The Efficacy and Safety of Medical and Surgical Therapy in Patients With Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Both medical and surgical therapy represent potential management options for patients with asymptomatic primary hyperparathyroidism (PHPT). Because uncertainty remains regarding both medical and surgical therapy, this systematic review addresses the efficacy and safety of medical therapy in asymptomatic patients or symptomatic patients who decline surgery and surgery in asymptomatic patients. We searched Medline, Embase, Cochrane Central Register of Controlled Trials, and PubMed from inception to December 2020, and included randomized controlled trials in patients with PHPT that compared nonsurgical management with medical therapy versus without medical therapy and surgery versus no surgery in patients with asymptomatic PHPT. For surgical complications we included observational studies. Paired reviewers addressed eligibility, assessed risk of bias, and abstracted data for patient-important outcomes. We conducted random-effects meta-analyses to pool relative risks and mean differences with 95% confidence intervals and used Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) to assess quality of evidence for each outcome. For medical therapy, 11 trials reported in 12 publications including 438 patients proved eligible: three addressed alendronate, one denosumab, three cinacalcet, two vitamin D, and two estrogen therapy. Alendronate, denosumab, vitamin D, and estrogen therapy all increased bone density. Cinacalcet probably reduced serum calcium and parathyroid hormone (PTH) levels. Cinacalcet and vitamin D may have a small or no increase in overall adverse events. Very-low-quality evidence raised the possibility of an increase in serious adverse events with alendronate and denosumab. The trials also provided low-quality evidence for increased bleeding and mastalgia with estrogen therapy. For surgery, six trials presented in 12 reports including 441 patients proved eligible. Surgery achieved biochemical cure in 96.1% (high quality). We found no convincing evidence supporting an impact of surgery on fracture, quality of life, occurrence of kidney stones, and renal function, but the evidence proved low or very low quality. Surgery was associated with an increase in bone mineral density. For patients with symptomatic and asymptomatic primary hyperparathyroidism, this review provides evidence to inform clinical decision making.
PHPT, who are not candidates for parathyroid surgery, cinacalcet probably reduced serum calcium and PTH levels; anti-resorptives increased bone density. For patients with asymptomatic PHPT, surgery usually achieves biochemical cure. These results can help to inform patients and clinicians regarding use of medical therapy and surgery in PHPT.

**Introduction**

Parathyroidectomy is recommended for patients with symptomatic primary hyperparathyroidism (PHPT).\(^1\) Whether surgery is indicated in patients with asymptomatic PHPT—which constitutes more than 80% of PHPT in the United States and Western Europe—remains less certain.\(^2,3\) Moreover, guidelines for surgery in asymptomatic PHPT have not been updated for 7 years.\(^4\)

Medical approaches do not cure PHPT as surgery does. They do, however, represent a possible management option in certain situations, such as in asymptomatic patients with low bone density or those who present with concerning serum calcium levels, or symptomatic patients who decline surgery.

To support guidelines for the medical management of PHPT, we conducted two systematic reviews and meta-analyses of randomized controlled trials addressing the management of these patients. One addresses the impact of medical therapy versus no medical therapy in patients who have declined surgery. The second addresses the desirable and undesirable consequences of surgery in patients with asymptomatic PHPT. Symptomatic PHPT is defined as associated with skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, or nephrolithiasis and/or nephrocalcinosis. Asymptomatic PHPT is defined as no overt symptoms; typically discovered by biochemical screening. Two forms of asymptomatic PHPT are defined after evaluation: with target organ involvement; without target organ involvement.

This review provides context to other articles in this series. In those other articles, topics discussed in much greater depth with specific regard to clinical issues include the different presentations of PHPT, target organ involvement, surgical approaches, evaluation, and management.\(^4-7\)

**Methods**

We registered the protocols of these two systematic reviews with PROSPERO (CRD42021228695, CRD42021228687) on July 2, 2021.

**Search strategy**

In collaboration with a research information specialist, the review team developed the literature search for medical therapy that included Medline, Embase, the Cochrane Central Register of Controlled Trials from inception to December 9, 2020, and a PubMed search for studies not yet indexed in Medline. The search strategy contained two parts: population (PHPT) and medical therapy (Appendix S1). The review team also developed the literature search of surgery that included same databases from inception to December 3, 2020, and a PubMed search for studies not yet indexed in Medline. The search strategy contained two parts: population (asymptomatic PHPT) and surgery (Appendix S2).

Team members also reviewed reference lists of all included studies and relevant systematic reviews for additional references as well as searching Clinicaltrials.gov.

**Study selection**

For both reviews, seven reviewers working in pairs independently screened titles and abstracts and reviewed the full texts of potential eligible studies to determine. Reviewers resolved disagreements by discussion or by referral to a third reviewer.

For both reviews, we included only randomized controlled trials that enrolled PHPT patients and reported on at least one of our outcomes of interest. For the nonsurgical management review, eligible trials compared medical therapy versus no medical therapy aside from calcium supplements. Medical therapies included bisphosphonates (alendronate, risedronate, ibandronate, or zoledronic acid), denosumab, calcimimetics (cinacalcet), vitamin D, or estrogen therapy. We excluded patients with normocalcemic PHPT. If we suspected the presence of the first drug would influence the effect of the second (drug interaction), we excluded comparisons in which one candidate drug was added to another. Patient important outcomes included mortality, fracture, kidney stones, renal failure, quality of life, adverse events of interventions (eg, hypocalcemia), and serum calcium and parathyroid hormone (PTH) levels. Corresponding surrogate outcomes included 24-hour urinary calcium excretion for kidney stones, estimated glomerular filtration rate for renal failure, and dual-energy X-ray absorptiometry (DXA) for the assessment of osteoporosis.

The review of surgery in PHPT included randomized trials enrolling asymptomatic patients and compared surgery to no surgery, either strategy with or without medical therapy, and reporting on at least one of our outcomes of interest. For two trials in which the authors did not clearly report biochemical cure, we contacted the investigators for further information. Patient important outcomes included biochemical cure defined as one measurement of calcium in the normal range, fracture, kidney stones, renal failure, quality of life, congestive heart failure, stroke, myocardial infarction, mortality, costs, and complications of surgery (recurrent laryngeal nerve injury, symptomatic hypocalcemia, bleeding, infection). Bone density was also considered a patient-important outcome, because it defines the existence of an additional or concomitant diagnosis, that of osteoporosis. Corresponding surrogate outcomes included 24-hour urinary calcium excretion for kidney stone risk, estimated glomerular filtration rate for renal dysfunction, blood pressure for stroke and myocardial infarction risk, and ejection fraction and left ventricular hypertrophy for heart failure risk. We included observational studies that addressed surgical complications.

Our registered protocol included plans to include randomized controlled trials and, if we failed to identify eligible randomized trials, observational studies. For all benefit outcomes, the available randomized controlled trials provided higher quality than...
did the observational studies; for these outcomes therefore, we included only the randomized controlled trials.

Data extraction

Six reviewers undertook the data extraction with subsequent checks to ensure accuracy. Reviewers abstracted the following items with adjudication by a third reviewer: study characteristics (year of publication); population characteristics (age; sex; sample size; baseline serum calcium, PTH, and 24-hour urinary calcium excretion; and follow up period); description of interventions and comparators; and outcomes and their definitions.

Risk of bias assessment

Two reviewers independently assessed the risk of bias for each randomized controlled trial using a modified Cochrane Collaboration tool that includes sequence generation, allocation concealment, blinding, and missing outcome data (we judged high risk of bias if the rate of missing data was more than 10%). Each criterion was judged as definitely or probably low risk of bias, or definitely or probably high risk of bias. We did not summarize the overall risk of bias for studies across criteria. We resolved discrepancies by discussion and where needed, by third reviewer adjudication.

Data synthesis and analysis

We used random effects models for data synthesis and calculated risk ratios (RRs) or risk differences (RDs) and corresponding 95% confidence intervals (CIs) for all dichotomous outcomes, and mean differences (MDs) with corresponding 95% CI for continuous outcomes. For continuous outcomes, we used the inverse variance method; for dichotomous outcomes, the Mantel-Haenszel method. Our planned use of the Egger test to assess the publication bias proved not feasible because of an insufficient number of trials.

If trials reported data only in figures without specific data, we used WebPlotDigitizer to calculate the specific data from the figures. We used percentage change of g/cm² as the unit of bone mineral density (BMD) in data analysis and the mean and standard deviation (SD) of percentage change multiplied by baseline mean to estimate the mean and SD of change. If trials reported mean and 95% CI or standard error, we converted them to SD. If studies reported only data regarding baseline and posttreatment BMD, we calculated the mean and SD of change between baseline and posttreatment based on Cochrane handbook with the assumption of r of 0.5.

The analysis used mg/dL as the unit of serum calcium, pg/mL as the unit of serum PTH, and mg/24-hours as the unit of 24-hour urinary calcium excretion, converting data to these chosen units when necessary. If investigators reported a single outcome in more than one paper, analyses included the data with highest precision or, if the precision was similar, the longer follow up. We used an equation to convert serum creatinine to the estimated glomerular filtration rate, assumed they are female if the proportion of female more than 50%, and assumed patients were non-black race.

Separate analyses addressed each medical therapy. For vitamin D, alfalcacidol, and cholecalciferol were considered equivalent. The small number of studies precluded subgroup analysis for these forms of vitamin D.

Some trials reported the change between baseline and posttreatment, and some only the baseline and posttreatment data. On the basis of a prior methodological study, we assumed there is no relevant difference between follow-up and change data standardized mean differences, and combined these estimates.

In the surgery review, we defined biochemical cure as normalization of the serum calcium concentration after surgery. We used 10.3 mg/dL as the upper threshold of normal calcium and, when authors did not explicitly report biochemical cure, assumed the posttreatment calcium as normally distributed. We used the posttreatment serum calcium concentration to calculate the proportion of individuals below 10.3 mg/dL who became the proportion of patients whose serum calcium concentration had normalized after surgery. We did not use PTH concentration to define biochemical cure, because persistently elevated PTH levels for up to a year have been reported in those who have been cured. The binomial exact approach provided the method for calculating the CI for the proportion of patients in whom surgery achieved biochemical cure.

Assessment of certainty of evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, in which randomized, controlled trials (RCTs) start as high quality, to assess the quality of evidence, considering rating down for high risk of bias, imprecision (sometimes by more than one level), indirectness, inconsistency, and publication bias. We judged imprecision by comparing the CI to decision thresholds ultimately approved by the guideline panel with thresholds of important vertebral and nonvertebral fracture reduction of 1%; 5 in scores in Short Form-36 survey (SF-36) for domains of quality of life; 4% for kidney stones; and 5% for serious adverse events. Because most of the eligible trials did not report kidney stones, we used surrogate endpoints of 24-hour urinary calcium excretion. This index is generally recognized to predict kidney stones and, thus, it seems reasonable to make inferences on kidney stones based upon this surrogate end point. We also used serum creatinine to infer estimated glomerular filtration rate and renal function.

When studies reported missing data (loss to follow-up), complete cases constituted the primary analysis. By conducting a plausible worst case sensitivity analysis, this review also investigated the robustness of outcomes in which the confidence interval excluded no effect. For continuous outcomes, we used the worst mean score among the control arms of the eligible trials for those with missing data in the intervention arm, and the best mean score among the intervention arms of the eligible trials for missing data in the control arm. If significant effects remained in this analysis, we did not rate down for missing outcome data.

On the basis of the association between urinary calcium excretion and stone risk, this review used the surrogate outcome of 24-hour urinary calcium excretion to infer kidney stone risk at 10 years. Because the precise relationship between a reduction in urinary calcium excretion and a reduction in kidney stones is not clearly established, we rated down twice for indirectness of inferences regarding kidney stones from 24-hour urinary calcium excretion.

Consistent with GRADE guidance, when evidence is of moderate quality, we describe the intervention as “likely” or “probably” to produce the putative effect. When the evidence is of low quality, we state that the intervention “may” or “possibly” will produce the putative effect. Also consistent with GRADE guidance, if both direct and indirect evidence for the same outcome proved available, we presented only the one with higher quality in the summary of findings tables.
Results

Medical therapy of PHPT

Description of eligible trials

For medical therapy, Fig. 1 presents details of the study selection process. Of 3872 citations, 130 proved potentially eligible after title and abstract screening of which 11, reported in 12 publications, proved eligible.\(^{25-36}\) The number of patients ranged from 15 to 78, providing a total of 438 followed for 12 weeks to 2 years. Three trials compared alendronate versus no alendronate or placebo,\(^{25-27}\) one trial denosumab versus placebo,\(^{28}\) two trials estrogen therapy versus placebo,\(^{34,35}\) three trials cinacalcet versus placebo,\(^{29,30,36}\) and two trials (three reports) vitamin D versus placebo.\(^{31-33}\) Table 1 presents details of study characteristics and Appendix S3 summarizes risk of bias for each study.

Alendronate (Table 2)

Fracture

One trial including 37 patients reported no patient had a vertebral or nonvertebral fracture at 1 year in either the alendronate or no-alendronate group (very low quality).\(^{25}\) Forest plots of these results are shown in Appendix S4.

BMD (Table 3)

Two trials including 59 patients reported the total hip BMD at 1 to 2 years.\(^{25,26}\) In these two reports, alendronate significantly increased total hip BMD (MD 5.50; 95% CI, 3.71–7.30) compared with no alendronate. Three trials including 95 patients reported the lumbar spine BMD and femoral neck BMD at 1 to 2 years.\(^{25-27}\) Alendronate increased lumbar spine BMD (MD 5.55; 95% CI, 2.88–8.21) and femoral neck BMD (MD 3.63; 95% CI, 2.09–5.17) compared with no alendronate. The sensitivity analysis that took into account missing data did not appreciably change the results. Forest plots of these results are shown in Fig. 2A-C.

Serum calcium, PTH, and 24-hour urinary calcium excretion

Three trials including 95 patients reported serum calcium and PTH at 1 to 2 years and demonstrated no significant effects on serum calcium (MD –0.08; 95% CI, –0.28 to 0.12) and PTH (MD 11.71; 95% CI, –16.09 to 39.52).\(^{25-27}\) Three trials including 95 patients showed no significant effect of alendronate upon 24-hour urinary calcium excretion at 1 to 2 years (MD 5.83; 95% CI, –29.22 to 40.87).\(^{25-27}\) As an indirect measure of kidney stone risk, these results on 24-hour urinary calcium excretion infer no important effect on incidence of kidney stones. Forest plots of these results are shown in Appendix S4.

Adverse events

One trial, including 40 PHPT patients, reported two patients with serious adverse events in the alendronate group and three in the control group.\(^{27}\) Another trial including 37 PHPT patients reported that no patient experienced gastrointestinal symptoms or other adverse effects in either alendronate or no-alendronate group.\(^{25}\) Forest plots of these results are shown in Appendix S4.

Denosumab (Table 4)

Only one trial including 31 patients compared denosumab versus placebo in PHPT at 1 year.\(^{28}\)
| Study                        | Eligibility criteria                                                                 | Age (years) (mean ± SD) | Males (%) | Baseline serum calcium (mg/dL) | Baseline PTH (pg/mL) | Baseline urine calcium (mg/24 hours) | Interventions (drug name, duration, route, dose, and sample size of intervention group) | Comparisons (name of comparison group, sample size of comparison group) | Follow-up period |
|-----------------------------|---------------------------------------------------------------------------------------|-------------------------|-----------|-------------------------------|----------------------|--------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------|
| Chow and colleagues (27)    | Postmenopausal women with PHPT who: (1) did not meet criteria for surgery (NIH guidelines); (2) opted against surgery; (3) too high surgical risk; or (4) on the waiting list for surgery | 70 ± 9.3               | 0         | 11.3 ± 0.7                    | 208 ± 130           | 193 ± 106                            | Alendronate 10 mg/day for 48 weeks *(n = 20)*                                     | Placebo for 48 weeks *(n = 20)*                                        | 72 weeks         |
| Filopanti and colleagues (36) | Patients with genetically confirmed MEN1 affected by PHPT                              | 42.3 ± 12.2             | 46.7      | NR                            | NR                   | NR                                   | Crossover trial, seven patients received cinacalcet and eight patients were administered with placebo. After titration, the mean cinacalcet dosage was 40 ± 16 mg/day (3 months). After 1-month washout, treatments were switched between the two groups. After titration, the mean cinacalcet dosage was 48 ± 27 mg/day (3 months) *(n = 15)* |                                                                             | 7 months         |
| Grey and colleagues (35)     | Postmenopausal women with mild PHPT                                                   | 66.5 ± 7.7              | 0         | 10.6 ± 0.2                    | 77.9 ± 9.6          | NR                                   | Continuous combined therapy with conjugated equine estrogens, 0.625 mg/day, and medroxyprogesterone acetate, 5 mg/day for 2 years *(n = 21)* | Identical placebo tablets for 2 years *(n = 21)*                         | 2 years          |
| Khan and colleagues (25)     | Confirmed hypercalcemia and elevated PTH; reduced bone density, T < −1.0, at one or more skeletal sites | 67.0 ± 10               | 24.3      | 10.6 ± 0.4                    | 154 ± 113           | 215 ± 112                            | 10 mg alendronate daily for 1 year *(n = 22)*                                     | Placebo tablet for 1 year *(n = 22)*                                     | 1 year           |
| Khan and colleagues (29)     | Age >18 years, diagnosis of PHPT based on total adjusted calcium >11.3 mg/dL and <12.5 mg/dL and plasma PTH >55 pg/mL on two separate occasions at least | 72.3 ± 11.0             | 22.4      | 11.8 ± 0.5                    | 164 (131–211)       | NR                                   | Cinacalcet, a starting dose of 30 mg twice a day on day 1, sequentially increased to 60 mg twice daily, 90 mg twice daily or 90 mg three times daily for 28 weeks *(n = 33)* | Placebo for 28 weeks *(n = 34)*                                         | 28 weeks         |

(Continues)
| Study                        | Eligibility criteria                                                                 | Age (years) | Males (%) | Baseline serum calcium (mg/dL) | Baseline PTH (pg/mL) | Baseline urine calcium (mg/24 hours) | Interventions (drug name, duration, route, dose, and sample size of intervention group)                                                                 | Comparisons (name of comparison group, sample size of comparison group)                        | Follow-up period |
|-----------------------------|----------------------------------------------------------------------------------------|-------------|-----------|--------------------------------|----------------------|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------|
| Leere and colleagues\(^{28}\) | 7 days apart within the past 6 months before entry; and plus one of the following criteria: failed parathyroidectomy, cardiovascular or other comorbid conditions contraindicating surgery or surgery not considered appropriate or feasible, failure to find the parathyroid gland for removal, or ectopic parathyroid gland | 66.7 ± 2.4  | 19.4      | 10.9 ± 0.1                      | 115 ± 16             | NR                                  | 60 mg denosumab was administered subcutaneously every 6 months as prolia for 52 weeks (n = 15)                                                                 | Placebo for 52 weeks (n = 15)                                                               | 52 weeks        |
| Lind and colleagues\(^{33}\) | Age > 18 years; T-score between -1.0 and -3.5 at the lumbar spine, femoral neck, or total hip | 65 (48—80)  | 18.2      | 10.6 ± 0.3                      | 43 ± 15              | NR                                  | Alfacalcidol, the dose was raised by 0.25 μg in four 2-week intervals. After 8 weeks, receiving 1 μg daily for 6 months (n = 16) 30 mg cinacalcet twice daily for 52 weeks. The dose was increased sequentially to 40 and 50 mg twice daily at study week 4 and 8 if patients were still hypercalcemic (serum calcium 0.3 mg/dL) (n = 40) | Placebo for 6 months (n = 16)                                                                | 6 months        |
| Peacock and colleagues\(^{30}\) | Serum calcium concentration > 10.3 mg/dl and < 12.5 mg/dl and plasma PTH > 45 pg/mL       | 62 (27–83)  | 26.9      | 10.7 ± 0.5                      | 112 ± 46             | 290 ± 120/g Cr                      | Received 30 mg cinacalcet twice daily for 52 weeks. The dose was increased sequentially to 40 and 50 mg twice daily at study week 4 and 8 if patients were still hypercalcemic (serum calcium 0.3 mg/dL) (n = 38) | Received placebo twice daily for 52 weeks (n = 38)                                            | 52 weeks        |
|                            |                                                                                        | 58 (29–77)  | 24        |                                |                      |                                     |                                                                                                                                                |                                                                                                 | 52 weeks        |
### Table 1. Continued

| Study                      | Eligibility criteria                                                                 | Age (years) (mean ± SD) | Males (%) | Baseline serum calcium (mg/dL) | Baseline PTH (pg/mL) | Baseline urine calcium (mg/24 hours) | Interventions (drug name, duration, route, dose, and sample size of intervention group) | Comparisons (name of comparison group, sample size of comparison group) | Follow-up period |
|----------------------------|---------------------------------------------------------------------------------------|--------------------------|-----------|--------------------------------|----------------------|--------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------|
| Rolighed and colleagues    | >18 years; established PHPT with hypercalcemia on at least two occasions and vitamin D insufficiency. All were eligible for PTX | 11.3 (11.1–11.4)        | 123 (104–111) | 376 (320–432)                  |                      |                                      | Daily oral supplement of 70 μg (2800 IU) cholecalciferol (vitamin D3) for 52 weeks (n = 23) | Daily oral                  |                  |
| Rossini and colleagues     | Aged 67–81 years with osteoporosis and mild PHPT. All patients were unwilling or considered unfit for surgery because of advanced age or cardiovascular problems | 73.0 ± 4.5               | 0          | 11.0 ± 0.4                     | 150 ± 41             | NR                                   | 10 mg of alendronate taken orally on alternate days for 2 years (n = 13)                     | No treatment for 2 years (n = 13)                                      | 2 years          |
| Rubin and colleagues       | Postmenopausal women with asymptomatic PHPT. Did not meet NIH guidelines for PTX, had refused surgery or had previously undergone unsuccessful surgery | 62 ± 3                   | 0          | 10.68 ± 0.2                    | 220 ± 55             | 240 ± 41                             | Raloxifene 60 mg daily for an 8-week period, followed by a 4-week washout period (n = 9)     | Placebo tablet for an 8-week period, followed by a 4-week washout period (n = 9) | 12 weeks         |

PTX = parathyroidectomy; RCT = randomized, controlled trial.
Vertebral and total hip BMD (MD 4.1; 95% CI, 2.5 to 7.68%). These data infer that the incidence of kidney stones fluenced by denosumab. Forest plots of these results are shown in Appendix S5.

Serum calcium, PTH, and 24-hour urinary calcium excretion

The results showed that denosumab did not affect the serum calcium concentration (MD 0.08; 95% CI, −0.42 to 0.58), but significantly increased PTH (MD 33.33; 95% CI, 25.09–41.57). Investigators reported no difference in percentage change in 24-hour urinary calcium excretion (−3.10%; 95% CI, −13.88% to 7.68%). These data infer that the incidence of kidney stones may not be influenced by denosumab. Forest plots of these results are shown in Appendix S5.

Adverse events

Authors reported one serious event in a patient treated with denosumab (atypical focal epilepsy) and three in those given placebo (unstable angina pectoris, infected traumatic skin lesion, and gastritis). Forest plot of this result is shown in Appendix S5.

Cinacalcet (Table 5)

Fracture

One patient in the denosumab group experienced a wrist fracture while participating in the study; no new vertebral fractures had occurred at study end (very low quality). Forest plots of these results are shown in Appendix S5.

BMD (Table 3)

Denosumab significantly increased lumbar spine BMD (MD 6.9; 95% CI, 4.2–9.6), femoral neck BMD (MD 3.8; 95% CI, 1.4–6.3), and total hip BMD (MD 4.1; 95% CI, 2.5–5.8). Forest plots of these results are shown in Fig. 3A–C.

Serum calcium, PTH, and 24-hour urinary calcium excretion

Three trials including 114 patients reported serum calcium and PTH at 28 to 52 weeks (29,30,36) Cinacalcet significantly reduced serum calcium (MD −1.60; 95% CI, −2.07 to −1.13; moderate quality) and PTH (MD −29.99; 95% CI, −41.21 to −18.76; moderate quality). A sensitivity analysis that took into account missing data did not appreciably change the results of serum calcium and PTH. Cinacalcet reduced the serum calcium concentration into the normal range to a greater extent than it reduced the PTH level. Two trials reported no difference in 24-hour urinary calcium excretion at 28 to 52 weeks (29,30,36) Using this urinary index, the data did not infer any influence on incidence of kidney stones.

Table 2. GRADE Summary of Findings for Alendronate in PHPT Patients

| Outcomes (duration of follow-up in studies) | Relative effects (95% CI; number of patients and trials) | Baseline risk for control group | Difference (95% CI) | Quality of evidence | Plain language summary |
|---------------------------------------------|----------------------------------------------------------|--------------------------------|----------------------|----------------------|------------------------|
| Vertebral fracture                          | Not estimable; 37 patients in one trial                  | Not applicable                 | 0% (−10% to 10%)²   | Very low (serious risk of bias and very serious imprecision) | We are very uncertain of the effect of alendronate on vertebral fracture |
| Nonvertebral fracture                       | Not estimable; 31 patients in one trial                  | Not applicable                 | 0% (−10% to 10%)²   | Very low (serious risk of bias and very serious imprecision) | We are very uncertain of the effect of alendronate on nonvertebral fracture |
| Serious adverse events (1 year)             | RR 0.67 (0.12 to 3.57); 40 patients in one trial         | Not applicable, differences calculated directly from absolute estimates | −5% (−25% to 15%)² | Very low (rate down three times for very serious imprecision) | We are very uncertain of the effect of alendronate on serious adverse events |

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; RR = risk ratio.

²We calculated the risk difference directly in Revman.

Table 3. Effect of Medical Therapy on BMD by DXA in PHPT

| Drug               | Lumbar spine | Femoral neck | Total hip | 1/3 Radius |
|--------------------|--------------|--------------|-----------|------------|
| Alendronate        | 5.55 (2.88 to 8.21) | 3.63 (2.09 to 5.17) | 5.50 (3.71 to 7.30) |
| Denosumab          | 6.9 (4.2 to 9.6) | 3.8 (1.4 to 6.3) | 4.1 (2.5 to 5.8) | No effect |
| Cinacalcet         | No effect    | No effect    | No effect  | No effect  |
| Vitamin D          | 2.50 (0.70 to 4.30) | 0.60 (−1.33 to 2.53) | MD −0.50 (−2.17 to 1.17) | −0.10 (−1.96 to 1.76) |
| Estrogen           | 6.60 (3.44 to 9.76) | 4.80 (0.39 to 9.21) | −0.70 (−4.73 to 3.33) | 5.40 (2.21 to 8.59) |

Data presented as MD with 95% CI.

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; MD = mean difference.
Table 4. GRADE Summary of Findings for Denosumab in PHPT Patients

| Outcomes (duration of follow-up in studies) | Relative effects (95% CI); number of patients and trials | Baseline risk for control group | Difference (95% CI) | Quality of evidence | Plain language summary |
|---------------------------------------------|----------------------------------------------------------|--------------------------------|---------------------|---------------------|------------------------|
| Vertebral fracture                           | Not estimable; 31 patients in one trial                  | Not applicable                 | 0% (−12% to 12%)a   | Very low (very serious imprecision)b | We are very uncertain of the effect of denosumab on vertebral fracture |
| Nonvertebral fracture                        | RR 2.82 (0.12 to 64.39); 31 patients in one trial       | Not applicable                 | 6% (−10% to 22%)a   | Very low (very serious imprecision)b | We are very uncertain of the effect of denosumab on nonvertebral fracture |
| Serious adverse events (1 year)              | RR 0.31 (0.04 to 2.68); 31 patients in one trial        | Not applicable, differences calculated directly from absolute estimates | −14% (−37% to 10%)a | Very low (rate down three times for very serious imprecision) | We are very uncertain of the effect of denosumab on serious adverse events |

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation.

aWe calculated the risk difference directly in Revman.

bWe rated down three times because of very serious imprecision.
Table 5. GRADE Summary of Findings for Cinacalcet in PHPT Patients

| Outcomes (duration of follow-up in studies) | Relative effects (95% CI); number of patients and trials | Absolute difference (95% CI) | Quality of evidence | Plain language summary |
|--------------------------------------------|---------------------------------------------------------|-----------------------------|---------------------|-----------------------|
| Fractures (52 weeks)                        | No data reported                                        |                             | Moderate (serious imprecision) | Cinacalcet probably normalizes serum calcium levels |
| Serum calcium (28–52 weeks)                 | 110 patients in two trials                              | MD −1.39 (−1.76 to −1.02)   |                     | Cinacalcet probably normalizes serum calcium levels |
| Serum PTH (28–52 weeks)                     | 110 patients in two trials                              | MD −29.73 (−43.99 to −15.47)| Moderate (serious imprecision) | Cinacalcet probably normalizes serum PTH levels |
| QoL-Physical component summary (SF-36)      | Not applicable                                          | MD 2.90 (−0.28 to 6.08); 55 patients in one trial | Low (serious risk of bias and serious imprecision) | Cinacalcet may have a small or no effect on physical component summary |
| (28 weeks)                                 |                                                         |                             |                     | Cinacalcet may have a small or no effect on physical component summary |
| QoL-Mental component summary (SF-36)        | Not applicable                                          | MD 4.30 (0.01 to 8.59); 55 patients in one trial | Low (serious risk of bias and serious imprecision) | Cinacalcet may have a small or no effect on mental component summary |
| (28 weeks)                                 |                                                         |                             |                     | Cinacalcet may have a small or no effect on mental component summary |
| Serious adverse events (28–52 weeks)       | RR 1.08 (0.49 to 2.40); 145 patients in two trials     | 0% (−11% to 11%)            | Low (rate down twice for very serious imprecision) | Cinacalcet may have a small or no effect on serious adverse events |

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; RR = risk ratio.

*Rated down for high risk of missing outcome data.

*In the sensitivity analysis considering the missing data, results on mental component summary lost statistical significance, mandating rating down for risk of bias.

*We calculated the risk difference directly in Revman.
stone incidence. Forest plots of serum calcium and PTH are shown in Fig. 4A, B, forest plot of 24-hour urinary calcium excretion is shown in Appendix S6.

Quality of life
One trial including 55 patients reported the quality of life at 28 weeks. As measured by the SF-36 scale, cinacalcet did not affect the composite physical component score (MD 2.90; 95% CI, 0.28 to 6.08; low quality) nor the composite mental component score (MD 4.30; 95% CI, 0.01–8.59; low quality). A crossover trial including 15 patients reported that similar scale scores were recorded in cinacalcet and placebo treatments. Forest plots of these results are shown in Appendix S6.

Adverse events
Two trials including 145 patients reported small or no serious adverse events associated with cinacalcet (risk ratio [RR] 1.08; 95% CI, 0.49–2.40; 0%, low quality). One of the trials

Table 6. GRADE Summary of Findings for Vitamin D in PHPT Patients

| Outcomes (duration of follow-up in studies) | Relative effects (95% CI); number of patients and trials | Absolute effect estimates | Quality of evidence | Plain language summary |
|--------------------------------------------|--------------------------------------------------------|--------------------------|---------------------|------------------------|
| Fractures (25 weeks)                        | No data reported                                        |                          |                      |                        |
| QoL-Physical component summary (% change) (25 weeks) | Not applicable                                          | MD = –7.47 (–14.75 to –0.19); 40 patients in one trial | Very low (serious risk of bias and very serious imprecision)* | We are very uncertain of the effect of vitamin D on physical component summary |
| QoL-Mental component summary (% change) (25 weeks) | Not applicable                                          | MD = –6.88 (–18.91 to 5.15); 40 patients in one trial | Very low (serious risk of bias and very serious imprecision) | We are very uncertain of the effect of vitamin D on mental component summary |

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; QoL = quality of life.

*In the sensitivity analysis considering the missing data, results on physical component summary lost statistical significance, mandating rating down for risk of bias.

(A) Serum calcium

(B) Serum PTH

Fig. 4. Effects of cinacalcet on serum calcium and PTH in patients with asymptomatic primary hyperparathyroidism patients. (A) Serum calcium. (B) Serum PTH.

Journal of Bone and Mineral Research
Fig. 5. Effects of vitamin D on BMD in patients with asymptomatic primary hyperparathyroidism patients. (A) Lumbar spine. (B) Femoral neck. (C) Total hip. (D) Proximal 1/3 of distal forearm.

Table 7. GRADE Summary of Findings for Estrogen Therapy in PHPT Patients

| Outcomes (duration of follow-up in studies) | Relative effects (95% CI); number of patients and trials | Absolute effect estimates | Quality of evidence | Plain language summary |
|---------------------------------------------|--------------------------------------------------------|--------------------------|---------------------|-----------------------|
| Fractures (2 year) Vaginal bleeding (2 years) Mastalgia (2 years) | No data reported 33 patients in one trial Not applicable, differences calculated directly from absolute estimates 33 patients in one trial | Baseline risk for control group: 53% (29% to 77%) Calculated directly from baseline risk for control group: 45% (15% to 75%) | Low (rate down twice for very serious imprecision) Low (rate down twice for very serious imprecision) | Estrogen therapy may increase vaginal bleeding Estrogen therapy may increase mastalgia |

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation.
Fig. 6. Effects of estrogen therapy on BMD in patients with asymptomatic primary hyperparathyroidism patients. (A) Lumbar spine. (B) Femoral neck. (C) Proximal forearm.

1628 records identified from literature search (MedLine = 488, Embase = 487, CENTRAL = 194, PubMed = 455, ClinicalTrials.gov = 4)

1251 records after duplicates removed

1095 records excluded

156 full text articles assessed for eligibility

144 full text articles excluded

66 Not randomized controlled trials

43 Inappropriate population

12 Inappropriate intervention or comparison

12 Duplicates (overlapping populations)

10 Inappropriate outcomes

1 Ongoing trial

12 studies included (6 trials)

Fig. 7. Flowchart showing the selection process of literature search of surgery in patients with asymptomatic primary hyperparathyroidism.
| Study                        | Eligibility criteria                                                                 | Age, years (mean ± SD) | Males, % | Baseline serum calcium (mg/dL) | Baseline PTH (pg/mL) | Baseline urine calcium (mg/24 hours) | Concomitant medical therapies | Comparisons                      | Follow-up period |
|------------------------------|---------------------------------------------------------------------------------------|------------------------|----------|-------------------------------|---------------------|-------------------------------------|-------------------------------|-------------------------------|-----------------|
| Almqvist and colleagues      | Age >45 years. Hypercalcemia: 10.2 to 11.8 mg/dL; inappropriately elevated PTH (>40 ng/L) | 69 ± 9                 | 8        | 10.5 ± .44                    | 79.7 ± 29           | 258 ± 121                           | NR                            | Surgery (n = 25); No surgery (n = 25) | 1 year          |
| Ambrogini and colleagues     | Age 50–75 years, No NIH criteria for PTX with the following criteria: asymptomatic PHPT; albumin-adjusted serum calcium <1 mg/dL above the upper limit of normal (11.2 mg/dL) on at least three occasions; 24-hour urine calcium excretion <400 mg; no creatinine clearance or reduced by no more than 30% compared with age matched controls; age- and sex-matched BMD at the distal third of radius > -2.0 (Z-score) | 64.5 ± 6.0             | 8        | 10.2 ± .45                    | 112 ± 42            | 237 ± 72                            | NR                            | Parathyroidectomy (n = 24); No parathyroidectomy (n = 26) | 1 year          |
| Ejlsmark-Svensson and colleagues | Age >18 years; eligible for PTX as per NIH guidelines                                   | 64 (56–69)             | 28       | 11.3 (11.1–11.7)              | 98 (75–125)         | 264 (200–392)                       | Statins (28%); Antihypertensive (39%) | PTX (n = 40); No surgery (n = 39) | 3 months        |
| Morris and colleagues       | Age > 50 years. Biochemically confirmed PHPT; no NIH guidelines for PTX and asymptomatic | 65.5 ± 10              | 16.7     | 10.4 ± .38                    | 122 ± 40            | NR                                  | NR                            | Surgical group (parathyroidectomy) (n = 9); Control group (observed for 6 months) (n = 9) | 6 months        |
| Perrier and colleagues      |                                                                                        |                        |          |                               |                     |                                     |                               | Surgery (n = 96); Observation (n = 95) | 10 years        |
| SIPH trial                  |                                                                                        | 64.2 ± 7.4             | 13.6     | 10.8 ± .32                    | 97.6 ± 32           | NR                                  | NR                            |                               |                 |

(Continues)
including 67 patients reported that treatment-associated adverse events (serious and nonserious) were similar between groups (27 cinacalcet versus 20 placebo) at 28 weeks. Hypocalcemia was not seen in either the cinacalcet or placebo groups.\(^{29}\) Another trial reported, as the two most common adverse events, nausea (28% cinacalcet, 16% placebo) and headache (23% cinacalcet, 41% placebo).\(^{30}\) The crossover trial reported no significant difference in gastrointestinal and neuromuscular symptoms.\(^{36}\) Forest plots of these results are shown in Appendix S6.

Estimated glomerular filtration rate

One trial reported no significant difference between treatment and control in the post treatment serum creatinine.\(^{36}\) Forest plot of this result is shown in Appendix S6.

**Vitamin D (Table 6)**

Fracture

No data reported.

**BMD (Table 3)**

One trial including 40 patients reported that vitamin D significantly increased BMD in the lumbar spine at 25 weeks (MD 2.50; 95% CI, 0.70–4.30) but not in the femoral neck (MD 0.60; 95% CI, −1.33 to 2.53), total hip (MD −0.50; 95% CI, −2.17 to 1.17) or proximal 1/3 of distal forearm (MD −0.10; 95% CI, −1.96 to 1.76).\(^{31}\) The sensitivity analysis considering the missing data did not appreciably change the result on lumbar spine. Forest plots of these results are shown in Fig. 5A–D.

Serum calcium, PTH, and 24-hour urinary calcium excretion

Two trials reporting on serum calcium and PTH at 6 months did not detect significant effects on serum calcium (MD 0.07; 95% CI, −0.12 to 0.26) or PTH (MD −7.14; 95% CI, −15.24 to 0.96).\(^{31,33}\) One trial reported no effect on 24-hour urinary calcium excretion at 6 months (MD −8.00; 95% CI, −113.88 to 97.88).\(^{31}\) Forest plots of these results are shown in Appendix S7.

**Quality of life**

Another publication from the same trial reported on change in quality of life as measured by the SF-36 scale from baseline to week 25.\(^{32}\) The results do not provide support for an effect of vitamin D on the composite physical component score (MD −7.47%; 95% CI, −14.75% to −0.19%; very low quality) or the composite mental component score (MD −6.88%; 95% CI, −18.91% to 5.15%; very low quality). Forest plots of these results are shown in Appendix S7.

**Adverse events**

One trial reported that both the vitamin D and placebo were well tolerated and that compliance to study medication was high (96%) with no difference between groups. Authors reported no statistically significant difference in adverse events in the two groups.\(^{31}\)
Estimated glomerular filtration rate
One trial reported no significant difference between treatment and control in the posttreatment serum creatinine. Forest plot of this result is shown in Appendix S7.

Estrogen therapy (Table 7)
Fracture
No data reported.

BMD (Table 3)
One trial including 33 patients receiving continuous combined therapy with conjugated equine estrogens (0.625 mg/day) and medroxyprogesterone acetate (5 mg/day) reported on BMD in the lumbar spine, femoral neck, and 1/3 forearm at 2 years. This trial reported significant gains in lumbar spine BMD (mean change in %, 6.60; 95% CI, 3.44 to 9.76), femoral neck BMD (mean change in %, 4.80; 95% CI, 0.39 to 9.21), and proximal forearm BMD (mean change in %, 5.40; 95% CI, 2.21 to 8.59). Forest plots of these results are shown in Fig. 6A-C.

Serum calcium, PTH, and 24-hour urinary calcium excretion
Two trials including 49 patients reported no significant effect on the serum calcium concentration (mean change in mg/dL, 0.21; 95% CI, 0.50 to 0.07), PTH (mean change in pg/mL, 11.02; 95% CI, −18.19 to 40.24), or 24-hour urinary calcium (mean change in mg/day, −39.89; 95% CI, −90.60 to 10.82). Forest plots of these results are shown in Appendix S8.

Adverse events
One trial including 33 patients reported nine patients with vaginal bleeding in the estrogen therapy group versus no patient in the placebo group at 2 years (absolute difference 53%; 95% CI, 29% to 77%; low quality). Fourteen patients had mastalgia in the estrogen therapy group versus six patients in placebo group (absolute differences 45%; 95% CI, 15% to 75%; low quality). Forest plots of these results are shown in Appendix S8.

Surgery in PHPT

Description of eligible trials
For surgery, Fig. 7 presents details of the study selection process. Of 1628 citations from the literature search, 156 proved potentially eligible after title and abstract screening, of which six trials reported in 12 publications proved eligible. The number of patients ranged from 18 to 191, providing a total of 441 followed for 0.25 to 10 years. Table 8 presents details of study characteristics and Appendix S9 summarizes risk of bias assessment for each study.

Serum calcium and PTH
Three trials reported posttreatment serum calcium and PTH level in both surgery and no surgery groups. The results showed that surgery significantly reduced serum calcium concentration (mean decline in mg/dL, 1.02; 95% CI, −1.15 to −0.89) and in PTH (mean decline in pg/mL, 40.54; 95% CI, −59.35 to −21.74). Forest plots of these results are shown in Fig. 8A-B.

Biochemical cure (Table 9)
We inferred biochemical cure from five trials including 316 patients. One study reported three patients who developed recurrent hyperparathyroidism after surgery, another study reported one patient with persistent hypercalcemia after surgery, and the lead investigator of one trial...
Table 9. GRADE Summary of Findings for Surgery Versus No Surgery in Patients with Asymptomatic PHPT

| Outcomes (duration of follow-up in studies) | Relative effects and/or MD (95% CI); number of patients and trials | Baseline risk for control group | Difference (95% CI) | Quality of evidence | Plain language summary |
|---------------------------------------------|---------------------------------------------------------------|---------------------------------|---------------------|-------------------|----------------------|
| Biochemical cure (0.5 to 5 years)           | 316 patients in five trials                                  | 0                               | 96.1% (92.1% to 98.4%) | High               | Surgery results in a very high rate of biochemical cure; cure does not occur in patients who do not undergo surgery |
| Vertebral fracture (1 to 5 years)           | RR 0.18 (0.02 to 1.48); 156 patients in two trials          | Not applicable                   | –7% (–13% to –1%)    | Very low (serious risk of bias and very serious imprecision) | We are very uncertain of the effect of surgery on vertebral fracture |
| Nonvertebral fracture (2 to 5 years)        | RR 0.81 (0.19 to 3.44); 159 patients in two trials          | Not applicable                   | –1% (–6% to 5%)      | Very low (serious risk of bias and very serious imprecision) | We are very uncertain of the effect of surgery on non-vertebral fracture |
| Quality of life (1 to 10 years)             | 225 patients in three trials                                | Not applicable                   | Social functioning CI excluded no effect, other seven domains CI included both benefit and harm –1% (–4% to 3%) | All domains rated down for risk of bias and imprecision, some domains rated down twice for imprecision | We are very uncertain of the effect of surgery on Quality of Life |
| Kidney stone (1 to 5 years)                 | RR 0.55 (0.10 to 3.10); 248 patients in three trials        | 0                               | 0 (–7%, 7%)          | Very low (serious risk of bias and very serious imprecision) | We are very uncertain of the effect of surgery on kidney stones |
| Renal failure (2 years)                     | RR not estimable; 53 patients in one trial                  | 0                               | 0 (–7%, 7%)          | Low (very serious imprecision)                             | Surgery may have a small or no effect on renal failure |
| Surgical complications (1 year)             | RR not estimable; 50 patients in one trial                  | 0                               | 0 (–7%, 7%)          | Low (very serious imprecision)                             | Surgical complications may be very rare |

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; RR = risk ratio.

*We calculated the risk difference directly in Revman.

provided unpublished results that three patients had unchanged postoperative calcium and PTH levels. Four trials including 258 patients reported lumbar spine BMD at 1 to 5 years. Surgery significantly increased lumbar spine BMD compared with no surgery (MD 4.82; 95% CI, 2.55–7.09). Three trials including 208 patients reported femoral neck BMD at 2 to 5 years (MD 3.18; 95% CI, –0.95 to 7.31). Two trials including 103 patients reported total hip BMD at 2 to 5 years (MD 4.41; 95% CI, 2.62–6.20). The increase in BMD at the total hip, but not femoral neck, was significant. Two trials including 136 patients reported 1/3 radius BMD at 1 to 5 years (MD 0.28; 95% CI, –1.25 to 9.58). One trial including 53 patients reported forearm BMD at 2 years (MD –1.47; 95% CI, –10.13 to 7.19). Forest plots of these results are shown in Appendix S10.

Fracture (Table 9)

Two trials including 156 patients reported vertebral fracture at 1 to 5 years. Surgery may reduce the rate of vertebral fracture (RR 0.18; 95% CI, 0.02–1.48; 7% fewer; very low quality). Two trials including 159 patients reported nonvertebral fracture at 2 to 5 years, and the result provided very low quality evidence (RR 0.81; 95% CI, 0.19–3.44; 1% fewer; very low quality). Forest plots of these results are shown in Appendix S10.

Kidney stones and renal failure (Table 9)

Three trials including 248 patients reported three kidney stones in 127 control group patients and one kidney stone in
121 surgery patients at 1 to 5 years. By our methodological criteria, the evidence for reduced kidney stones was deemed to be very low quality. One trial reported the change in 24-hour urinary calcium excretion (mg/24 hours) at 1 year (MD 135.20; 95% CI, 188.69 to 81.71). It suggests no important effect on incidence of kidney stone.

One trial reporting on renal failure at 2 years, found no renal dysfunction in either surgery or no surgery groups. The evidence for stable renal function proved to be low quality. Forest plots of these results are shown in Appendix S10.

Quality of life

Three trials with 225 patients reported the quality of life in eight domains at 1 to 10 years using the SF-36 scale. There are no clear and consistent effects of surgery on any of the eight domains of the SF-36 scale. The impossibility of blinding introduces risk of bias, and the small sample sizes result in wide CIs in assessing the effect of surgery on these quality domains of life. This review provided low quality evidence for change in social functioning (MD 6.51; 95% CI, 1.04 to 11.98), vitality (MD 6.42; 95% CI, −1.93 to 14.77), mental health (MD 4.38; 95% CI, −0.34 to 9.10), and physical functioning (MD 0.34; 95% CI, −4.56 to 5.24); and very low quality evidence for change in bodily pain (MD 7.04; 95% CI, −10.22 to 24.31), emotional role functioning (MD 3.80; 95% CI, −7.10 to 14.70), general health perceptions (MD 5.88; 95% CI, −2.15 to 13.91), and physical role function (MD 4.37; 95% CI, −15.60 to 24.34). Forest plots of these results are shown in Appendix S10.

One trial reported the effect of surgery on the Comprehensive Psychopathological Rating Scale at 10 years, and there were no significant differences between two groups.

Mortality

Only one trial including 191 patients reported mortality at 5 years: two patients died in the surgery group, one in the no surgery group. Surgery probably has a small or no effect on mortality (risk difference (RD) 1%; 95% CI, −2% to 5%; low quality). Forest plot of this result is shown in Appendix S10.

Surgical complications (Table 9)

One trial reported that no surgical complications occurred. In another, one patient required an overnight postoperative drain in the neck. Because of the small number of patients and the resulting wide CIs, the evidence proved of low quality. Forest plot of this result is shown in Appendix S10.

Observational studies reporting post-parathyroidectomy complications were reviewed. Early postoperative complications include hypocalcemia and hematoma. The incidence of hematoma after parathyroidectomy is exceedingly low, on the order of 0.3%. Postoperative hypocalcemia occurs across a wide range (5% to 47%). It is generally transient and managed with calcium supplementation in the outpatient setting. Longer-term complications are rare, but include recurrent laryngeal nerve injury (<1%) and permanent hypoparathyroidism (from 0% to 3.6%). Other complications including infection, superior laryngeal nerve dysfunction, and pseudogout were even more rare.
Two trials in 214 patients reported the effect of surgery versus observation on change of mean systolic blood pressure (MD 3.11; 95% CI, –0.37 to 6.60) or diastolic blood pressure (MD 2.02; 95% CI, 0.06–3.98). Two trials reported left ventricular mass index and ejection fraction. Two trials reported the serum creatinine, which we used to calculate the estimated glomerular filtration rate. There are no significant effects for these outcomes, and we did not make inferences regarding patient-important outcomes.

One trial including 145 patients found there was no difference between groups in cardiovascular events (five patients in surgery, eight in no surgery) or cerebrovascular complications (three patients in surgery, one in no surgery). Forest plots of these results are shown in Appendix S10.

Discussion

Surgical management

Surgery achieved a biochemical cure in over 95% of patients enrolled in randomized trials (Table 2). The evidence regarding other patient-important outcomes, including fracture, kidney stones, quality of life, renal failure, and surgery complications proved low or very low quality.

Surgery was associated with increased spine and total hip BMD. Nevertheless, the paucity of direct fracture data after surgery in PHPT limits inferences regarding the impact of surgery on fracture. Confidence in the closeness of the relation between bone density increase and fracture reduction in postmenopausal women is limited, and the BMD fracture risk relationship may differ in PHPT versus postmenopausal osteoporosis.

Strength and limitations

Strengths of this review include a comprehensive search to identify eligible trials; independent duplicate assessment of study selection and risk of bias assessment; and application of the GRADE approach to rate the quality of evidence including optimal use of evidence from surrogate outcomes.

This review has several limitations. First, we used the WebPlotDigitizer tool to obtain the exact numbers for those trials that only provided figures without specific results; results are less precise than would be the case if explicitly reported. Second, we made assumptions to convert the data into consistent units for statistical analysis. This, however, required pooling the results among the limited number of trials. Third, the number of included trials and patient number for each medical therapy was in most cases so small as to provide only low-quality or very-low-quality evidence. Fourth, the trials did not address the burden of surgery (including discomfort, period of decreased function, lost time at work). Finally, there is clinical heterogeneity (measure methods and population) between included trials. We addressed this in our choice of random effect models, and carefully considering rating down for inconsistency in our GRADE ratings.

Relation to prior work

With respect to medical therapy, authors published a relevant systematic review and meta-analysis addressing medical therapy in 2017. Data regarding denosumab was not available at the time of the prior review. Our review included more trials and used GRADE to assess the quality of evidence. We obtained more data on BMD, serum calcium and PTH, urinary calcium, quality of life, and were able to convert data across the trials to the same units.

A recently published systematic review and meta-analysis addressing cinacalcet provided results consistent with our review that cinacalcet resulted in substantial reductions in serum calcium and PTH, but this review did not use the GRADE to rate the quality. Two studies included in the prior review did not meet eligibility criteria in ours and Shoback and colleagues' study is a subset of the data in Peacock and colleagues' and our review only included Peacock and colleagues'. Leere and colleagues' compared cinacalcet plus denosumab versus denosumab plus placebo; our review did not include this trial because of possible interaction between cinacalcet and denosumab.

Unlike the most recent and relevant systematic review and meta-analysis regarding surgery published in 2021, our review included more trials and used GRADE to assess the quality
of evidence. We obtained more data on quality of life by abstracting data from figures and converted data to the same units. We found high-quality evidence that surgery results in a very high rate of biochemical cure; the previous systematic review did not address this outcome. A much larger body of evidence indicates that surgical cure is approximately 95% effective in obtaining cure, which is consistent with our results.  

As for surgery, given the limited number of publications that met the stringent criteria for this systematic review, a more expansive view of the published literature focusing on observational studies was undertaken and published separately. The larger literature is consistent with this systematic review with regard to the success of parathyroid surgery and postoperative changes in BMD. The wider literature also failed to identify sufficient fracture events to inform estimates of effects of surgery. Based upon changes in BMD, however, the broad range of publications in this area support the expectation that surgery reduces both vertebral and nonvertebral fracture risk in PHPT. This wider review, however, does not support a clear, salutary effect of parathyroid surgery on nonclassical manifestations of PHPT, such as quality of life. The only point in which there may be a difference in results from observational studies relates to the suggestion that the incidence of kidney stones is reduced after successful parathyroid surgery.  

Implications of study

This review provides information, conducted with an established systematic methodology, regarding the impact of candidate medical therapies in patients with symptomatic and asymptomatic PHPT. Cinacalcet probably normalized serum calcium levels. Alendronate, denosumab, vitamin D, and estrogen therapy increase BMD. This review provides the best available evidence to guide recommendations regarding the targeted use of medical therapies in PHPT. Pharmacological therapy, however, should be reserved for patients with PHPT who meet treatment criteria for parathyroid surgery but who are not going to undergo parathyroid surgery. Specific pharmacologic therapy is reserved when it is indicated to increase BMD and/or to reduce the serum calcium concentration. The data should be useful in those situations in which there is a clinical indication to reduce the serum calcium and/or improve BMD.

This systematic review also provides important information regarding the effect of surgery in asymptomatic PHPT patients. Key messages are that surgery, in the hands of an experienced surgeon, will achieve biochemical cure in most patients. Thus, this review provides key evidence for the associated PHPT treatment guidelines, which use additional context and methodology to produce recommendations for clinical practice. This review also highlights areas in which high-quality data are lacking and points to areas for future research.

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Conflicts of Interest

MLB: Honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB; grants and/or speaker: Abiogen, Alexion, Amgen, Bruno Farmaceutici, Echolight, Eli Lilly, Kyowa Kirin, SPA, Theramex, UCB; consultant: Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB. BC: Consultant for Takeda/Shire, Amolyt Pharma, Calcilytix; grants from Takeda/Shire, Ascendis. AAK: Speaker for Amgen, Shire/Takeda, Ultragenyx, Alexion, Chugai; grants from Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx; consultant for Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx. Michael Mannstadt: Consultant for Takeda, Amolyt, and Chugai; Grants from Takeda and Chugai. JPB: Consultant for Amgen, Radius, Ascendis, Calcilytix, Takeda, Amolyt, Rani Therapeutics, MBX, Novo-Nordisk, Ipsen, Ultragenyx; Speaker for Amgen and Radius; Research, Abiogen. None of other authors’ relationships relate in any way to this work.
Ethical Statement

This paper is a systematic review and did not require ethics committee approval.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4685.

Data Availability Statement

The data that support the findings in this study are openly available in PubMed, MEDLINE, EMBASE, and the Cochrane databases.

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