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Parathyroid Hormone Therapy for Managing Chronic Hypoparathyroidism: A Systematic Review and Meta-Analysis

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ABSTRACT

The efficacy and safety of parathyroid hormone (PTH) therapy for managing long-term hypoparathyroidism is being evaluated in ongoing clinical trials. We undertook a systematic review and meta-analysis of currently available randomized controlled trials to investigate the benefits and harms of PTH therapy and conventional therapy in the management of patients with chronic hypoparathyroidism. To identify eligible studies, published in English, we searched Embase, PubMed, and Cochrane CENTRAL from inception to May 2022. Two reviewers independently extracted data and assessed the risk of bias. We defined patients' important outcomes and used grading of recommendations, assessment, development, and evaluation (GRADE) to provide the structure for quantifying absolute effects and rating the quality of evidence. Seven randomized trials of 12 publications that enrolled a total of 386 patients proved eligible. The follow-up duration ranged from 1 to 36 months. Compared with conventional therapy, PTH therapy probably achieves a small improvement in physical health-related quality of life (mean difference [MD] 3.4, 95% confidence interval [CI] 1.5–5.3, minimally important difference 3.0, moderate certainty). PTH therapy results in more patients reaching 50% or greater reduction in the dose of active vitamin D and calcium (relative risk [RR] = 6.5, 95% CI 2.5–16.4, 385 more per 1000 patients, high certainty). PTH therapy may increase hypercalcemia (RR =2.4, 95% CI 1.2–5.04, low certainty). The findings may support the use of PTH therapy in patients with chronic hypoparathyroidism. Because of limitations of short duration and small sample size, evidence from randomized trials is limited regarding important benefits of PTH therapy compared with conventional therapy. Establishing such benefits will require further studies. © 2022 American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PARATHYROID HORMONE THERAPY; EPIDEMIOLOGY; HYPOPARATHYROIDISM

Received in original form February 5, 2022; revised form July 22, 2022; accepted August 8, 2022.
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Additional Supporting Information may be found in the online version of this article.
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Journal of Bone and Mineral Research, Vol. 00, No. 00, Month 2022, pp 1–9.
DOI: 10.1002/jbmr.4676

Introduction

Hypoparathyroidism (hypoPTH) is a rare disorder characterized by hypocalcemia in which the parathyroid glands fail to produce sufficient amounts of parathyroid hormone (PTH) or the parathyroid hormone produced lacks biologic activity. Long-term manifestations may include nephrocalcinosis/nephrolithiasis, renal failure, seizures, arrhythmia, ischemic heart disease, depression, cataracts, infection, increased mortality, and impaired quality of life.[1–4] Hypoparathyroidism occurs most commonly after neck surgery, accounting for 75% of patients with hypoparathyroidism.[5] The majority of postoperative cases of hypocalcemia resolve in the first weeks after surgery, and approximately 25% of such cases develop chronic or permanent hypoparathyroidism.[6,7]

The optimal treatment strategies for patients with chronic hypoparathyroidism remain uncertain. Conventional therapy with calcium and activated vitamin D analogs (calcitriol, alfacalcidol, or dihydrotachysterol) is necessary to maintain serum calcium and treat symptoms of hypocalcemia.[8,9] However, conventional therapy does not correct the underlying pathophysiology and is associated with long-term complications as cited above.[1–4,10]

PTH replacement therapy with either synthetic or recombinant human (rh) PTH(1–34) or intact rhPTH(1–84) has been evaluated in hypoparathyroidism. PTH(1–34) has been evaluated in both children and adults in varying treatment regimens. RhPTH(1–84) has also been evaluated in hypoparathyroidism and was approved in 2015 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an adjunctive treatment for patients with chronic hypoparathyroidism who cannot be well controlled on conventional therapy. TransCon PTH, a prodrug with rhPTH(1–34) transiently conjugated to polyethylene glycol, is not yet approved, but early data suggest it may provide stable PTH serum levels in the physiologic range for 24 hours.[11] This molecule has been evaluated in a phase 2 trial and a phase 3 trial in hypoparathyroidism.[12,13] PTH therapy is generally well tolerated with few adverse effects. In preclinical studies in rats, high doses of PTH(1–34) and PTH(1–84) were associated with dose- and duration-dependent osteosarcoma, which, however, has not been observed in humans.[14] The use of PTH therapy in chronic hypoparathyroidism patients should be based on evidence regarding potential benefit on patient-important outcomes.

With the goal to inform recommendations for the update of international guidelines on hypoparathyroidism,[7,15] we undertook this systematic review and meta-analysis to assess the effects of PTH therapy versus conventional therapy in managing patients with chronic hypoparathyroidism.

Methods

We submitted the systematic review protocol to PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=234774) for registration (CRD42021234774). This report follows the Preferred Reporting Items for a Systematic Review and Meta-Analysis (PRISMA)[16] (https://view.officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fprisma-statement.org%2Fdocuments%2FPRISMA_2020_checklist.docx&wdOrigin=BROWSELINK).

Data sources

Relying in part on a prior review,[17] we searched Embase (https://www.elsevier.com/solutions/embase-biomedical-research), PubMed (https://pubmed.ncbi.nlm.nih.gov/), and Cochrane CENTRAL (https://www.cochranelibrary.com/central) from inception to May 2022 using key words hypoparathyroidism, hypocalcemia, hypocal*, hypoPT, parathyroid hormone, PTH, rhPTH, PTH(1–34), teriparatide, PTH(1–84), TransCon PTH, and random*. MeSH terms implemented in various combinations increased search sensitivity. Searching the reference lists of publications of primary studies and relevant narrative reviews and guidelines provided another strategy for identifying additional references.

Study selection

We merged studies from the different sources and databases and removed duplicates. Paired reviewers screened the studies in two stages: (i) title and abstract and (ii) full text. For full-text review, two reviewers independently adjudicated eligibility and resolved conflicts by discussion.

Eligible studies included patients diagnosed with chronic hypoparathyroidism; compared PTH therapy versus conventional therapy (eg, calcium, calcitriol, alfacalcidol, vitamin D); used randomized controlled study trial design; and were published in English. Studies were excluded if they: (i) were intervention studies of <4 weeks' duration; (ii) were duplicate publications, review articles, single-case articles, editorials, or letters; and/or (iii) examined only temporary hypoparathyroidism as defined by the study.

Outcomes of interest

The selection of patient-important outcomes (defined as characteristics or variables that reflect how a patient feels, functions, or survives) referred to one systematic review that investigated the major complications related to chronic hypoparathyroidism, including nephrolithiasis, renal failure, seizures, arrhythmia, ischemic heart disease, depression, cataracts, infection, and all-cause mortality.[18] In addition, the guideline panel added another four outcomes as patient-important based on their experience managing patients (fracture, 50% or greater reduction in dose of active vitamin D and calcium, quality of life, and adverse events).

In the presence of limited evidence for patient-important outcomes, we also included the following surrogate outcomes: hypocalcemia, hypercalcemia, hypercalciuria, 24-hour urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxy vitamin D3, serum magnesium, serum alkaline phosphatase, serum osteocalcin, urine deoxypyridinoline, urine pyridinoline, mean creatinine clearance levels, and bone mineral density (BMD).

Data abstraction

For each included article, team members, using a standardized form, independently extracted author, year, country, patient demographics, interventions, doses, frequency, duration, and outcomes data. When one reviewer completed the data abstraction, a second reviewer independently reviewed the data.

Risk of bias and quality of evidence

A modified Cochrane risk of bias tool provided the basis for risk of bias assessment.[19,20] Two reviewers independently rated the risk of bias; a third senior reviewer resolved any disagreement. We used the grading of recommendations, assessment,

development, and evaluation (GRADE) system for assessing certainty in the evidence as high, moderate, low, or very low based on study design and considerations of risk of bias, consistency, precision, directness, and publication bias.[21,22]

Data synthesis

We performed a random-effects meta-analysis using DerSimonian and Laird approach,[23] which uses the inverse-variance method and assumes that studies are estimating different, yet related, intervention effects. We presented relative risks (RR) and 95% confidence intervals (95% CI) for dichotomous outcomes. For continuous outcomes, weighted mean differences (WMD) and 95% CI using DerSimonian and Laird random-effects model provided pooled results. Chi-square tests and I^2 statistics provided methods for assessing statistical heterogeneity. All primary analyses were performed with STATA v15.1 (StataCorp, College Station, TX, USA).

Results

Study selection

The search identified 6835 records; after removal of duplicates, 5138 remained, among which 311 articles proved potentially eligible on the title and abstract review and 11 publications[12,13,24–33] reporting on seven studies (Fig. 1) met eligibility criteria.

Characteristics of included studies

Table 1 summarizes the characteristics of eligible studies, all randomized trials, of which six used parallel and one crossover design. The seven eligible studies included 386 patients, of whom 76% were female. The follow-up duration of the seven studies ranged from 1 to 36 months. Supplemental Table S1 presents the risk of bias assessment.

Main outcomes

None of the studies reported patient-important outcomes of nephrocalcinosis/ nephrolithiasis, seizures, arrhythmia, ischemic heart disease, cataracts, fracture, infection, or all-cause mortality. Three studies reported physical health-related quality of life by SF-36 instruments and suggested a very small possible benefit of treatment (MD 3.4, 95% CI 1.5–5.3, minimally important difference 3.0, moderate certainty, Table 2).[13,29,30] One study reported depression and suggested no important differences in the impact of interventions on depression (MD 0, 95% CI −0.2 to 0.1, moderate certainty, Table 2).[29] Two studies reported that PTH(1–84) therapy versus conventional therapy resulted in more patients reaching 50% or greater reduction in the doses of active vitamin D and calcium (RR = 6.5, 95% CI 2.5–16.4, 385 more per 1000 patients, high certainty evidence, Table 2).[12,25]

Five studies reported 21 (9%) patients had serious adverse events in the PTH group and 10 (9%) in the conventional group, including hypocalcemia, hypercalcemia, diarrhea, anaphylactic reaction, etc, but there was no evidence of important differences between groups based on the limited data available (RR = 1.14, 95% CI 0.6–2.2, 9 more per 1000 patients, low certainty evidence).[12,13,25,27,33] There were also no important differences in the discontinuation of the study due to adverse events (RR = 1.0, 95% CI 0.1–9.8, 0 more per 1000 patients, low certainty evidence).[13,25] Supplemental Table S2 presents a summary of the findings specifically reporting adverse events. Many adverse events were more frequently found in the PTH group than in the conventional therapy group; however, differences were

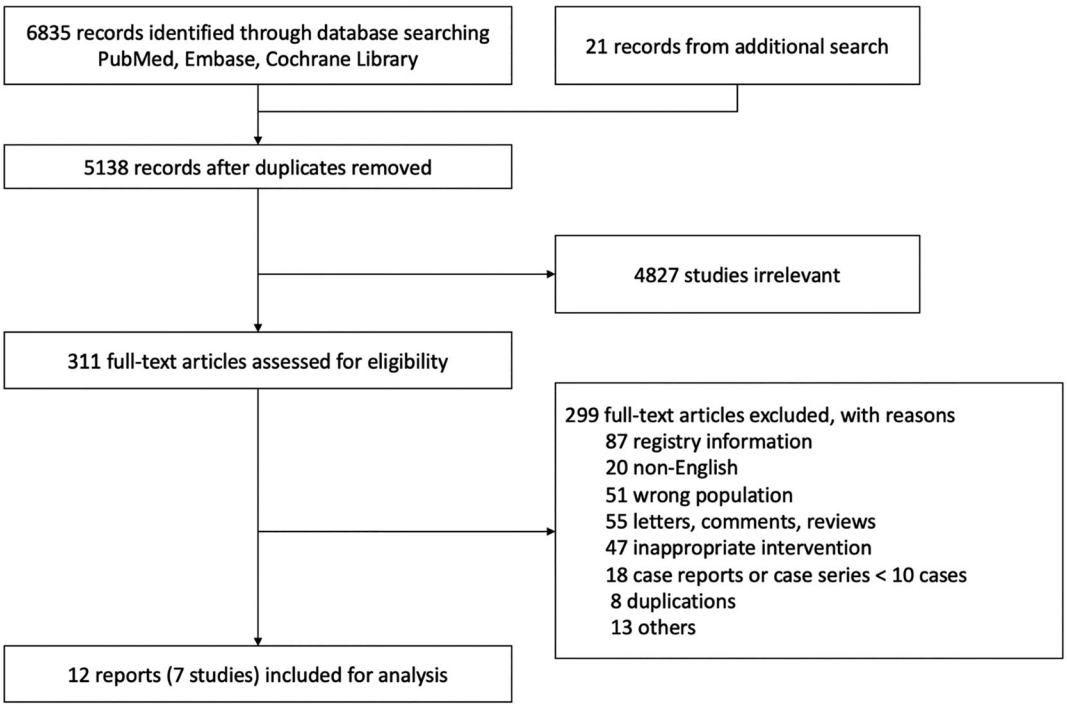

Fig. 1. Study selection.

Table 1. Characteristics of Included Studies

Study	Country	Study design	No. of patients in PTH/ control	Age (mean)	Female	Surgical patients	Treatment group	Control group	Outcomes	Follow-up duration (months)	Key findings
REPLACE[24,25,30]	North America and Europe	Parallel RCT	90/44	47.5	78%	74%	rhPTH (1–84); active vitamin D; calcium	Placebo; active vitamin D; calcium	Patient important outcomes: adverse events, 50% or greater reduction in dose of vitamin D and calcium, quality of life Surrogate outcomes: hypocalcemia, hypercalcemia, hypercalciuria, 24-h urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-Dihydroxyvitamin D3	6	Serum phosphate levels decreased rapidly from the upper normal range and remained lower with rhPTH (1–84). At week 24, serum calcium–phosphate product was lower with rhPTH (1–84) vs. placebo. rhPTH (1–84) treatment resulted in significant reductions in oral calcium dose compared with placebo while maintaining serum calcium. The proportions of patients who had at least one adverse event and serious adverse events were similar between groups
Sikjaer, 2011-2014[26–29]	Denmark	Parallel RCT	32/30	52.0	85%	94%	rhPTH (1–84); alfacalcidol/ calcitriol/ ergocalciferol	Placebo; calcium and alfacalcidol/ calcitriol/ ergocalciferol	Patient important outcomes: adverse events, quality of life Surrogate outcomes: hypocalcemia, hypercalcemia, 24-h urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D3, serum magnesium, Serum alkaline phosphatase, Serum osteocalcin, BMD.	6	Asymptomatic hypercalcemia was present in 71% of the rhPTH (1-84) treated patients. Compared with placebo, 24-hour urinary calcium, phosphate, and magnesium did not change,
Winer, 2003[31]	USA	Parallel RCT	14/13	45.0	63%	41%	PTH (1–34); elemental calcium	Calcitriol and calcium	Patient important outcomes: adverse events Surrogate outcomes: 24-h urine calcium excretion, serum calcium, serum magnesium, phosphate excretion, mean creatinine clearance, Serum alkaline phosphatase, Serum osteocalcin, Urine deoxypyridinoline, Urine pyridinoline, BMD	36	(1) Serum calcium levels were similar in both treatment groups within or just below the normal range; (2) mean urinary calcium excretion was within the normal range from 1-3 yr in PTH-treated patients but remained above normal in the calcitriol group; (3) bone mineral content and bone mineral density showed no significant between-group differences over the 3-yr study period.
Winer,1996[32]	USA	Crossover RCT	10	46.5	40%	40%	PTH (1-34); dietary elemental calcium	Calcitriol; dietary elemental calcium	Patient important outcomes: adverse events Surrogate outcomes: hypercalcemia, 24-h urine calcium excretion, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D3, Serum alkaline phosphatase, Serum osteocalcin, Urine deoxypyridinoline, Urine pyridinoline	2.5	Once-daily treatment with PTH (1-34) maintained serum calcium in the normal range with decreased urine calcium excretion compared with calcitriol treatment. Biochemical markers of bone turnover increased significantly during PTH (1-34) treatment.

(Continues)

Table 1. Continued

Study	Country	Study design	No. of patients in PTH/ control	Age (mean)	Female	Surgical patients	Treatment group	Control group	Outcomes	Follow-up duration (months)	Key findings
Winer, 2010[33]	USA	Parallel RCT	7/5	9.6	33%	NR*	PTH (1-34); dietary elemental calcium; magnesium supplement	Calcitriol; calcium and cholecalciferol; magnesium supplement	Patient important outcomes: adverse events, Surrogate outcomes: hypocalcemia, 24-h urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D3, serum magnesium, mean creatinine clearance, Serum alkaline phosphatase, Serum osteocalcin, Urine deoxypyridinoline, Urine pyridinoline, BMD	36	Mean predose serum calcium levels were maintained at, or just below, the normal range, and urine calcium levels remained in the normal range throughout the 3-yr study, with no significant differences between treatment groups. Creatinine clearance, corrected for body surface area, did not differ between groups and remained normal throughout the study.
Khan, 2021[12]	North America and Europe	Parallel RCT	44/15	49.2	81%	80%	TransCon PTH; oral elemental calcium; active vitamin D	Placebo; oral elemental calcium; active vitamin D	Patient important outcomes: adverse events, 50% or greater reduction in dose of vitamin D and calcium, quality of life Surrogate outcomes: hypocalcemia, hypercalcemia, serum calcium, serum phosphate	1	91% of participants treated with TransCon PTH achieved independence from standard of care. Mean 24-hour urine Ca decreased from a baseline mean of 415 mg/24h to 178 mg/24h by Week 26 while normal serum Ca (sCa) was maintained, and serum phosphate and serum calcium-phosphate product fell within the normal range. TransCon PTH was well tolerated with no treatment-related serious or severe adverse events.
Khan, 2022[13]	North America and Europe	Parallel RCT	61/21	48.6	78%	85%	TransCon PTH; oral elemental calcium; active vitamin D	Placebo; oral elemental calcium; active vitamin D	Patient important outcomes: adverse events, quality of life Surrogate outcomes: 24-h urine calcium excretion, serum calcium, hypocalcemia, hypercalcemia	6.5	93% of participants treated with TransCon PTH achieved independence from conventional therapy. Treatment with TransCon PTH over 26 weeks also normalized mean 24-hour urine calcium. Most adverse events were mild or moderate. No study drug-related withdrawals occurred.

NR = not reported.

Table 2. GRADE summary of findings

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain text summary
		Conventional therapy[a]	PTH[a]		
Quality of life (physical health)	Measured by: SF-36[b] Scale: 0–100 high better Based on data from 263 patients in 3 studies[13,29,30] Follow up 6 months	**−0.1** Mean	**3.3** Mean Difference: **MD 3.4 higher** (CI 95% 1.5 higher–5.3 higher)	**Moderate** Due to serious imprecision[c]	PTH therapy probably results in a small improvement in quality of life (physical health)
Quality of life (mental health)	Measured by: SF-36[b] Scale: 0–100 high better Based on data from 179 patients in 2 studies[29,30] Follow up 5 months	**−2.8** Mean	**3** Mean Difference: **MD 5.8 higher** (CI 95% 4.9 lower–16.5 higher)	**Low** Due to very serious imprecision[d]	PTH therapy may have small improvement in quality of life (mental health)
Depression	Measured by: WHO-5-well-being Scale: 0–5 high better Based on data from 59 patients in 1 study[29] Follow up 6 months	**0.1** Mean	**0.1** Mean Difference: **MD 0 lower** (CI 95% 0.2 lower–0.1 higher)	**Moderate** Due to serious imprecision[e]	PTH therapy probably has little or no impact on depression
50% or greater reduction in doses of active vitamin D and calcium	Relative risk: 6.5 (CI 95% 2.5–16.4) Based on data from 191 patients in 2 studies[12,25] Follow up 21 months	**70** per 1000	**455** per 1000 Difference: **385 more per 1000** (CI 95% 200 more–744 more)	**High**	PTH(1-84) and TransCon PTH therapy allow a 50% or greater reduction in doses of active vitamin D and calcium
Serious adverse events	Relative risk: 1.1 (CI 95% 0.6–2.2) Based on data from 349 patients in 5 studies[12,13,25,27,33] Follow up 6 months	**90** per 1000	**99** per 1000 Difference: **9 more per 1000** (CI 95% 36 fewer–108 more)	**Low** Due to very serious imprecision[d]	PTH therapy may have little or no impact on serious adverse events
Discontinued the study due to adverse events	Relative risk: 1.0 (CI 95% 0.1–9.8) Based on data from 216 patients in 2 study[13,25] Follow up 6 months	**15** per 1000	**15** per 1000 Difference: **0 more per 1000** (CI 95% 42 fewer–72 more)	**Low** Due to very serious imprecision[d]	PTH therapy may have little or no impact on discontinuation due to serious adverse events

[a]For continuous outcomes, absolute effect estimates in conventional therapy and PTH groups were difference of baseline and follow up.
[b]Minimally important difference (MID) is 3 points.[34]
[c]The confidence interval included trivial and small benefits.
[d]The confidence interval included serious harms and important benefits.
[e]The small sample sizes.

significant only for thirst during PTH(1–84) versus conventional therapy (RR = 6.5, 95% CI 1.2–34.2, 77 more per 1000 patients, low certainty evidence, Supplemental Table S2).

Supplemental Table S3 summarized the results of the surrogate outcomes and suggests that PTH therapy in comparison to conventional therapy is associated with higher serum calcium (MD 0.11 mmol/L, 95% CI 0.02, 0.20), lower serum phosphorus (MD −0.2 mmol/L 95% CI −0.4, −0.03), serum 25-hydroxyvitamin D (MD −9.2 ng/mL, 95% CI −12.2 to −6.1), serum magnesium (MD −0.06 mmol/L 95%CI −0.1, −0.01). Additionally, there was a higher incidence of hypercalcemia for patients receiving PTH(1–84) (RR = 2.4, 95% CI 1.2–5.04). We found no persuasive evidence of an impact of PTH (1–34) versus conventional therapy on creatinine clearance (MD 3.9 mL/min, 95% CI −2.4 to 10.3). Neither group demonstrated a difference in mean renal function.

Discussion

Main findings

Eligible studies did not report on patient-important outcomes of nephrocalcinosis/nephrolithiasis, seizures, arrhythmia, ischemic heart disease, cataracts, fracture, infection, and mortality. This may have been attributable to the small sample size of the studies and their relatively short-term duration. The study results obtained to date provide evidence that PTH(1–84) therapy allows more patients to reduce or stop taking calcium and active vitamin D. Reduction in dose or complete cessation of conventional therapy was not tracked in the controlled studies with PTH(1–34). There was a small or no impact on health-related quality of life (Table 2). Serious adverse events were infrequent, and although a number of adverse events occurred more frequently in the PTH group (Supplemental Table S2), the results were significant only for thirst. Regarding the surrogate outcomes, PTH therapy was associated with increased hypercalcemia, serum alkaline phosphatase, serum osteocalcin, and urine pyridinoline and reductions in serum phosphate, serum 25-hydroxyvitamin D, and serum magnesium (Supplemental Table S3).

Strengths and limitations

The strengths of this review include a comprehensive search; registration of our study protocol before starting; and evaluation of the quality of evidence using the GRADE approach. This review also has limitations. The most important limitation is the small sample size of the available studies, resulting in essentially insufficient evidence regarding many of the outcomes important to patients. The small sample size resulted in imprecision of estimates (there may be additional adverse effects that the studies were unable to detect) and precluded any subgroup analyses. Because of the short-term duration, the existing studies failed to address most patient-important outcomes. In addition, PTH may have effects in different etiologies of hypoparathyroidism.[35]

Comparison with other studies

One prior review included similar studies to our review and focused on the same questions.[36] However, the prior review did not include all publications based on the same population. For example, three publications addressed different outcomes for the REPLACE trial: one reported safety outcomes, one reported health-related quality of life, and one reported surrogate outcomes;[24,25,30] the prior review only included the first publication.[25] Similarly, we found another review addressing both adults and pediatric patients with chronic hypoparathyroidism that included five clinical trials; however, it only reported biochemical outcomes.[37] In comparison to prior reviews, our review adds additional studies and highlights the low-quality evidence measuring of most major patient-important outcomes and the likelihood that effects on physical health-related quality of life are small.

Interpretation and application

The available studies are small and provide limited evidence regarding major patient-important outcomes. The results suggest that benefits on quality of life may be small. PTH therapy (PTH(1–84) and TransCon PTH) might result in more patients being able to discontinue calcium and active vitamin D supplements, thus potentially reducing the pill burden of the disease, but because the quality of evidence is low, further study of this effect is needed. PTH therapy was also shown to lower serum phosphate. This may have potential benefits with respect to lowering the risk of ectopic calcification as well as nephrocalcinosis and declines in renal function. The impact of the reduction in serum phosphate requires further study. More definitive evidence requires considerably longer and larger studies, which may be challenging for clinical studies for a rare disease.

This review highlights the limitations in available evidence regarding the impact of PTH on patient-important outcomes. Results did, however, suggest a small impact of PTH therapy on physical health-related quality of life. The benefits include a reduction in serum phosphate. The reduction in phosphate may have important benefits on lowering the long-term complications of chronic hypoparathyroidism and requires further study. A reduction in the dose of the calcium and active D requirements was observed. The adverse events with PTH therapy in comparison to conventional therapy may be limited to a higher incidence of hypercalcemia. We found no other convincing evidence of important adverse events.

Disclosures

AAK: speaker and / or grants from Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, and Ultragenyx; consultant for Alexion, Amgen, Amolyt, Ascendis, Radius, Takeda, and Ultragenyx. JPB: consultant for Amgen, Radius, Ascendis, Calcilytix, Takeda, Amolyt, Rani Therapeutics, MBX, Novo-Nordisk, and Ipsen. MLB: has received honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, and UCB; grants and/or speaker: Abiogen, Alexion, Amgen, Bruno Farmaceutici, Echolight, Eli Lilly, Kyowa Kirin, SPA, Theramex, and UCB; consultant: Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, and UCB. BLC: consultant for Takeda/Shire, Amolyt Pharma, and Calcilytix; grants from Takeda/Shire and Ascendis. LR: speaker for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, and Ultragenyx; consultant for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, and Ultragenyx; grants from Takeda and Kyowa Kirin. MM: consultant for Takeda, Amolyt, and Chugai; grants from Takeda and Chugai.

Acknowledgments

We acknowledge unrestricted financial support from Amolyt, Ascendis, Calcilytix, and Takeda. 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, its content, or conclusions.

Authors' roles: Design/conceptualization of the project: AAK, JPB, MM, LR, MLB, BLC, and GG. Data acquisition, review, analysis, methodology: LY, MLB, XH, JL, KY, CL, DT, MK, AS, NM, DSA, KD, AAK, JPB, MM, LR, MLB, BLC, and GG. Project administration, including acquisition of funding: AAK, JPB, MM, LR, MLB, BLC. Original drafting and preparation of the manuscript: LY, JL, ML. Review/editing of the manuscript: LY, ML, XH, JL, KY, CL, DT, MK, AS, NM, DSA, KD, AAK, JPB, MM, LR, MLB, BLC, and GG.

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Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4676.

Data Availability Statement

NA

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