



ORIGINAL ARTICLE

The hidden burden of asymptomatic primary hyperparathyroidism: renal and bone complications in incidentally diagnosed patients

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ABSTRACT

Background: Primary hyperparathyroidism (PHPT) is increasingly diagnosed incidentally through routine biochemical screening. However, a critical question remains: is incidentally discovered PHPT truly asymptomatic, or does it already cause subclinical renal and bone damage? This study aimed to quantify the hidden burden of incidentally discovered PHPT by comparing clinical, biochemical, and complication profiles with symptomatic PHPT. **Methods:** Retrospective cohort study of 166 consecutive patients who underwent parathyroidectomy for PHPT between 2019 and 2025 at a tertiary referral center in Algeria. Patients were classified as incidental (completely asymptomatic, n=91, 54.8%) or symptomatic (n=75, 45.2%) after rigorous reclassification (patients with any symptom attributable to PHPT, including mild neurodigestive symptoms, were assigned to the symptomatic group). Preoperative PTH, calcium, vitamin D, renal lithiasis, bone mineral density (including distal radius), fractures, and surgical outcomes were compared. Multivariate logistic regression identified predictors of symptomatic presentation. **Results:** Among completely asymptomatic patients, a substantial proportion already exhibited target organ damage: 28% had renal lithiasis, and 38% had osteoporosis (based on DXA-available patients). The mean distal radius T-score was -1.8 SD. Compared to symptomatic patients, incidental patients had significantly lower PTH (median 120 vs 215 ng/L, p<0.001), lower calcium (114±11 vs 129±15 mg/L, p<0.001), and higher vitamin D (21.5±9.0 vs 14.0±7.5 ng/mL, p<0.001). However, the prevalence of osteoporosis was only 22 percentage points lower (38% vs 60%), and renal lithiasis was 19 percentage points lower (28% vs 47%). In other words, one in three incidental patients already had osteoporosis, and one in four already had kidney stones. Surgical success was 94% in both groups. **Conclusion:** Incidentally discovered (completely asymptomatic) PHPT is not a benign condition. A substantial proportion of patients already have significant renal and bone complications at diagnosis. These findings argue against a purely observational approach and support routine biochemical screening to enable earlier diagnosis and timely surgical intervention before irreversible complications occur.

Keywords: Primary hyperparathyroidism, incidental diagnosis, asymptomatic, osteoporosis, nephrolithiasis, parathyroidectomy.

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1. INTRODUCTION

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder, characterized by excessive parathyroid hormone (PTH) secretion leading to chronic hypercalcemia and complications such as nephrolithiasis, osteoporosis, and fractures [1]. The widespread use of routine biochemical screening has profoundly modified the clinical presentation of PHPT in developed countries, where up to 80% of patients are now asymptomatic at diagnosis [2,3].

However, a critical question remains: is incidentally discovered PHPT truly asymptomatic, or does it already cause subclinical renal and bone damage? Several studies have shown that patients labeled as "asymptomatic" often report improvement in non-specific symptoms after parathyroidectomy, suggesting that many symptoms were present but unrecognized [4]. More importantly, even in the absence of symptoms, target organ damage can occur. PHPT has a predilection for cortical bone, leading to preferential bone loss at the distal radius, and hypercalciuria can promote stone formation without overt renal colic [5,6].

In resource-limited settings, routine calcium screening is not widely implemented, and symptomatic forms remain common [7]. This provides a unique opportunity to compare incidentally discovered patients (who presumably represent an earlier stage of the disease) with symptomatic patients (who represent a more advanced stage). By quantifying the burden of renal and bone complications in completely asymptomatic patients, we can determine whether "asymptomatic" truly means "without harm."

The present study aimed to: (1) quantify the prevalence of renal lithiasis, osteoporosis, and fractures in completely asymptomatic PHPT; (2) compare these findings with symptomatic PHPT to understand the continuum of disease progression; (3) evaluate surgical outcomes in both groups to determine whether early intervention is equally effective; and (4) identify independent predictors of symptomatic presentation.

2. PATIENTS AND METHODS

Study design and population

A retrospective, observational, single-center cohort study was conducted at the Department of General Surgery, EHS of Organ and Tissue Transplantation, Blida, Algeria. All consecutive patients who underwent parathyroidectomy for sporadic PHPT between January 2019 and December 2025 were included. Data collection was completed in July 2026, after all patients had reached the 6-month postoperative follow-up.

Inclusion criteria: (i) preoperative hypercalcemia with elevated or inappropriately normal intact PTH; (ii) histologically confirmed parathyroid adenoma; (iii) complete clinical, biochemical, and imaging data. Exclusion criteria: secondary or tertiary hyperparathyroidism, parathyroid hyperplasia (without a dominant adenoma), parathyroid carcinoma, familial syndromes (MEN1, MEN2a, HPT-JT).

Ethical considerations

Informed consent was given for all patients for the surgical procedure and for the use of their anonymized data for research purposes. The study was conducted in accordance with the Declaration of Helsinki.

Definition of groups

Incidental PHPT (completely asymptomatic, n=91, 54.8%): patients diagnosed fortuitously during routine biochemical assessment (general check-up, preoperative workup, or evaluation of unrelated medical conditions) with absolutely no clinical manifestations attributable to PHPT (no bone pain, no renal colic, no pathological fractures, no neurodigestive symptoms such as asthenia, confusion, constipation, or nausea). The presence of silent renal stones or silent osteoporosis (without symptoms) did not reclassify the patient as symptomatic.

Symptomatic PHPT (n=75, 45.2%): patients presenting with at least one clinical manifestation clearly attributable to PHPT, including: nephrolithiasis with renal colic (painful stones), bone pain or pathological fractures, and neurodigestive symptoms (asthenia, confusion, constipation, nausea)

Importantly, the presence of osteoporosis or renal lithiasis alone, without associated symptoms, was NOT used to define the symptomatic group. This distinction avoids circularity and allows us to quantify the "hidden burden" in asymptomatic patients. Patients with mild neurodigestive symptoms (e.g., fatigue, occasional nausea) were reclassified from incidental to symptomatic to ensure rigorous international standards, resulting in 12 patients moving to the symptomatic group.

Preoperative biochemical evaluation

Blood samples were collected before any surgical intervention. Parameters included intact PTH (ng/L, normal range 15–80), total serum calcium (mg/L, normal 85–105) corrected for albumin, 25-OH vitamin D (ng/mL, deficiency defined as <20 ng/mL), serum phosphorus (mg/L, normal 25–45), alkaline phosphatase (U/L), serum creatinine (mg/L), and estimated glomerular filtration rate (eGFR, CKD-EPI). Twenty-four-hour urinary calcium excretion was measured in a subset of patients.

Bone evaluation

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) at the lumbar spine (L1-L4), femoral neck, total hip, and distal radius when available. Osteoporosis was defined as a T-score ≤ -2.5 at any site. Pathological fractures were documented by clinical history and confirmed by imaging. Bone pain was assessed by patient history. Alkaline phosphatase was used as a surrogate marker of bone turnover. Prevalence of osteoporosis was calculated based only on patients with available DXA data (142 patients, 86% of the cohort). This avoids underestimation.

Renal evaluation

Renal lithiasis was assessed by preoperative renal ultrasound. The presence of at least one kidney stone (any size) was recorded. Nephrocalcinosis was noted when present.

Preoperative imaging and localization

All patients underwent cervical ultrasound. Sestamibi scintigraphy was performed in selected cases (approximately 40%) when ultrasound was negative, discordant, or when ectopic or multiglandular disease was suspected. SPECT-CT was used in complex cases.

Surgical procedures and outcomes

Indication for targeted mini-cervicotomy was based on concordant preoperative imaging. Bilateral neck exploration was performed when imaging was discordant or when intraoperative findings suggested multiglandular disease.

Surgical success was defined as normalization of serum calcium (<105 mg/L) and a >50% drop in PTH from preoperative value on postoperative day 1, sustained at 6 months. Severe hypocalcemia was defined as serum calcium <70 mg/L OR <75 mg/L with clinical symptoms OR need for intravenous calcium infusion. Hungry bone syndrome was defined as severe hypocalcemia with hypophosphatemia (<25 mg/L) and elevated alkaline phosphatase (>2× upper normal limit) requiring intravenous calcium for >3 days.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). Comparisons used Student's t-test, Mann-Whitney U test, or χ^2 /Fisher's exact test. Multivariate logistic regression (backward stepwise) was performed to identify independent predictors of symptomatic presentation, including variables with $p < 0.10$ in univariate analysis (age, sex, BMI, PTH, calcium, phosphorus, vitamin D, alkaline phosphatase, adenoma weight). Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Model performance was assessed by AUC and the Hosmer-Lemeshow test. Two-tailed $p < 0.05$ was considered significant. Analyses used SPSS v26.

3. RESULTS

Baseline characteristics

After rigorous reclassification, 91 patients (54.8%) were completely asymptomatic (incidental) and 75 (45.2%) were symptomatic. The most common presenting symptoms were renal colic (32 patients, 19.3%), bone pain (22 patients, 13.3%), and neurodigestive symptoms (18 patients, 10.8%).

Table 1 shows baseline characteristics. Symptomatic patients were slightly younger (52.0 ± 12.0 vs 56.0 ± 12.5 years, $p = 0.06$), and sex distribution was similar (83% vs 82% female, $p = 0.81$). BMI did not differ (26.4 ± 4.5 vs 26.1 ± 4.2 kg/m², $p = 0.55$). Neurodigestive symptoms were present in 24% of symptomatic patients vs 0% of incidental patients (by definition).

The hidden burden: renal and bone complications in asymptomatic patients

Table 2 presents the prevalence of renal and bone complications. Among completely asymptomatic patients, 28% already had renal lithiasis (silent stones) documented on ultrasound, and 38% had osteoporosis (based on DXA-available patients). The mean distal radius T-score – a sensitive marker of cortical bone loss in PHPT – was already -1.8 SD. Pathological fractures were absent (0%) in incidental patients.

Table 1. Baseline characteristics and preoperative biochemical parameters.

Variable	Incidental (n=91)	Symptomatic (n=75)	p
Age (years, mean±SD)	56.0 ± 12.5	52.0 ± 12.0	0.06
Female sex, n (%)	75 (82%)	62 (83%)	0.81
BMI (kg/m ² , mean±SD)	26.1 ± 4.2	26.4 ± 4.5	0.55
PTH (ng/L), median (IQR)	120 (110–200)	215 (160–380)	<0.001
Serum calcium (mg/L, mean±SD)	114 ± 11	129 ± 15	<0.001
Vitamin D (ng/mL, mean±SD)	21.5 ± 9.0	14.0 ± 7.5	<0.001
Serum phosphorus (mg/L, mean±SD)	27.8 ± 8.5	23.2 ± 7.0	0.01
Urinary calcium (mg/24h, mean±SD)	287 ± 32	296 ± 35	0.18
Alkaline phosphatase (U/L), median (IQR)	76 (60–102)	98 (72–148)	0.02

Table 2. Renal and bone complications.

Complication	Incidental (n=91)	Symptomatic (n=75)	p
Renal lithiasis, n (%)	25 (28%)	35 (47%)	0.01
Osteoporosis (any site), n (%)*	33/87 (38%)	33/55 (60%)	0.02
Lumbar spine T-score (mean±SD)*	-1.2 ± 1.1	-1.9 ± 1.3	0.02
Femoral neck T-score*	-1.0 ± 0.9	-1.5 ± 1.1	0.03
Distal radius T-score*	-1.8 ± 1.4	-2.6 ± 1.6	0.01
Pathological fractures, n (%)	0	7 (9%)	0.01
Brown tumors, n (%)	0	3 (4%)	0.08

*DXA data available in 142 patients (87 incidental, 55 symptomatic); percentages calculated based on these denominators.

Key message: One in three completely asymptomatic patients already has osteoporosis; one in four already has silent kidney stones.

Adenoma characteristics and surgical findings

Table 3 summarizes surgical characteristics. Symptomatic patients had larger adenomas (2.9±2.1 vs 1.5±1.2 g, p=0.002) and larger median volume (2700 vs 1400 mm³, p=0.001). Multiglandular disease was more common in symptomatic patients (16% vs 6%, p=0.04). Bilateral neck exploration was required more often in symptomatic patients (29% vs 15%, p=0.03).

Table 3. Adenoma characteristics and surgical findings.

Variable	Incidental (n=91)	Symptomatic (n=75)	p
Adenoma weight (g, mean±SD)	1.5 ± 1.2	2.9 ± 2.1	0.002
Adenoma volume (mm ³), median (IQR)	1400 (900–2300)	2700 (1600–4600)	0.001
Multiglandular disease, n (%)	5 (6%)	12 (16%)	0.04
Targeted mini-cervicotomy, n (%)	76 (84%)	53 (71%)	0.04
Bilateral neck exploration, n (%)	14 (15%)	22 (29%)	0.03

Postoperative outcomes

Table 4 shows postoperative outcomes. Surgical success was 94% in both groups (p=0.96). Severe hypocalcemia occurred in 9% of incidental patients vs 12% of symptomatic patients (p=0.48). Hungry bone syndrome was not observed in incidental patients but occurred in 4% of symptomatic patients (p=0.09). Hospital stay was similar (2.8±0.9 vs 3.2±1.2 days, p=0.08). No permanent nerve injury or death occurred.

Table 4. Postoperative outcomes.

Parameter	Incidental (n=91)	Symptomatic (n=75)	p
Surgical success, n (%)	86 (94%)	70 (94%)	0.96
Severe hypocalcemia, n (%)	8 (9%)	9 (12%)	0.48
Hungry bone syndrome, n (%)	0	3 (4%)	0.09
Hospital stay (days, mean±SD)	2.8 ± 0.9	3.2 ± 1.2	0.08
Recurrent laryngeal nerve injury, n (%)	0	0	–

Multivariate analysis of predictors of symptomatic presentation

Table 5 presents the multivariate logistic regression model. After stepwise selection, independent predictors of symptomatic presentation were: higher PTH (OR 2.4 per 100 ng/L increase, 95% CI 1.5–4.0, $p=0.01$), larger adenoma weight (OR 2.2 per gram increase, 95% CI 1.3–3.8, $p=0.02$), and lower vitamin D (OR 0.6 per 10 ng/mL increase, 95% CI 0.4–0.9, $p=0.03$). Serum calcium and phosphorus were not retained ($p>0.10$). The model had an AUC of 0.78 (95% CI 0.71–0.85) and Hosmer-Lemeshow $p=0.35$.

Table 5. Multivariate logistic regression for symptomatic presentation.

Variable	Adjusted OR	95% CI	p
PTH (per 100 ng/L increase)	2.4	1.5–4.0	0.01
Adenoma weight (per gram increase)	2.2	1.3–3.8	0.02
Vitamin D (per 10 ng/mL increase)	0.6	0.4–0.9	0.03

4. DISCUSSION

This study provides three main findings. First, completely asymptomatic PHPT is associated with a substantial burden of renal and bone complications: one in three patients already has osteoporosis, and one in four already has silent kidney stones. Second, compared to symptomatic patients – who represent a more advanced stage – the prevalence of complications is only 19–22 percentage points lower, indicating that most of the disease burden is already present in the asymptomatic phase. Third, parathyroidectomy is equally effective in both groups, with 94% cure rates and low complication rates.

Asymptomatic PHPT is not benign: the hidden burden

The term "asymptomatic" is potentially misleading. In this study, 38% of completely asymptomatic patients met DXA criteria for osteoporosis, and 28% had silent renal stones. These patients had no symptoms (bone pain, renal colic, or neurodigestive complaints), yet they already had significant target organ damage. This finding has major clinical implications.

Our results are consistent with the literature. In a large US cohort of 582 patients undergoing parathyroidectomy, only 9.3% of those initially classified as asymptomatic remained asymptomatic after surgery [4]. This suggests that many "asymptomatic" patients actually have unrecognized symptoms. Furthermore, bone loss in PHPT preferentially affects cortical sites such as the distal radius, and this loss occurs early, often before symptoms appear [5,6]. In our cohort, the mean distal radius T-score in incidental patients was already -1.8 SD, well into the osteopenic range.

The continuum of disease progression

The comparison between incidental and symptomatic patients reveals a continuum. Symptomatic patients had higher PTH, higher calcium, lower vitamin D, larger adenomas, and higher rates of complications. However, the differences were quantitative rather than qualitative. The 19–22 percentage point gap in osteoporosis and lithiasis prevalence suggests that the asymptomatic phase is not a separate benign entity but simply an earlier stage along the same pathophysiological continuum.

This has important implications for clinical guidelines. Current guidelines (NIH 2009, AACE 2016) recommend parathyroidectomy for asymptomatic patients who meet certain criteria: age <50 years, serum calcium >1 mg/dL above normal, reduced bone density (T-score ≤ -2.5 at any site), renal stones, or reduced creatinine clearance [3]. Our findings support these criteria but also suggest that they may be too restrictive. In our cohort, many asymptomatic patients had osteoporosis or lithiasis – i.e., they already met surgical criteria – yet they were initially considered asymptomatic because they had no pain or colic.

Vitamin D deficiency as an aggravating factor

Incidental patients had significantly higher vitamin D levels than symptomatic patients (21.5 vs. 14.0 ng/mL, $p<0.001$). This is expected because vitamin D deficiency is known to exacerbate PHPT by further stimulating PTH secretion. However, even in incidental patients, the mean vitamin D level was only 21.5 ng/mL – borderline deficient by many standards (deficiency defined as <20 ng/mL). This suggests that many incidentally discovered patients have relative vitamin D insufficiency, which may have contributed to the development of secondary hyperparathyroidism on top of primary disease.

Surgical outcomes: early intervention is effective

Despite the higher disease burden in symptomatic patients, surgical success was identical (94%) in both groups. This confirms that parathyroidectomy is equally effective in asymptomatic patients. Moreover, the rate of severe postoperative hypocalcemia was similar (9% vs. 12%), and hungry bone syndrome was rare (0% vs. 4%). These findings argue against delaying surgery in asymptomatic patients who already have complications.

Comparison with international series

The clinical presentation of PHPT varies widely across geographic regions. In developed countries, up to 80% of patients are asymptomatic at diagnosis [2]. In contrast, in many resource-limited settings, symptomatic forms remain predominant [7]. Our cohort occupies an intermediate position: after rigorous reclassification, 55% were completely asymptomatic. Our asymptomatic patients had comparable PTH and calcium levels to Western series, but the prevalence of silent osteoporosis and lithiasis was substantial, highlighting the need for systematic screening. Surgical outcomes in our series (94% cure) are fully comparable with international benchmarks (94-99%) [8].

What this study adds

This study quantifies the hidden burden of completely asymptomatic PHPT. It demonstrates that asymptomatic PHPT is not benign: one in three patients already has osteoporosis, and one in four already has silent kidney stones. It also shows that the gap between asymptomatic and symptomatic disease is relatively narrow, supporting the concept of a continuum. Finally, it confirms that parathyroidectomy is safe and effective in asymptomatic patients.

Clinical implications

- Routine DXA with radius measurement should be performed in all patients with incidentally discovered PHPT, regardless of symptoms.
- Renal ultrasound should also be routine, as one in four asymptomatic patients has silent stones.
- Surgical referral should not be delayed until symptoms appear. Early intervention can prevent progression to more severe bone and renal disease.
- Vitamin D repletion should be considered in all patients with PHPT, with careful monitoring to avoid worsening hypercalcemia.

5. CONCLUSION

Completely asymptomatic primary hyperparathyroidism is not a benign condition. One in three patients already has osteoporosis, and one in four already has silent kidney stones at diagnosis. Compared to symptomatic patients, the burden of complications is only modestly lower, supporting the concept of a disease continuum. Parathyroidectomy is equally safe and effective in asymptomatic patients. These findings argue against a purely observational approach and support routine biochemical screening to enable earlier diagnosis and timely surgical intervention before irreversible complications occur.

Take-home message: Asymptomatic PHPT does not mean harmless. Early detection through routine calcium screening and timely parathyroidectomy can prevent irreversible renal and skeletal damage.

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