Management of Primary Hyperparathyroidism

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Published in:
Journal of Bone and Mineral Research

DOI:
10.1002/jbmr.4682

Publication date:
2022

Document version:
Final published version

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Citation for published version (APA):

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Download date: 15. Sep. 2023
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ABSTRACT
Since the last international guidelines were published in 2014 on the evaluation and management of primary hyperparathyroidism (PHPT), new information has become available with regard to evaluation, diagnosis, epidemiology, genetics, classical and nonclassical manifestations, surgical and nonsurgical approaches, and natural history. To provide the most current summary of these developments, an international group, consisting of over 50 experts in these various aspects of PHPT, was convened. This paper provides the results of the task force that was assigned to review the information on the management of PHPT. For this task force on the management of PHPT, two questions were the subject of systematic reviews using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology. The full report addressing surgical and nonsurgical management of PHPT, utilizing the GRADE methodology, is published separately in this series. In this report, we summarize the results of that methodological review and expand them to encompass a much larger body of new knowledge that did not specifically fit the criteria of the GRADE methodology. Together, both the systematic and narrative reviews of the literature, summarized in this paper, give the most complete information available to date. A panel of experts then considered the last set of international guidelines in light of the newer data and assessed the need for their revision. This report provides the evidentiary background to the guidelines report. In that report, evidence from all task forces is synthesized into a summary statement and revised guidelines for the evaluation and management of PHPT. © 2022 The Authors. Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PARATHYROID-RELATED DISORDERS; DISORDERS OF CALCIUM/PHTHOSPHATE METABOLISM; PTH/VIT D/FGF23; CELL/TISSUE SIGNALING—ENDOCRINE PATHWAYS; CLINICAL TRIALS
Introduction

Since the last international workshop on the evaluation and management of primary hyperparathyroidism (PHPT) in 2014,\(^1\) recognition of its various clinical presentations, its epidemiology, diagnosis, genetics, identification of target organ involvement utilizing new imaging technologies, surgical and medical approaches, natural history, and outcomes after intervention has led to new insights and new concepts. The purpose of this report, as well as the three preceding reports, the systematic reviews, and the summary statement with revised management guidelines is to provide an evidence-based update on these new developments. Preceding reports provided a summary of epidemiology, pathophysiology and genetics, classical and nonclassical features, and surgical aspects. This report presents the conclusions of the task force assigned to the management of PHPT. In particular, this report first addresses questions about the surgical management of PHPT—its efficacy and effect and which patients should be sent for surgery—and, second, how to manage those patients who do not undergo parathyroidectomy (PTX).

Methods

Review of sections of this paper was assigned to sets of task force members. The systematic reviews were headed by two of us (ZY, GG). An extensive search for relevant papers included the following search engines: Medline, Embase, Cochrane, and PubMed. Two systematic reviews were related to surgery and the medical management of asymptomatic PHPT. Recommendations based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology resulted. The reviews utilized classical methods designed to search the relevant literature, with provision for identifying duplicate assessment of eligibility, risk of bias, and data abstraction. The GRADE recommendations are accompanied by rating of the quality of the evidence.

Because the criteria for the GRADE methodology necessarily excluded publications that also contribute to our understanding, these were evaluated separately, forming narrative sections of this report. No prior systematic reviews were performed, and therefore we included all available trials. For the narrative reviews, we focused on new information that has become available since the last international guidelines workshop was conducted in 2013 (published 2014). Our conclusions are based upon both the systematic and narrative reviews.

Surgical management of PHPT

Surgery is the only option for curing PHPT. An investigation of patient-important outcomes of surgery demonstrated a paucity of high-quality data regarding several outcomes. Therefore, in addition to the systematic review, a narrative review of available data concerning existing or potential guidelines for surgery in PHPT informed the suggested guidelines for surgery.

Systematic review

In this series, a systematic review, alluded to earlier, included a review of the surgical management of PHPT.\(^2\) This systematic review included trials in which patients with asymptomatic PHPT were randomized to surgery with or without medical therapy or management without surgery with or without medical management. Six trials presented in 12 reports, including 441 patients, proved to be eligible.\(^3-10\) For patients with asymptomatic PHPT, surgery achieved a biochemical cure in 97.8% (high quality evidence for cure rate). This percentage is consistent with the majority of outcomes published from major medical centers with expertise in this disease.\(^5,15,16\) The review summarizes the data that associate successful parathyroid surgery with increases in bone mineral density. As noted earlier, any conclusions that these increases in bone density are associated with a reduction in vertebral or nonvertebral fracture risk are inferential owing to insufficient direct data on postoperative reductions in fracture incidence in PHPT. The reader is referred to a review that presents these results in detail.\(^2\) In tabular form (Table 1), we summarize the papers reviewed, the characteristics of the study subjects, and a summary of the results. The limited evidence available does not provide with any confidence evidence that surgery is associated with an effect on quality of life, occurrence of kidney stones, or renal function.

Narrative review

Given the very limited number of publications that met the stringent criteria for this systematic review, we also undertook a more expansive view of the published literature. This narrative review is generally consistent with the results of the systematic review summarized earlier. Other surgical aspects of PHPT are presented in another article in this series.\(^17\)

PTX is a safe and well-tolerated operation. It is associated with excellent outcomes, results in durable improvement in biochemical manifestations, and halts the worsening of classic end-organ features. Since the first parathyroid operation was reported in the literature in 1925 by Felix Mandl, tremendous advances have been made in diagnosis, imaging, and surgical treatment. The published literature historically included innumerable retrospective, observational, and single-institution studies. More recent contributions have included randomized clinical trials and population-based approaches.

In the hands of experienced parathyroid surgeons, PTX is a very successful operation. Most patients with PHPT who have a benign single-gland adenoma can be cured by identification and resection of the single offending gland. Multigland diseases, including double adenoma and four-gland hyperplasia, are more challenging to diagnose and require a different operative approach. While bilateral neck explorations have historically been associated with 95% success rates,\(^13\) the advent of advanced imaging modalities (e.g., high-resolution neck ultrasound, technetium-99 m-sestamibi subtraction scintigraphy, or contrast-enhanced four-dimensional CT [4D-CT]) have facilitated the operative approach. When focused operations are offered to appropriate patients and combined with intraoperative PTH monitoring (ioPTH) using a structured protocol, these minimally invasive approaches achieve success rates of 95%–97%. The potential benefits of these focused, minimally invasive approaches include shorter operative time, less tissue scarring, less risk to surrounding structures, and decreased hospital costs.\(^18\) Technical details of the operation are provided in a companion paper.\(^17\)

Recent studies support the safety of PTX even in elderly patients or in those identified with physiologic frailty.\(^18\)

Narrative data supporting specific guidelines for PTX

Outcomes after successful PTX are excellent for patients with symptomatic PHPT. Most of the published research focuses on
the effects of PTX on kidney function, bone density, and neurocognitive symptoms. Extensive review of the data that have emerged since 2013 was undertaken to determine the suitability of the prior guidelines (2014) and the need for additional surgical criteria. Updated guidelines for PTX are presented in Table 2A.

### Table 1. Trials Included in Systematic Review of Surgery\(^{(2)}\)

<table>
<thead>
<tr>
<th>References</th>
<th>Eligibility</th>
<th>Serum calcium (mg/dL)</th>
<th>Serum PTH (pg/mL)</th>
<th>Urinary calcium (mg/day)</th>
<th>Conclusions of systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almqvist et al.(^{(9,10)})</td>
<td>Age &gt; 45 years; biochemical data</td>
<td>10.5 ± .44</td>
<td>79.7 ± 29</td>
<td>258 ± 121</td>
<td>Surgery results in a high rate of biochemical cure; patients are not cured if they do not undergo surgery. Surgery is associated with an increase in bone mineral density. See text and systematic review(^{(2)}) for more details.</td>
</tr>
<tr>
<td>Ambrogini et al.(^{(4)})</td>
<td>Age 50–75 years; asymptomatic; no surgical criteria</td>
<td>10.2 ± .45</td>
<td>112 ± 42</td>
<td>237 ± 72</td>
<td></td>
</tr>
<tr>
<td>Ejlsmark-Svensson et al.(^{(11)})</td>
<td>Age &gt; 18 years: eligible for PTX</td>
<td>11.3 (11.1–11.7)</td>
<td>98 (75–125)</td>
<td>264 (200–392)</td>
<td></td>
</tr>
<tr>
<td>Morris et al.(^{(12)}); Perrier et al.(^{(13)})</td>
<td>Age &gt; 50 years; asymptomatic; no surgical criteria</td>
<td>10.4 ± .38</td>
<td>122 ± 40</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>SIPH Trial(^{(5-14)})</td>
<td>Asymptomatic</td>
<td>10.8 ± .32</td>
<td>97.6 ± 32</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Rao et al.(^{(3)})</td>
<td>Age 50–75 years; asymptomatic; no surgical criteria</td>
<td>10.4 ± .54</td>
<td>82 ± 31</td>
<td>240 ± 135</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; PTX, parathyroidectomy.

### Serum Calcium Threshold for Surgery

There were no new data to support any specific calcium cut point for intervening with parathyroid surgery.

### Renal Guidelines for Surgery

Renal calculi/nephrocalcinosis

1. **Urinary calcium threshold:** Although hypercalcuria is a known risk factor for renal calculi, urinary calcium excretion is variable day to day, and hypercalcuria by itself cannot fully explain the increased risk for nephrolithiasis seen in PHPT. It is likely that other biochemical abnormalities, including renal acidification defects, partly contribute to this elevated risk.\(^{(19,20)}\) Whether screening for other common causes of renal calculi, such as hyperuricosuria, hypomagnesuria, hyperoxaluria, hypocitraturia, or cystinuria, is needed in all patients with PHPT is not established. Recent data confirm that 24-hour urine calcium is higher in patients with PHPT and nephrolithiasis when compared with patients with PHPT and no nephrolithiasis.\(^{(21)}\) Further, hypomagnesuria and the urine calcium/magnesium ratio were recently shown to have potential utility as clinical risk factors, in addition to hypercalcuria, for renal calculi in patients with asymptomatic PHPT.\(^{(22)}\)

The Fourth International Workshop on Asymptomatic PHPT recommended surgical intervention in asymptomatic PHPT when the 24-hour urinary calcium excretion was markedly elevated, >400 mg (>10 mmol)/day, and if there was evidence of increased stone risk.\(^{(11)}\) No studies have confirmed the performance characteristics (sensitivity or specificity) of this particular cut-off value of 400 mg/day (10 mmol/day). In the general population, urinary calcium levels are usually considered elevated if they are >250 mg (6.25 mmol) /24 hours and >300 mg (7.5 mmol)/24 hours in women and men, respectively.

### Table 2. Recommendations for Surgical Management of PHPT

#### A. Surgery to be recommended if one of the following is present:

1. Serum calcium >1 mg/dL (0.25 mmol/L) above upper limit of normal
2. Skeletal features:
   - Fracture by VFA or vertebral X-ray
   - BMD by T-score ≤ −2.5 at any site
3. Renal features:
   - eGFR or CrCl <60 cc/minute
   - Nephrocalcinosis or nephrolithiasis on X-ray, ultrasound, or other imaging modality
4. Age < 50

#### B. Surgery to be recommended if one of the following occurs in follow-up\*:

1. Serum calcium consistently is measured >1 mg/dL (0.25 mmol/L) above upper limit of normal
2. Fracture
3. Kidney stone
4. Significant reduction in BMD to a T-score of ≤ −2.5.
5. Significant reduction in CrCl**

\* Represents a change from prior international workshop guidelines.\(^{(1)}\)

\** For monitoring of renal function, the calculated CrCl is preferred over the estimate of eGFR\(^{(13,17)}\). Worsening kidney function that is thought to be clinically meaningful (e.g., a verified annual decline of 3 mL/min over several years to below 60 cc/min).

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; PHPT, primary hyperparathyroidism.
respectively. The recommendation for the cut point of >400 mg (10 mmol)/24 hours in the Fourth International Workshop was based on evidence available at that time.\(^{(1)}\) The UK NICE guidelines do not use elevated 24-hour urinary calcium excretion as a criterion for PTX, although they do recommend renal ultrasound at the time of diagnosis to evaluate for the presence of nephrolithiasis.\(^{(23,24)}\) However, the Canadian recommendations do advise surgery in the presence of hypercalciuria.\(^{(25)}\) In patients who have kidney stones, it should be recognized that they may not necessarily be due to PHPT since these are two relatively common conditions. Moreover, in PHPT, marked hypercalciuria is seen in only a third of such patients.\(^{(26,27)}\) Thus, although one implicates PHPT as etiologic in anyone with PHPT and stones, the possibility that the stones are due to other factors makes an argument in this setting for a more comprehensive analysis of stone risk, including elements in the urinary milieu that might promote or inhibit stone formation. The case for a stone risk profile in those without hypercalciuria and without kidney stones is weak and not recommended. The case for a stone risk profile in those with hypercalciuria with or without stones is reasonable since, as noted earlier, other risk factors unrelated to PHPT may contribute to stones in those with hypercalciuria.

2. The panel recognizes variables that influence urinary calcium excretion (e.g., sex, body size, race, salt intake, urinary creatinine excretion), making it difficult to assign a single definition of hypercalciuria for all individuals. Nevertheless, the panel favored defining hypercalciuria as noted earlier as >250 mg/day for women and >300 mg/day for men and, based upon expert opinion, recommended changing the guideline for surgery to those with hypercalciuria so defined. In those with hypercalciuria by these definitions, a urinary stone risk profile is in order.

3. Genetic factors: Genetic factors may contribute to the development of renal calculi in PHPT. Patients harboring the AGQ haplotype of the calcium sensing receptor (CaSR)\(^{(28)}\) were found to be at a greater risk of developing renal calculi, whereas those with the SRQ haplotype were found to be at a lower risk. However, more confirmatory data are required to verify these observations. It is premature to recommend evaluation of these haplotypes of the CaSR to identify the risk for renal calculi or advisability of surgery in PHPT.

4. Renal imaging: Newer data add to reports that clinically silent renal calculi are seen in up to 22% of patients with asymptomatic PHPT.\(^{(29)}\) Renal imaging is recommended in patients with PHPT to detect nephrolithiasis, and if it is detected, PTX should be recommended.\(^{(3)}\) Spiral CT scans of the kidneys or renal ultrasound can also detect nephrolithiasis and nephrocalcinosis, although the radiation exposure associated with CT may preclude its use in routine clinical practice.

Threshold of renal function

The threshold creatinine clearance value below which deleterious effects of PHPT on renal function occur is unclear. It is also unclear whether reduced renal function in those who present with PHPT is due to the disease itself or to other independent factors. Since the last guidelines workshop, there has been additional support for the threshold value of 60 mL/minute used as a cut point for surgery. This comes from observations after PTX. Patients with PHPT and concomitant renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/minute) at baseline who underwent PTX had no decline in eGFR at follow-up compared with those with better kidney function who had a significant decrease.\(^{(30)}\) In another study with a multiethnic South East (SE) Asian population, renal function was better on long-term follow-up in patients with PHPT who underwent PTX compared with patients who were either medically treated, primarily with bisphosphonates, or observed. This was also noted in patients who had a normal baseline eGFR.\(^{(31)}\)

Previous data showed that reductions in eGFR <70 mL/minute were associated with greater reductions in BMD, particularly at cortical sites, in individuals with PHPT.\(^{(32)}\) More recently, in a study from India, patients with renal manifestations, such as nephrocalcinosis and nephrolithiasis, had significantly lower eGFR than those who did not (78.8 versus 93.9 mL/minute/1.73 m\(^2\)).\(^{(33)}\) The findings from these two studies suggest that mild reductions in eGFR can result in adverse renal and skeletal effects in PHPT. However, it must be noted that evidence to support a precise eGFR threshold below which PTX should be recommended is still lacking. The eGFR threshold in PTPT below which further elevations of PTH levels occur, if at all, has also not been established, with a recent study showing no correlation between PTH values and eGFR.\(^{(31)}\) In the absence of conclusive data, and based upon the preponderance of available information, we continue to recommend a cut point of 60 cc/minute as a recommendation for surgical referral.

### Skeletal Guidelines for Surgery

DXA remains a valuable tool for the initial skeletal evaluation of biochemically proven PHPT. Marked improvements in BMD are noted following PTX in short-term (up to 2 years) follow-up in randomized controlled trials, all done before the 2014 guidelines workshop.\(^{(9,35)}\) Earlier guidelines had recommended surgery in those with osteoporosis at any site.\(^{(3)}\) However, it must be noted that longer-term follow-up results are only available from observational studies. We continue to support measurement of BMD at the one-third radius, lumbar spine, and hip every 1–2 years in patients with PHPT who do not undergo surgery initially, with surgery to be considered if there is a significant and clinically relevant decrease in BMD on follow-up. Newer studies show significant individual gains in BMD in almost half of the normocalcemic PHPT patients with osteoporosis undergoing surgery.\(^{(34)}\) Therefore, evaluation of BMD should also be a component of the initial evaluation of patients with normocalcemic PHPT. Although no published data exist, there is an argument for including the FRAX absolute fracture risk assessment tool in the evaluation of fracture risk in PHPT. It is likely that FRAX risk factors are as important in PHPT as they are in subjects without PHPT. However, since results are awaited from ongoing studies, current guidelines were not revised in this regard.

Notwithstanding the utility of DXA in PHPT, recent studies applying newer imaging and analytical approaches have demonstrated trabecular bone involvement in PHPT and have corrected earlier views that PHPT spares trabecular bone. Older epidemiological studies had shown an increased fracture risk at both vertebral and nonvertebral sites in PHPT.\(^{(35,36)}\) Data obtained using high-resolution peripheral QCT (HRpQCT) that measures volumetric BMD in both cortical and trabecular bone compartments and trabecular bone score (TBS), a noninvasive index of trabecular microarchitecture, confirm the presence of trabecular bone abnormalities in PHPT, explaining the increase in vertebral fracture risk.\(^{(37,38)}\) HRpQCT data available since the
last guidelines workshop demonstrate that women with PHPT had decreased trabecular and cortical volumetric densities, thinner cortices, and more widely spaced trabeculae at both radial and tibial sites.\textsuperscript{38,39} The radius was more severely affected with thinner and fewer trabeculae.\textsuperscript{38} These and newer studies utilizing HRpQCT would appear to be more representative of skeletal features in PHPT than DXA or the transiliac bone biopsy.\textsuperscript{40} Despite these many advantages, we do not currently recommend HRpQCT as part of the management of PHPT because the technology is not available in most medical centers.

The 2014 guidelines workshop reviewed available data on TBS in PHPT, showing that vertebral fractures were independently associated with the reduction of TBS, that a TBS value <1.2 was a predictor of vertebral fractures in patients with PHPT,\textsuperscript{37} and that TBS scores improved 2 years after PTX.\textsuperscript{41} This influenced the 2014 guidelines that recommended an evaluation of the trabecular compartment of bone with TBS and a vertebral X-ray/vertebral fracture assessment (VFA) by DXA or TBS as part of the initial evaluation of PHPT.\textsuperscript{1} Recently, the value of TBS in PHPT has been called into question. In a cohort of symptomatic PHPT patients, although TBS was in the partially degraded range, it was not independently associated with fractures.\textsuperscript{42} Moreover, degraded TBS values did not correlate with the presence of vertebral fractures.\textsuperscript{43} The clinical utility of TBS in identifying an increased risk of fracture in those with PHPT requires further study. At this time, it seems reasonable to recommend that, if available, TBS be used as a semiquantitative measure of bone quality in PHPT. However, the uncertainty surrounding its utility mitigated against its inclusion as a stand-alone guideline for surgery.

### Age < 50 Years as a Guideline for Surgery

There were no new data confirming or supporting a refinement in the existing age-related criterion for PTX.

### Evaluation for Non-classical Manifestations

Newly available data since the last workshop were reviewed to assess advisability for inclusion as new guideline(s) for parathyroid surgery.

1. **Neuropsychiatric manifestations and quality of life:** The Fourth International Workshop guidelines concluded that there was no clear evidence to suggest that PHPT was associated with neuropsychological dysfunction and that there did not exist clear evidence to recommend formal neurocognitive or neuropsychiatric testing as part of management decisions in PHPT.\textsuperscript{1} However, studies published since the last international workshop in the psychiatric and surgical literature continue to emphasize the association of otherwise asymptomatic PHPT with depression and decreased quality of life.\textsuperscript{44,45} The surgical literature recommends that neuropsychiatric symptoms be assessed in all patients with PHPT and that they should be considered as a relative indication for PTX.\textsuperscript{46} The American Association of Endocrine Surgeons in 2016 recommended PTX in patients with neurocognitive or neuropsychiatric symptoms that are attributable to PHPT. How these symptoms should be assessed or defined is not stated in these guidelines.\textsuperscript{47} A recent Scandinavian investigation on PHPT argues against this recommendation. This study was a prospective randomized well-controlled trial with 10-year follow up that compared PTX with observation alone in 191 patients with PHPT, where data were available on 120 subjects after 10 years.\textsuperscript{47} The study concluded that although there was some improvement in some of the mental domains of the SF-36 quality-of-life scale, including vitality, following PTX, no significant differences in the Comprehensive Psychopathological Rating Scale (CPRS) between the two groups was noted.\textsuperscript{47} The treatment effects between the groups were subtle and of uncertain clinical significance. These recent results underscore previous recommendations from the endocrinological literature that quality of life should not be a specific factor in the decision to recommend PTX. If there are mechanisms underlying putative neurocognitive manifestations, the methodologies are not well defined, and randomized controlled trial (RCT) data do not demonstrate clear or consistent reversibility after PTX. Thus, our panel concluded that PTX should not be recommended solely on the basis of neurocognitive or neuropsychiatric symptoms in the absence of other complications and that such complaints should not be added as a new indication for surgery. Although most of the available data do not support a clear and consistent link to PHPT, anecdotal and uncontrolled published reports lead some physicians and patients to feel that surgery will ameliorate these features. The clinician dealing with this dilemma should honestly present the evidence but acknowledge reports that have not shown conclusive results. This area continues to need additional studies, aimed perhaps by utilizing a disease-specific quality-of-life tool for PHPT.\textsuperscript{48,49}

2. **Cardiovascular/metabolic:** Previous small studies reported an increased risk of hypertension,\textsuperscript{50} left ventricular hypertrophy, and impaired diastolic filling in patients with PHPT,\textsuperscript{51} although the pathophysiologic mechanisms underlying these associations have not been identified. Patients with both normocalcemic and classic PHPT have been shown to exhibit similar rates of cardiovascular risk factors and comparable indices of arterial stiffness.\textsuperscript{52} Despite these findings, studies have not reported consistent improvements in these cardiovascular manifestations following PTX, nor have changes in glucose, insulin, or Homeostatic Model of Assessment-Insulin Resistance (HOMA-IR) following PTX been observed.\textsuperscript{53} Nevertheless, a recent case-controlled study showed improvements in blood pressure, serum total cholesterol, HOMA-IR, and the Framingham Cardiovascular Risk Score in patients with both normocalcemic and classical PHPT after PTX.\textsuperscript{54} These recent observations run counter to earlier studies in which only minimal differences in echocardiographic variables, such as left ventricular mass index and diastolic dimensions of the interventricular septum, were demonstrable.\textsuperscript{8} With such uncertain data, with regard to both the presence of and improvement in cardiovascular features after PTX, the panel decided against including any cardiovascular criteria in management decisions regarding surgery for PHPT.

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**Guidelines for Surgery in Patients Followed Without Surgery**

Prior international workshops on PHPT management did not specifically address the issue of surgical intervention in those patients initially followed without PTX. Recognizing that the decision to pivot toward surgical management is an important...
issue for patients and their physicians, the panel now provides this guidance in Table 2B.

Medical management of PHPT

Systematic review

In this series, a systematic review of the management of PHPT is presented.\(^2\) One aspect of this systematic review included randomized trials comparing nonsurgical management with medical therapy versus without medical therapy in patients with PHPT. Ten trials reported in 11 publications including 423 patients proved eligible: 3 addressed alendronate, 1 denosumab, 2 cinacalcet, 2 vitamin D, and 2 estrogen or estrogen analogue therapy. The results indicate that alendronate and denosumab both increase bone density. Increases in bone density have also been reported with vitamin D and estrogen. Although meta-analyses have correlated improved bone density in osteoporotic cohorts treated with pharmacological agents with reductions in fracture incidence, it is uncertain whether one can draw similar conclusions in PHPT. The only data suggesting that alendronate or denosumab reduce fracture risk in PHPT are inferential, based upon improvements in BMD. Cinacalcet probably reduces serum calcium into the normal range and to a greater extent than it reduces PTH levels. The reader is referred to the review that presents these results in detail including a discussion of adverse events.\(^3\) In tabular form (Table 3), we summarize the papers that were reviewed, the characteristics of the study subjects, and the results. Because of limitations in data quality and only inferential effect on patient important outcomes such as fracture, there are no specific GRADE recommendations for medical therapy of PHPT.

Given the very limited number of publications that met the stringent criteria for this systematic review, we also undertook a more expansive view of the published literature on the medical management of PHPT. This narrative review in general is consistent with the results of the systematic review summarized earlier.

Narrative review

Calcium intake

Many clinicians recommend restriction of dietary or supplemental calcium in PHPT. Dietary calcium restriction, though perceived as reasonable in clinical terms, can be perceived differently by abnormal parathyroid tissue that retains some responsiveness to fluctuations in the serum calcium. Thus, by restricting calcium intake, PTH levels could rise further.\(^55,56\) The subtle point is not that the serum calcium is going to measurably fluctuate by restricting calcium intake but that parathyroid tissue could sense a dietary calcium deficit and be further stimulated to secrete PTH. Given that serum calcium levels are stable in PHPT over a range of dietary calcium intake and in the absence of new data to the contrary, it seems prudent to follow the Institute of Medicine nutritional guidelines for calcium\(^57\) in PHPT.

Vitamin D supplementation

A meta-analysis of 10 studies including 340 patients with PHPT was published after the last guidelines workshop.\(^58\) There was no significant worsening of hypercalcemia following vitamin D supplementation, with only 2.2% of patients developing serum calcium above 12 mg/dL. In most studies, cholecalciferol and ergocalciferol were used, with significant heterogeneity across them. Doses ranged from 800 IU daily to 50,000 IU twice weekly. Serum PTH decreased on average by 33% \((p = 0.003)\).\(^58\) The pathophysiological processes leading to the overproduction of PTH in PHPT could be worsened by a secondary stimulation of PTH due to inadequate vitamin D levels. Adequate supplementation of vitamin D in PHPT should thus help to control any tendency for PTH levels to rise further. However, what the threshold value is for 25-hydroxyvitamin D (25-OH-D) remains controversial and relates not only to patients with PHPT but also to subjects without known metabolic bone disease.\(^57,58\) It has been shown in patients with osteoporosis and osteopenia that increases in 25-OH-D, up to 30 ng/mL, are associated with a reduction in PTH levels.\(^59\) With specific reference to PHPT, several reports have become available since the prior guidelines workshop. Walker et al. showed that levels below 30 ng/mL were associated with a further increase in PTH levels.\(^60\) This observation was also made in a meta-analysis by Song et al.\(^61\) The safe use of vitamin D supplementation is also relevant to recommendations. In newer studies, such as the one by Rolighed et al., vitamin D, up to 2800 IU/day, was found to be safe and was associated with reductions in both serum PTH and C-telopeptide (CTX) without any changes in serum or urine calcium or serum creatinine.\(^62,63\) An older study by Lind et al. utilizing active

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### Table 3. Trials Included in Systematic Review of Medical Therapy\(^2\)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>References</th>
<th>Serum calcium (mg/dL)</th>
<th>Serum PTH (pg/mL)</th>
<th>Urinary calcium (mg/day)</th>
<th>Conclusions of systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Chow et al.(^{109})</td>
<td>11.3 ± 0.7</td>
<td>208 ± 130</td>
<td>193 ± 106</td>
<td>BMD increases</td>
</tr>
<tr>
<td>Khan et al.</td>
<td>(^{110})</td>
<td>10.6 ± 0.4</td>
<td>154 ± 113</td>
<td>215 ± 112</td>
<td></td>
</tr>
<tr>
<td>Rossini et al.(^{111})</td>
<td>11.0 ± 0.4</td>
<td>150 ± 41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td>Gray et al.(^{71})</td>
<td>10.4 ± 0.16</td>
<td>77.9 ± 9.6</td>
<td>NR</td>
<td>Estrogen increases BMD</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Rubin et al.(^{72})</td>
<td>10.7 ± 0.16</td>
<td>220 ± 55</td>
<td>240 ± 41</td>
<td></td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Khan et al.(^{77})</td>
<td>11.8 ± 0.5</td>
<td>164 (131–211)</td>
<td>NR</td>
<td>Reduces serum calcium (and PTH)</td>
</tr>
<tr>
<td>Peacock et al.(^{75})</td>
<td>10.7 ± 0.4</td>
<td>112 ± 46</td>
<td>290.0 ± 120 /g Cr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Leere et al.(^{79})</td>
<td>10.9 ± 0.1</td>
<td>115 ± 16</td>
<td>NR</td>
<td>Increases BMD</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Lind et al.(^{64})</td>
<td>10.6 ± 0.3</td>
<td>43 ± 15</td>
<td>NR</td>
<td>Increases BMD</td>
</tr>
<tr>
<td>Roglighed et al.(^{62,63})</td>
<td>11.3 (11.1–11.4)</td>
<td>123 (104–111)</td>
<td>376 (320–432)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reported.
vita

din D did not show reductions in PTH. The meta-analyses by Loh et al. and by Song et al. concur that over a range of vitamin D concentrations, serum calcium and urine calcium excretion remain stable. Thus, despite the complex relationship between vitamin D and PHPT, it seems prudent, based on the most recent evidence, to recommend levels of 25-OH-D > 30 ng/ml in PHPT. This point is particularly relevant when normocalcemic PHPT is part of the differential diagnosis of an elevated level of PTH (see following discussion). Although some earlier studies used higher doses of vitamin D (50,000 IU), in general, replacement should be cautious to prevent further increases in the serum or urinary calcium concentration.

Bisphosphonates

Since the last guidelines workshop, additional data have been reported supporting the effect of bisphosphonates to improve bone density, with data on a comparison of the effects of oral risedronate versus parathyroid surgery on DXA measurements. In a 2-year open-label study of 32 postmenopausal women (mean serum calcium 10.9 mg/dL and PTH 122 pg/mL), 16 underwent PTX and 16 were treated with risedronate plus calcium and vitamin D. The increments in areal BMD favored risedronate at the lumbar spine (PTX/risedronate: lumbar spine BMD [LSBMD]: +3.5%/5.6%) but PTX at hip sites (PTX/risedronate: femoral neck BMD [FNBMD]: +6.3%/1.2%; total hip BMD [THBMD]: +4.2%/1.7%). In addition, trabecular volumetric BMD (vBMD) increased by 4.6% after PTX versus 0.24% with risedronate (p < 0.05). Cortical vBMD increased 0.39% after PTX versus a reduction of 0.26% with risedronate (p < 0.05). This is consistent with older reports in which BMD was found to increase at the lumbar spine and hip sites but not the more cortical one-third radius. Despite the plethora of data using bone density as the skeletal endpoint, data on fracture risk reduction are still lacking.

Estrogens and SERMs

No new data on hormone therapy have emerged since the last guideline workshop. In older studies, a double-blind, randomized, placebo-controlled trial, 42 postmenopausal women were treated with conjugated estrogens 0.625 mg, per day (CE/MP) for 2 years with extension for an additional 2 years. In an older 8-week randomized, placebo-controlled study, 42 postmenopausal women were treated with conjugated estrogens 0.625 mg plus medroxyprogesterone 5 mg, per day (CE/MP) for 2 years with extension for 7.3%. Despite the plethora of data using bone density as the skeletal endpoint, data on fracture risk reduction are still lacking.

Denosumab

Data on denosumab in PHPT have become available since the last guidelines workshop. A 1-year study retrospectively evaluated the effects of denosumab or PTX in 39 patients. Although increases in BMD were seen both after surgery and with denosumab, the changes were greater after surgery: LSBMD: 11.2% versus 6% (p = 0.005), FNBMD: 7.9% versus 4.3% (p = 0.1), THBMD: 7.5% versus 3.7% (p = 0.048). On the other hand, increases in TBS favored denosumab (by 3%; p = 0.007). Mean serum phosphate decreased by 0.2 mg/dL (p < 0.05), serum PTH increased by 28% (p < 0.05), and serum calcium did not change with denosumab. In another retrospective study, this one involving 50 elderly women, denosumab increased BMD to a greater extent over 2 years than it did in osteoporotic patients without PHPT.

A significant increase in BMD was seen more commonly in women with PHPT (92%) than in those with osteoporosis (52%, p < 0.05), and it was 13.4 times as likely in women with PHPT as in those with osteoporosis (p = 0.02).

Cinacalcet and combination therapy

Data available at the prior guidelines workshop demonstrated that oral cinacalcet led to the achievement of the primary endpoint (proportion of patients with serum calcium below 10.3 mg/dL and a fall from baseline of 0.5 mg/dL or more on a 52-week randomized, placebo-controlled study) in 73% of patients in comparison to 5% on placebo (p < 0.001). Mean serum PTH decreased 7.6% with cinacalcet and increased 7.7% with placebo (p < 0.01). No differences in BMD were observed between groups. An open-label extension showed long-term duration of cinacalcet effects, but bone density did not change.

Additional data have become available since the 2014 guidelines workshop. In a phase 3 multicenter RCT of 67 patients with PHPT, cinacalcet was compared to placebo (1:1) for 28 weeks. Serum calcium normalized in 75.8% of cinacalcet-treated patients in comparison to no one in the placebo group (p < 0.001). The drug was well tolerated with similar adverse events in both groups, which were limited to nausea and muscle spasm. The efficacy and safety of cinacalcet in PHPT has recently been reviewed.

Combination therapy with cinacalcet and denosumab was also recently evaluated in a 50-week parallel randomized, placebo-controlled study on 45 patients (15 placebo-placebo, 16 denosumab-placebo, 14 cinacalcet-denosumab). Serum calcium normalized in 64% of patients on combination therapy with no changes in the other groups. LSBMD/FNBMD increased by 5.4%/4.5% in combination and 4.1%/3.8% in denosumab groups respectively in comparison with placebo (p < 0.001/p = 0.0008). Mean serum PTH rose by 40% in denosumab and combination groups at Week 2 and then progressively declined, remaining 13% higher in comparison with placebo by the end of the trial (p = 0.0001).

Management of normocalcemic PHPT

Review of the literature regarding management of normocalcemic PHPT (NPHPT) is complicated due to the lack of consistent diagnostic criteria. Although many studies excluded secondary causes of hyperparathyroidism, including vitamin D deficiency and renal failure, some studies did not provide cutoffs for these values, and few studies measured ionized calcium. It is important to note that some studies in which patients did not meet rigorous diagnostic criteria may have included patients with classic hyperparathyroidism. In particular, it is important that concomitant vitamin D deficiency be corrected before making the diagnosis of NPHPT. Correction of low vitamin D levels may...
lead to the emergence of hypercalcemia, thereby unmasking hypercalcemic PHPT. To assure adequate vitamin D levels, we recommend a level of 30 ng/mL before a diagnosis of NPHPT is made.

Since the last guidelines workshop several small studies have been conducted evaluating alendronate and cinacalcet, which have demonstrated benefit in hypercalcemic disease, in normocalcemic patients. In a 52-week, randomized study of 30 post-menopausal women with NPHPT, allocated to alendronate or placebo, BMD increased by 0.3% in the alendronate group and decreased by 0.8% in the placebo group. (81) In another study, (82) cinacalcet was shown to reduce PTH levels by 43% and improve symptoms in patients with normocalcemic PHPT. (83)}

Regarding the surgery itself, the minimally invasive approach is important in operative management of PHPT. Some studies have shown that in normocalcemic disease, the value of preoperative localization studies is not as clear as it is in hypercalcemic disease. In a comparison of three widely used methods, 4D-CT performed better (56% positivity) than ultrasound (22% positivity) or sestamibi (11% positivity). Nevertheless, all methods were less successful in localizing tissue than in hypercalcemic disease (4D-CT: 56% versus 75%; ultrasound: 22% versus 58%; sestamibi: 11% versus 75%). In normocalcemic patients who became hypercalcemic, localization success with sestamibi improved from 14% to 73%. (90) Other studies support the hypothesis that localization studies are not as successful in normocalcemic than hypercalcemic PHPT. (91-93) The issues with parathyroid localization in NPHPT may be due to a greater incidence of multiglandular disease and smaller adenoma size. The preoperative identification of multiglandular disease is important in operative management since minimally invasive PTX is not appropriate and four-gland exploration, a more challenging approach with increased surgical risk, is required. Studies have demonstrated an approximately two- to threefold higher prevalence of multiglandular disease in patients with normocalcemic versus hypercalcemic disease. (82,89) Moreover, the average size of the adenoma is smaller in normocalcemic versus hypercalcemic disease. (82,88) Although not all reports have confirmed this impression. (89) For all forms of PHPT, preoperative imaging approaches are reserved for those in whom the decision for surgery has been made. Parathyroid imaging is not used for diagnostic purposes.

Regarding the surgery itself, the minimally invasive approach is converted to a full bilateral neck exploration more often in normocalcemic than in hypercalcemic PHPT (13% versus 4%; p < 0.001). (83) Unsuccessful PTX is also more common in this form of the disease than in those with hypercalcemia. (88,90) Although additional newer data are available only on a small number of patients, successful PTX has been reported to result in improvements in BMD in NPHPT, similar to those with hypercalcemic disease, with the one-third radius typically being a more sluggish site. (82,84) Baseline alkaline phosphatase was a predictor for bone gain. Other predictors of improvement have included sites with the lowest T-score as well as those with overt skeletal disease. (88,90) Not all studies, however, have observed improvement in BMD after PTX. (93)

Little is known regarding the benefit of PTX on renal, cardiovascular, and quality-of-life outcomes in patients with NPHPT. A small study consisting of 10 patients with nephrolithiasis showed a 40% reduction rate in kidney stones after a mean 73 months of postoperative follow-up. (95) A similarly small study of 16 patients with normocalcemic disease and prediabetes showed improvement in fasting glucose concentrations and after an oral glucose load 32 weeks postoperatively compared with baseline and a control group with prediabetes alone. (92) In a case-controlled study of 31 patients with normocalcemic disease, blood pressure, total cholesterol, HOMA-IR, and cardiovascular risk score decreased 6 months postoperatively. (54) In a prospective, multi-center study of 32 patients, the physical component summary score of the quality-of-life metric improved. (93) Evidence for improvement with surgery or pharmacological approaches in normocalcemic PHPT mirrors hypercalcemic disease with improvements in target organ indices but uncertainties in nonclassical ones.

In summary, studies on the management of NPHPT are limited by the lack of consistent diagnostic criteria in study subjects and by the absence of evidence-based criteria for either surgical or medical intervention in the available reports. In the absence of such data, the panel concludes that we cannot provide specific guidelines for surgery in this phenotype of the disease at this time.

Management of PHPT in pregnancy

PHPT in pregnancy is a rare event. However, the actual incidence of PHPT in pregnancy is uncertain because diagnosis is missed or delayed because many of its nonspecific symptoms, such as fatigue, constipation, and nausea, may be mistaken for those normally associated with pregnancy. (94) The diagnosis of PHPT in pregnancy can also be confounded by expected pregnancy-related perturbations in serum levels of calcium and PTH and in urinary calcium levels. During pregnancy, serum total calcium levels fall due to a hemodilution effect and reduced serum albumin levels. For these reasons, ionized calcium may be a more reliable index. Another physiological event in normal pregnancy that can confound the diagnosis of PHPT is an expected reduction in PTH to low-normal levels during the first trimester and then a steady rise into the midnormal range by term. (96) Absorptive hypercalciuria that is noted from Week 12 of gestation may also make uncertain the urine calcium creatinine ratio (UCCR) and, thus, may make the distinction between familial hypercalciuric hypercalcemia (FHH) and mild PHPT difficult. In such cases, genetic testing for FHH may be necessary. Genetic testing should also be considered if any of the multiple endocrine neoplasia (MEN) syndromes associated with PHPT are suspected.

Most pregnant women with PHPT have mild disease, with serum calcium values within 1 mg/dL of the upper limit of normal. It is uncertain whether PHPT during pregnancy is generally associated with negative fetal outcomes, such as miscarriage, prematurity, low birth weight, or Apgar scores. Increased fetal loss was associated with higher serum calcium levels above 11.4 mg/dL in a study by Norman et al. (97) Maternal PHPT was not found to be associated with deleterious obstetric outcomes in a study performed in a large managed care organization in Israel, whereas a 3.5-fold increased rate of fetal loss was reported in a single-institution study from the USA. (98) The varying outcomes observed in these two studies could be related to the screening methodology used by Hirsch et al. (96) that readily identified those with even mild hypercalcemia. Maternal issues that have been observed with PHPT in
pregnancy include those that can be associated with pregnancy per se (e.g., hyperemesis gravidarum, preeclampsia) and those that are classically associated with PHPT (nephrolithiasis, hypercalcemic crisis).\(^96\)

Mild cases of PHPT are usually managed conservatively with hydration and close monitoring of serum calcium levels. The use of pharmacological agents has been reported. Calcitonin, a Category B drug, may be used because it does not cross the placenta\(^99\) but has only a limited and short-term effect in lowering serum calcium levels.\(^98\) Bisphosphonates, Category C medications, carry a theoretical risk of affecting endochondral bone development,\(^100\) and so should be avoided. Denosumab, a Category D drug, crosses the placenta and has been associated with fetal skeletal adverse outcomes in monkey studies and therefore should also be avoided in pregnancy.\(^101\) Individual case reports have described the use of cinacalcet, a Class C drug, in PHPT in pregnancy.\(^102\) It crosses the placenta, so more evidence of safety is required before its broad use in pregnancy can be advocated.

Because of the concerns associated with using pharmacological agents in PHPT during pregnancy, management in those with higher levels of serum calcium is focused on surgery in the second trimester. High-quality data supporting a specific cut-point for intervention are lacking.\(^94,97,98,103\) Many consider surgery if the serum calcium levels is >11.0 mg/dL. This is based mainly on prior data showing no deleterious outcomes in those with serum calcium less than 11.4 mg/dL (2.85 mmol/L).\(^97\)

Under general anesthesia during the first half of the second trimester,\(^97\) surgery is generally safe, in contrast to surgery during the third trimester when there is an increased risk of preterm labor.\(^98\) Preoperative imaging should be limited to ultrasound scanning, because the usual imaging modalities use radiation, or use contrast agents that cross the placenta.\(^104-106\)

Many patients can be managed without surgery during pregnancy. Patient education and maintaining good hydration are important measures.\(^103\) Most experts recommend PTX after the patient has delivered. If another pregnancy is desired, then the recommendation for PTX before the next pregnancy is even stronger.

In pregnant patients managed nonoperatively, maternal hypercalcemia can suppress the fetal parathyroids, resulting in neonatal hypocalcemia and tetany.\(^107\) It is therefore important to monitor the neonate closely after delivery, with frequent testing of serum calcium levels.

### Summary and Conclusions

In this review, we provide guidance for the management of PHPT based on evidence to date. In the absence of high-quality evidence, these recommendations are largely based on expert opinion of the panel.

Recommendations with regard to guidelines for parathyroid surgery and nonoperative management are found in Tables 3 and 4. In those who do not meet guidelines but for whom there are no medical contraindications, surgery is an acceptable alternative with the concurrence of patient and doctor. We recognize, however, that there are patients for whom a surgical guideline is met but in whom surgery will not be performed. This could be because of extenuating medical issues rendering surgery an unsafe alternative. Other patients who meet a guideline for surgery will refuse. In these situations, medical approaches are reasonable to consider to reduce serum calcium, improve bone density, or both (Table 4). Monitoring in those who do not have parathyroid surgery should include annual measurements of calcium and 25-OH-D and assessment of renal function. Bone density should be monitored at all three sites at least every 1–2 years. Imaging for nephrolithiasis or nephrocalcinosis is conducted at intervals as clinically indicated (Table 4). Along with the other reviews, as part of this series a set of formal recommendations, guidelines, and research needs is presented in a separate paper.\(^108\)

### Table 4. Recommendations for Nonsurgical Management of PHPT

<table>
<thead>
<tr>
<th>A. In patients who are not going to have surgery, the following nonsurgical approaches are reasonable:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Calcium intake should be consistent with nutritional guidelines.</td>
</tr>
<tr>
<td>2. Vitamin D should be maintained at &gt;30 ng/mL and &lt; the laboratory reference range for upper limit of normal. Replacement should be cautious to prevent further increases in serum calcium concentration.</td>
</tr>
<tr>
<td>3. When clinically indicated, to reduce serum calcium, cinacalcet is effective.</td>
</tr>
<tr>
<td>4. When clinically indicated, to increase BMD, bisphosphonates or denosumab can be used.</td>
</tr>
<tr>
<td>5. When clinically indicated, to lower serum calcium and increase BMD, bisphosphonates or denosumab and cinacalcet can be used.</td>
</tr>
</tbody>
</table>

B. Monitoring for those who are not to undergo PTX

In patients not undergoing parathyroid surgery, we recommend monitoring as follows:

1. Serum calcium and 25-OH-D concentrations: annually
2. Skeletal: a. Three-site DXA every 1 or 2 years b. Vertebral X-ray, VFA, or TBS if clinically indicated
3. Renal: a. CrCl (a creatinine clearance is preferred over eGFR), annually b. Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated

**Abbreviations:** eGFR, estimated glomerular filtration rate; PTX, parathyroidectomy; TBS, trabecular bone score; VFA, vertebral fracture assessment.

### Disclosures

**JPB:** Consultant for Amgen, Radius, Ascendis, Calciytix, Takeda, Amolyt, Rani Therapeutics, MBX, Novo-Nordisk, Ipsen, Ultragenyx; speaker for Amgen and Radius; research, Abiogen.

**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.

**MC:** Speaker for Amgen, Diethelm Keller Siber Hellner (DKSH) and Kyowa Kirin.

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**LR:** Speaker for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, Ultragenyx; consultant for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, Ultragenyx; grants from Takeda and Kyowa Kirin.

**NEC:** Speaker for Alexion; consultant for Ascendis Pharma; research for Shire Pharmaceuticals/Takeda.

**JTP:** Consultant for Radius.

No other coauthors have disclosures to make.
We acknowledge unrestricted financial support from Amolyt, Ascendis, CalciLytx, and Takeda Pharmaceutical Company. They had no input into the planning or design of the project, the conduct of the reviews, evaluation of the data, writing or review of the manuscript, or the content, conclusions, or recommendations contained herein.

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Ethical Statement

These papers are retrospective reviews 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.4682.

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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