improvement. The positive predictive value (PPV) was 81% and negative predictive value was 72%.

Patients with a high predictive score should be advised that they have a greater probability of symptom improvement compared with patients with a score ≤3.

Discussion

The aim of the study was to describe the numerous nonspecific symptoms correlated with mild pHPT, and to evaluate the evolution of these symptoms 3, 6, and 12 months after parathyroidectomy. This study also provided a preoperative score to detect patients who would most improve symptomatically postoperatively.

Many investigators currently agree that most patients with mild pHPT have a constellation of nonspecific symptoms that are not considered as the 'classic' symptoms of pHPT. Whether parathyroidectomy is beneficial in patients without classic symptoms remains a controversial issue. The questionnaire of nonspecific symptoms was based on literature reviews (8, 12, 16). The present series confirm that weight loss, fatigue, anxiety, and bone pain were the most frequent symptoms in patients with mild pHPT. Other authors have described the high prevalence of these symptoms. Joborn *et al.* had already used a psychiatric score, the Hopkins symptom checklist, to compare a group of control patients with a group of pHPT patients. They demonstrated that some psychiatric symptoms had a higher incidence in the pHPT group than in the control group (12). The most frequent symptoms were anxiety, depression, and cognitive impairment. Siperstein *et al.* (13) published a study on 42 patients with pHPT, in which fatigue, muscle weakness, high blood pressure, and bone and joint pain were frequently observed preoperatively regardless of the preoperative serum calcium levels. Roman *et al.* (17) showed that reduction in mood swings and anxiety symptoms were associated with reduction of PTH level in patients with pHPT who underwent successful parathyroidectomy. Weber *et al.* (18) confirmed that depression, anxiety, and impaired quality of life were related to pHPT. In their

Table 5 Nonspecific symptoms significantly improved at 1 year according to serum calcium level (<2.6 or ≥2.6 mmol/l).

Nonspecific symptoms significantly improved at 1 year	
≥2.6 mmol/l	<2.6 mmol/l
Appetite loss	Thirst
Thirst	Fatigue
Polyuria	
Headaches	
Bone pain	
Constipation	
Fatigue	
Depression	
Mood swings	
Irritability	
Anxiety	

Table 6 Calculation of the preoperative clinical score.

Variable	Response	Points
Age	≥ 70 years	0
	< 70 years	1
Weight loss	No	0
	Yes	2
Abdominal pain	Never or sometimes	0
	Often or always	3
Abdominal distension	Often or always	0
	Never or sometimes	1
Fatigue	Never or sometimes	0
	Often or always	3
Depressive symptoms	Often or always	2
	Never or sometimes	0
Score (sum)		12

series, successful parathyroidectomy reduced psychopathologic symptoms.

Similarly to prior studies, this study has shown that patients with mild pHPT had nonspecific symptoms that remained significantly improved 1 year after surgery. There was a weak significance ($P < 0.05$) for all improved symptoms. This is not surprising because all patients included were affected with asymptomatic HPT. There was a difference between 3 months (12 items improved), 6 months (six items), and 12 months (11 items) after surgery. At 3 months, patients can have a placebo effect of surgery. With time, effects of surgery appear. This could be an explanation for the better results at 12 than 6 months. Few randomized studies have been performed in asymptomatic PHPT showing no clear benefit in favor of surgery, but these studies showed a decrease of anxiety and phobia (10), an improvement of global health, mental health, and vitality (11) after surgical cure of mild pHPT (10, 11, 19). Differences observed between surgical literature and these randomised studies may be due to the fact that patients seen by surgeons are more symptomatic than those seen by endocrinologists.

Furthermore, the subgroup analysis showed a greater improvement in symptoms at 1 year in patients ≤ 70 years (nine vs four symptoms). Although older patients have more nonspecific symptoms than younger ones, including mood disorders, bone, and articular pains, the symptoms of fatigue, loss of appetite, headache, and polydipsia were still improved in patients > 70 years. Previous studies showed an improvement in these symptoms and quality of life in older patients, but most of these studies used 50 years old as the cut-off (20). In addition, we demonstrated that preoperative serum calcium level ≥ 2.6 mmol/l was associated with a greater improvement at 1 year of nonspecific symptoms compared with patients with a preoperative serum calcium level < 2.6 mmol/l (11 vs two symptoms). Finally, patients under 70 years or/and with serum calcium level ≥ 2.6 mmol/l have greater symptom improvement than all others groups.

To select more accurately patients for surgery, a clinical score based on age and the most relevant nonspecific symptoms was created. Several studies have attempted to develop more specific scores of pHPT, but were not focused on mild pHPT. Pasięka *et al.*, in a prospective study comparing pHPT patients with patients with a nontoxic thyroid nodule, used a questionnaire including 13 items. There were more symptoms in the pHPT than that in the thyroid group preoperatively ($P < 0.01$) (14). There was a significant improvement in symptoms between the preoperative and immediate postoperative period (between 7 and 10 days postoperatively). This study prospectively validated a score called Parathyroidectomy Assessment of Symptoms (PAS) score, specific to pHPT (18). This score was a scale to evaluate patients pre- and postoperatively. A multicentric study confirmed these results (15). The use of this score confirmed that patients with mild pHPT have more nonspecific symptoms than patients who underwent thyroidectomy. The improvement in the postoperative score was independent of 2008 Consensus Conference criteria (21). In this study, the PAS score was not used but a new predictive score has been developed, which incorporated some items from the PAS and other nonspecific symptoms from the literature. More recently, the first disease-specific HRQoL questionnaire for PHPT patients (PHPQoL-16) has been developed (22). As with the PAS score, it could not help to predict postoperative clinical improvement. This study allowed extracting a preoperative clinical score with relevant preoperative items: age, presence or absence of preoperative weight loss, abdominal pain, abdominal distension, fatigue, and depressive symptoms. This scoring system had a PPV of 81% for 'clinical improvement' and can be used by clinicians in consultation with patients preoperatively. Patients with a high predictive score should be advised that they have a higher probability of symptom improvement compared with patients with a score ≤ 3 . The vitamin D level did not influence the score pre- or postoperatively. This leads to consider that only surgery may explain health improvement.

There were some limitations in this study. This study did not compare surgery and medical treatment. However, other studies have shown that control of pHPT using these medications is not as effective (23). The issue of placebo effect may also play a role for these nonspecific symptom findings. This is hard to address and will remain to be a source of continued controversy. The analysis of hypophosphoremia had not been made. We do not think that the changes in phosphoremia were important enough to explain the health improvement, as the threshold for hypophosphoremia to become symptomatic is much lower (24). All patients were corrected at 3 months. Finally, a randomized study comparing surgery and medical management may be necessary to validate this improvement and the score.

Conclusion

In conclusion, mild pHPT nonspecific symptoms improve after parathyroidectomy. Younger patients and patients with a preoperative serum calcium level ≥ 2.6 mmol/l show the most improvement. However, improvement is still shown in patients > 70 years and with a serum calcium level < 2.6 mmol/l. Also, a clinical score > 3 has a PPV of 81% for improvement. Clinicians may incorporate this score into preoperative discussion with patients on symptom improvement postoperatively. Finally, although the predictive model has been developed, an external data set is required to validate these findings and is the goal of future projects.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Study concept and design: C Caillard, B Cariou, and E Mirallié. Acquisition of data: C Blanchard, M Mathonnet, F Sebag, C Caillard, A Hamy, V Wyart, D Drui, and J-F Henry. Analysis and interpretation of data: C Blanchard, D Drui, C Volteau, P Rodien, J-B Hardouin, and E Mirallié. Drafting of the manuscript: C Blanchard, M Roy, B Cariou, and E Mirallié. Critical revision of the manuscript for important intellectual content: B Cariou, J-F Henry, A Hamy, P Rodien, and F Archambeaud. Administrative, technical, statistical, and material support: C Volteau, J-B Hardouin, M-F Heymann, V Wyart, M Roy, and R Zarnegar. Study supervision: C Caillard and E Mirallié.

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