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Highlights

- This review confirms that the effect of PTH peptides, as osteoporosis therapies, on peripheral bone mineral density (BMD) is different to that at the spine and hip.
- PTH peptide monotherapy has trends for peripheral BMD losses compared to antiresorptives.
- PTH peptides combined with antiresorptives reduced peripheral BMD losses found with monotherapy.
- The peripheral fracture efficacy between PTH peptide mono and combined therapy remains uncertain.
- Novel technologies, including HrpQCT, should be utilised in the development of novel anabolic treatments to better characterise their effects on peripheral BMD.

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The effects of parathyroid hormone peptides on the peripheral skeleton of postmenopausal women. A systematic review.

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Abstract

Given current developments in anabolic therapy for bone, we wished to document the effects of the only currently available anabolic therapy, parathyroid hormone (PTH) peptides, on the peripheral skeleton of postmenopausal women.

We undertook a systematic review of English articles using MEDLINE, Scopus and the Cochrane Controlled Trials Register (final update 28th March 2016). Additional studies were identified through searches of bibliographies. Studies included those comparing PTH peptides with placebo, with anti-osteoporotic treatments and in combination therapies. Participants had to be postmenopausal women and outcomes included areal or volumetric bone mineral density (BMD) and measurements of bone microarchitecture at peripheral sites, such as the forearm and tibia. Data were extracted independently and reviewed by EMcC and LMM. Data on study design were also collected for methodological risk of bias assessment.

The heterogeneity between studies, regarding the drug dose and duration, and the site measured, prevented grouped meta-analysis. There were no significant differences in areal BMD between PTH peptides and placebo at peripheral skeletal sites at 12 months. A decrease in aBMD occurred with PTH(1-34) (larger dose) and PTH(1-84) treatment at 18 months follow-up in comparison to the placebo arms. Anti-resorptives seemed to attenuate losses of aBMD at peripheral sites when compared to PTH peptides monotherapy, likely mediated by lower cortical porosity. Finally, PTH peptides combined with bisphosphonates or denosumab attenuated peripheral BMD losses in comparison to PTH peptide monotherapy, with evidence of increased BMD at ultradistal peripheral sites when PTH(1-34) was combined with denosumab or hormone replacement therapy.

This summary should act as a reference point for the comparison of new anabolic therapies, specifically in comparison to PTH(1-34).

Keywords: Anabolics, PTH peptides, Postmenopausal, Osteoporosis, Bone density, Peripheral skeleton

1 Introduction

The treatment of osteoporosis is changing. The potential of anti-resorptive therapies to reduce fracture risk appears to have peaked with the development of easily administered, potent agents such as zoledronic acid and denosumab. However, despite increased efficacy of these agents to reduce vertebral fracture by approximately 65-70% versus placebo compared to 40-50% reductions seen with oral bisphosphonates versus placebo, anti-resorptive treatments have shown a relatively disappointing smaller relative risk reduction for non-vertebral, non-hip fractures (12-32%) versus placebo, when compared to the vertebral fracture risk reduction [1]. Non-vertebral, non-hip fractures, which include predominantly peripheral sites at the upper and lower limbs, comprise a significant proportion of the burden of fractures, especially at younger ages [2, 3]. However, even in 85+ year olds, they still comprise 40-50% of fractures [2, 3]. It is unclear whether such fractures are somehow beyond the reach of bone-targeted approaches, or at least anti-resorptive therapies, as they may relate more to fall risk and other neuromuscular risk factors.

Anabolic therapies may offer improved outcomes in this regard, though the data are relatively limited and the mechanisms remain unclear. Currently, PTH peptides are the only licensed anabolic therapy, either in the form of teriparatide (1-34 peptide fragment) or intact PTH (1-84 peptide). Both therapies are associated with early increases in bone-formation markers followed by a later increase in resorption markers [4, 5]. Improvements in aBMD with PTH(1-34), and PTH(1-84) to a lesser extent, have been established at the lumbar spine and proximal femur [6, 7] and both have been reported to reduce vertebral fracture risk. However, the effect of PTH peptides on peripheral fracture risk have been mixed; when comparing PTH(1-34) to placebo, there were reported reductions in wrist fractures in the pivotal phase III trial [8], but reductions were not found in the more recent ACTIVE phase III trial [9]. Furthermore, in the phase III study with PTH(1-84) there was no significant effect on wrist, upper-limb and lower-limb (non-hip) fractures [10].

Recently, the analogue of PTH-related peptide (PTHrP 1-34; Abaloparatide) has been reported to improve fracture risk at vertebral and non-vertebral sites [9], though the treatment has not yet been licensed. Additionally, two sclerostin-targeted antibody therapies, romosozumab and blosozumab, have been tested in phase 2 studies, with romosozumab currently undergoing evaluation in a large phase 3 clinical program. The impact of these approaches in the peripheral skeleton and on non-vertebral fracture risk are awaited with interest and will necessitate comparison with the effects of PTH peptides. For this reason, we have undertaken a systematic review of the efficacy of PTH peptides at peripheral skeletal sites to address three questions, comprising: (1) what is the effect of PTH peptides compared to placebo treatment on peripheral skeleton BMD? (2) What is the effect of PTH peptides compared to anti-resorptive treatments on peripheral skeleton BMD? (3) What is the effect of PTH peptides combined with other treatments compared to comparator monotherapy on peripheral skeleton BMD?

2 Methods

Following the PRISMA statement guidelines [11], we used a systematic approach to accurately identify all Level 1 eligible research to answer the questions outlined above.

2.1 Eligibility criteria

A stringent flow was used to identify eligible studies (Supplemental information 1). We searched for randomized studies in which participants were post-menopausal women and the interventions included at least one of the PTH peptide treatments (PTH(1-34) or PTH(1-84)) with a minimum 6 months of follow up on therapy and must have reported changes in BMD from baseline. Studies with either blinded or open treatment allocation were considered. Studies required a comparator, such as a placebo or an FDA-approved anti-resorptive treatment (including hormone replacement therapy, HRT). Quantitative outcome measures included areal BMD (aBMD) and/or volumetric BMD (vBMD) of peripheral skeletal sites (forearm, tibia, metacarpals or metatarsals). Studies were

restricted to the English language. Conference abstracts and unpublished findings were eligible, subject to the availability of study characteristics and data for outcome and risk of bias assessment.

2.2 Information sources

The search strategy included searching electronic databases, hand-searching the bibliographies of eligible articles and systematic reviews, and manufacturers of FDA-approved PTH peptides were contacted for unpublished findings. A piloted, electronic search strategy (Supplemental information 2) was undertaken in PubMed MEDLINE (all years), Scopus (all years) and the Cochrane Central Register of Controlled Trials (all years). Weekly updates were concluded on the 28th March 2016.

2.3 Study selection

Figure 1 provides a flow from search completion to study inclusion. Duplicates were removed and then the title, abstract and, where appropriate, the respective full-texts underwent data extraction.

2.4 Data collection process

In an attempt to avoid selective reporting bias from studies not presenting raw data, 6 authors (7 studies) were contacted by email for raw study data points. Four authors (5 studies) responded with two providing numerical data that had been presented previously in graphical format. To avoid double counting data across studies, full texts were reviewed for indications of whether the study was an extension or sub-study. This was completed through tracking citations, the name of studies or trials and author names. To provide further clarity, the types of patients included, treatment durations and doses, comparators and the study outcomes (e.g. bone sites measured) were reviewed and compared (Supplemental information 3).

2.5 Assessment of risk of bias

Both EMcC and LMM reviewed the risk of bias assessment in included studies. LMM initially reviewed the allocation sequence for randomization and its concealment from investigators, the blinding of patients and investigators, patients lost to follow up, early termination of trials and whether intention-to-treat analysis was undertaken. During data extraction it was identified that a

risk of bias may stem from the sample sizes for peripheral skeletal measurements, due to lower numbers of patients used for these analyses compared to lumbar spine or proximal femur BMD, which were typically primary outcomes for studies.

2.6 Summary measures

The review describes quantitative changes from individual studies, rather than in summative form (meta-analysis), due to heterogeneity in study durations, PTH peptide dose and sites of peripheral skeletal measurements. The primary outcome was the mean difference in BMD from baseline to study endpoints for each peripheral bone site between (1) PTH peptide and placebo treatments, (2) PTH peptide and comparator treatments and (3) PTH peptide combined with other treatments compared to the comparator monotherapy. 95% CI and effect sizes were calculated from the mean differences between groups. A significant difference was stated when the 95% CI excluded zero.

3 Results

From an original search output of 1668 articles (Figure 1), a total of 41 manuscripts were subjected to full-text review. 27 studies/reports were excluded for the following reasons: absence of an RCT design (n=6), being a sub-study or extension (n=7), mixed gender participation (n=3), no standardization of the comparator treatment (n=1), duration less than 6 months (n=2), no peripheral skeleton measurements made and/or reported (n=6) and studies only reported within conference abstracts without sufficient detail (n=2). 14 articles (from 13 studies) were included in the final review. Two articles from the DATA study were included as they separately presented aBMD [12] and vBMD data [13].

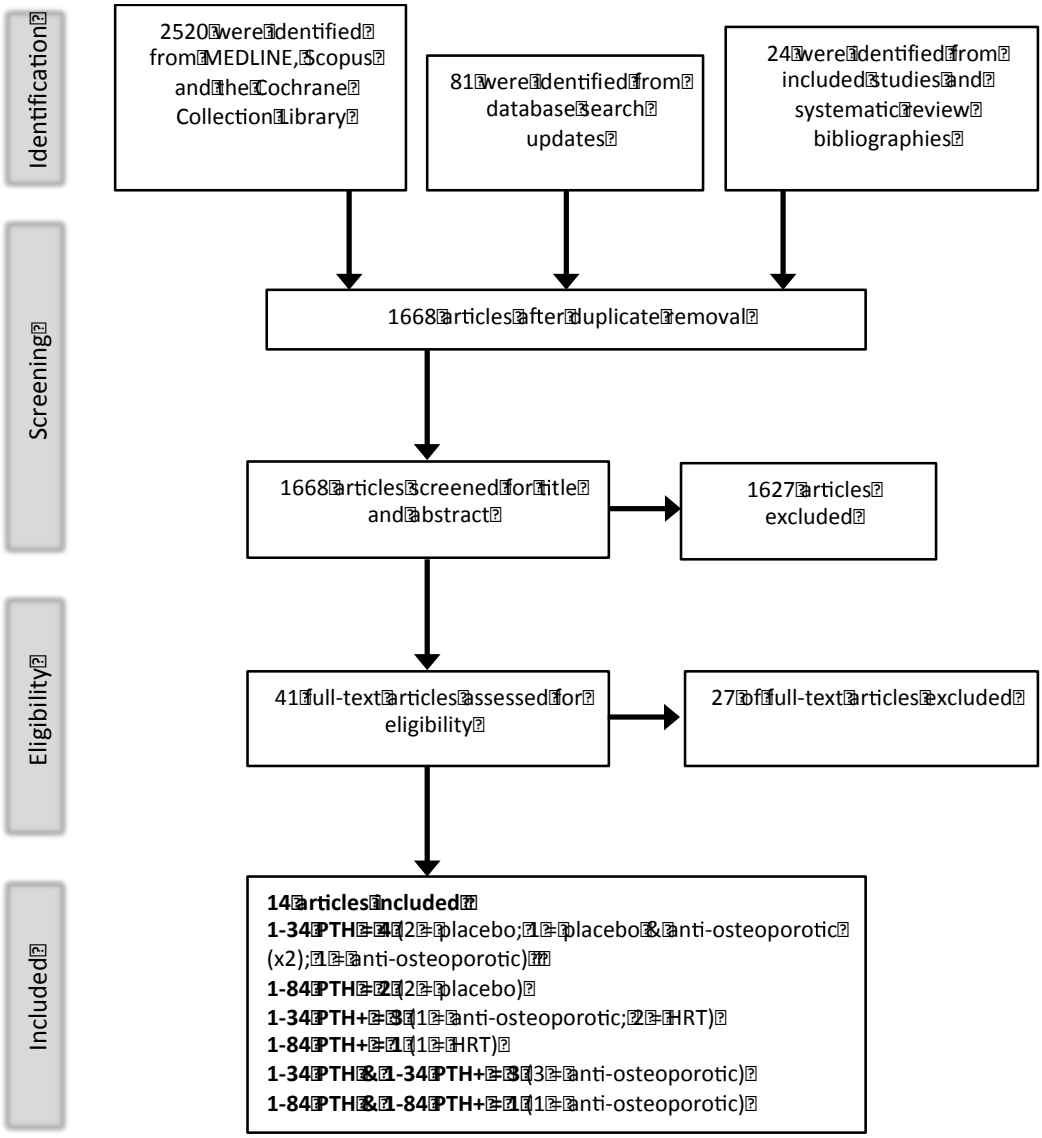

Figure 1. Study identification, screening, eligibility and inclusion in the review.

Abbreviations: + - combined with another treatment

The study characteristics, including study outcome measures, are shown in Table 1. Baseline characteristics of the women who participated in the 14 included studies are detailed in supplemental information 4. The previous use of osteoporosis therapy, garnered from inclusion and exclusion criteria varied between studies (Supplemental information 5); importantly, it was required that any pre-treated patients had been randomized to their respective treatment arms. All of the studies used concomitant daily calcium (500-1500mg daily) and/or vitamin D supplementation (400-1200IU, or to maintain serum levels). Five of the 14 reports included placebo arms [8, 10, 14-16] and

10 had anti-resorptive treatment comparators (including 3 with HRT) [4, 5, 12, 13, 16-21]; please note that one study had both placebo and active comparator [16]. One study comparing two anabolics (PTH(1-34) to romosozumab) was not included in the analysis as this phase II trial assessed the efficacy of 5 different romosozumab doses and this treatment was not licensed at the time of this analysis [16]. DXA scanning produced aBMD data while measurements of vBMD were gathered using MRI [14] or HRpQCT [13]. Eleven studies presented BMD data to allow calculation of mean differences, 95% confidence intervals and effect sizes between treatment groups. 2 manuscripts reported mean changes without variation measures [18, 20] and a further 2 reported changes in graphical format only [15, 17]: these studies could not have quantitative comparisons of treatment groups.

The degree of methodological risk of bias varied between studies (Supplemental information 6). All of the placebo-controlled trials were double-blind within at least some of the allocated treatment arms [8, 10, 14-16] but blinding was less common in studies comparing PTH peptides to other treatments, potentially due to difficulties in blinding injections compared to oral administration. Use of intention-to-treat analysis was reported in three placebo-controlled [10, 14, 15], four anti-resorptive treatment-controlled comparisons [4, 12, 13, 17] and two trials combining PTH peptides with HRT [19, 20]. Several trials had a loss to follow up of over 15% including two studies investigating PTH(1-34) [8, 16] and one study investigating PTH(1-84) [10] that were placebo-controlled, four PTH(1-34) peptide trials that were anti-resorptive treatment controlled [5, 12, 13, 17] and when PTH peptides were combined with HRT [19, 21]. Several studies reported early terminations due to reports of osteosarcoma in PTH peptide-treated rats [8, 17, 19, 21].

The data that the mean difference and 95% CI between the PTH peptide and comparator groups was calculated from has been compiled in the supplemental information (number 7 and 8).

3.1 PTH peptides compared to placebo

Both PTH peptides were associated with trends to decrease aBMD within radial sites but, while these effects were often numerically greater, they were usually not significantly different from changes observed in the placebo groups (Table 2). The following between group differences in the percent change in aBMD from baseline (with 95% CI and effect size (d)) were found: significantly greater losses were reported at 18 months at predominantly cortical sites of measurement in the radial shaft with PTH(1-34) at a dose of 40 μg/day (-1.9 [-2.8, -1.0] d=0.48) and PTH(1-84) 100 μg/day (-3.46 [-4.66, -2.26] d=0.74) compared to placebo groups. There were no significant differences from placebo at the radius shaft with PTH(1-34) 20 μg/day or PTH(1-84) 100 μg once weekly over 12-18 months of follow up. Interestingly, those studies that examined predominantly trabecular sites within the distal radius (ultradistal radius or distal radius) showed trends for increases with PTH, though this did not reach statistical significance with aBMD measurements (Table 2). However, using MRI to assess bone microarchitecture, there were significantly higher trabecular number (5.16 [1.41, 8.90] d=1.02) and lower trabecular spacing (-8.98 [-16.11, -1.85] d=0.3) with the once-weekly PTH(1-84) dose. Cortical thickness was measured, but not reported.

3.2 PTH peptides compared to anti-resorptive treatments

At cortical sites within the radius, both PTH peptides showed significant decreases in aBMD compared to treatment with the anti-resorptive agents, alendronate or denosumab (Table 3). The following between group differences in the percent change in aBMD from baseline (with 95% CI and effect size (d)) were found: a higher PTH(1-34) dose (mean 28.5 μg/day) over 24 months led to a larger decrease in aBMD (-7.8 [-9.96, -5.64] d=2.1) compared to the 20 μg/day PTH(1-34) over 12 months (-1.4 [-2.43, -0.37] d=0.24), in comparison to alendronate. PTH(1-84) at a dose of 100 μg/day appeared to have a numerically greater difference from alendronate (-2.67 [-3.69, -1.65] d=0.79) than PTH(1-34) 20 μg/day. A similar reduction in aBMD during PTH(1-34) 20 μg/day was observed when compared to denosumab alone over 24 months of treatment (-3.8 [-5.82, -1.78] d=0.97).

Tsai and colleagues [13] presented HRpQCT results as part of the DATA study at 24 months follow-up. There were no differences in parameters measuring trabecular architecture between the PTH(1-34) and denosumab treatment groups at either the radius or tibia, where trabecular vBMD was not statistically different between the treatments (presented in graphs). In contrast, at both sites, cortical vBMD was lower in patients receiving PTH(1-34) compared to denosumab, albeit mean differences could only be calculated for the radius. Other data presented in graphs, such as cortical thickness and cortical tissue mineral density (TMD), followed a similar trend and there was higher cortical porosity with PTH(1-34), at both sites.

3.3 PTH peptides combination therapy versus comparators

Analyses showing a comparison of PTH peptides combined with a variety of anti-resorptives to the anti-resorptive alone are shown in Table 4. The following between group differences in the percent change in aBMD from baseline (with 95% CI and effect size (d)) were found: in studies combining PTH peptides with HRT there was significantly higher ultradistal radius aBMD with 40ug/day PTH(1-34) and HRT compared to HRT monotherapy (2.36 [0.70, 4.02] d=0.57). However there was no difference at the 1/3 distal radius site for HRT-PTH(1-34) combination (-0.72 [-2.16, 0.72] d=0.20) and for HRT-PTH(1-84) combination (-1.35 [-3.09, 0.39] d=0.32) when compared to HRT monotherapy. A lower aBMD was found in one study that combined 40ug/day PTH(1-34) with alendronate (vs. alendronate alone) after 24 months follow-up (-3.2 [-5.33, -1.07] d=0.87); the decrease was somewhat less than that induced by the use of PTH(1-34) alone at the same dose and duration (-7.8 [-9.96, -5.64] d=2.1). No difference was observed for PTH(1-84) in combination with alendronate compared to the latter alone over a 12 month period (-0.49 [-1.49, 0.51] d=0.18).

Combination of PTH(1-34) with denosumab was not different to the effects of denosumab alone on aBMD at the 1/3 distal radius following 24 months treatment (0.1 [-1.55, 1.75] d=0.03). This was consistent with the distal radius for total vBMD, but this measurement increased with combined treatment at the distal tibia (1.60 [0.57, 2.63] d=0.96). Trabecular vBMD decreased with combined treatment at the radius, but changes were not different at the tibia, and there were no changes in

trabecular bone microarchitecture. Cortical vBMD and thickness were not different, plus no differences were reported in graphical representations of cortical TMD and porosity. There was no observed difference in distal radius stiffness (0.8 [-1.56, 3.16] d=0.18) and failure load (1.10 [-1.10, 3.30] d=0.26) with combined treatment compared to denosumab, and there was no differences found at the distal tibia between these groups (in graph).

4 DISCUSSION

This summary review confirms that the administration of PTH peptides commonly leads to decreases in aBMD at sites of the peripheral skeleton that are predominantly cortical bone, such as the radius shaft and 1/3 distal radius. The relatively small changes in aBMD at these sites during treatment over a 12-18-month period are in marked contrast to the more substantial increases in aBMD at the lumbar spine and, to a lesser extent, the proximal femur [6, 7, 22]. The impact on peripheral aBMD is more marked when treatment with PTH peptides alone is compared to the effects of anti-resorptive treatments, either alone or in combination with PTH peptides. The decrease in aBMD, particularly at higher doses of PTH peptides (e.g. 40 µg/day vs. 20 µg/day), likely reflects hypomineralization of newly formed osteoid [23] and an increase in Haversian canal area [24] in cortical bone, contributing to an apparent 'catabolic' effect on imaging measurements. The greater contrast when compared to anti-resorptives reflects the increased secondary mineralization and infilling of cortical porosity that occurs with the latter agents. The attenuation of markers of bone formation [3, 4, 11], as well as recent data in bone biopsies [25], support the attenuation of aBMD losses when PTH peptides are combined with anti-resorptives, compared to monotherapy [4, 5, 12, 13].

Indirect comparisons of PTH peptides across different placebo-controlled studies suggest that PTH(1-84) has a trend for a greater loss of 1/3 distal radius aBMD than PTH(1-34) [8, 10]. Similar findings are noted when compared to alendronate monotherapy [4, 16]. Local effects in radius aBMD compared to placebo may reflect the different wrist and upper-limb fractures risks between the PTH(1-34) and PTH(1-84) treatments [8, 10]. However, on assessing the upper-limb fragility fracture

efficacy of PTH(1-34) at 20μg/day in the two phase III trials, there was an approximate 55% reduction in the Fracture Prevention Trial [8], albeit with a small number of fractures, and a 5% reduction in ACTIVE [9] (Supporting information 9). When lower-limb and upper-limb fractures were combined in both trials, the peripheral fracture relative risk reduction [95% CI] decreased in both trials (Fracture Prevention Trial: 0.39 [0.14, 1.08]; ACTIVE: 0.78 [0.45, 1.37]). It is also worth noting that abaloparatide seemed to have better peripheral fracture efficacy compared to PTH(1-34) [9].

Given the more marked differences in peripheral BMD in head-to-head trials between PTH peptides and anti-resorptives, highlighted by large effects in aBMD [4, 5, 12, 16] and vBMD at peripheral sites [13], one can also ask whether differences are seen in the effects on peripheral skeleton fracture rates. Such assessments are limited by a paucity of direct head-to-head comparisons. Available studies, not limited to postmenopausal osteoporosis, have usually been insufficiently powered [17, 26, 27] and have reported non-vertebral fracture rates (i.e. hip, rib, pelvis and peripheral skeletal fractures combined) [26, 27]. Despite apparent larger reductions in the pivotal teriparatide trial [8] than seen with antiresorptive agents, a recent systematic review suggests only modest differences on non-vertebral fractures, including hip fractures, between PTH(1-34), bisphosphonates and denosumab [28].

Based on reported differences in distal radius aBMD during PTH(1-34) alone compared to peptides combined with denosumab and HRT [12, 21], lower peripheral fracture risk might be anticipated. It remains uncertain whether even the greater increase in lumbar spine aBMD that is seen with densoumab combination therapy confers greater vertebral fracture protection [12], particularly when compared to the already highly effective PTH peptide monotherapy [8, 10]. Perhaps the greater argument for combination therapy arises from the effects on the peripheral skeleton, where the higher turnover in cortical bone during PTH peptide monotherapy may not provide optimal fracture reduction. Again, this hypothesis remains unproven due to the absence of sufficiently powered studies; intriguingly, the comparative fracture study with abaloparatide, a PTH peptide

analogue with apparently lesser effects on the stimulation of bone resorption, showed a greater reduction in upper limb fractures than that seen with PTH(1-34) therapy [9].

This review highlights moderate heterogeneity in the trial design and outcomes used to assess the peripheral skeletal effects of PTH peptides in RCTs. In order to better inform future trials, particularly those with novel anabolic therapies, a number of recommendations can be made that will assist future synthesis of the data:

1. Treatment duration: comparisons should be assessed over the full treatment length to obtain data that could be clinically relevant to peripheral fracture risk.
2. Site selection: The 1/3 distal radius should be included as a comparator site for aBMD assessment using DXA; this has been the most frequently reported site in trials to date and may indicate mechanistic differences of treatments on cortical bone.
3. Utilization of HR-pQCT: HR-pQCT can quantify cortical and trabecular compartments and may shed more light on peripheral adaptations with different treatments [13, 29, 30] and should be undertaken in at least a subset of study subjects. The technique can provide information on apparent bone strength and stiffness through finite element modeling, and measure adaptations of the endocortical transitional zone and regional cortical porosity [31, 32].

This review has a number of limitations to consider. For example, the analysis has been limited to women with postmenopausal osteoporosis whereas trials have also been undertaken in men with osteoporosis [33, 34] and with glucocorticoid-induced osteoporosis [35]; importantly, where results on the peripheral skeleton aBMD were reported, trials have found a similar trend to those reported in our review [33-35]. Secondly, other factors not included in the analysis might have influenced the differences found between different treatments. For instance, poor adherence to the treatments may underestimate effects between the groups and variability in the cohort's age, ethnicity, previous fracture incidence and other characteristics must also be recognized (Supplemental information 4). Prior therapy use could also have an impact; for example, prior HRT use was prevalent in PTH peptide and HRT combination studies. Third, we were unable to undertake a direct

comparison of PTH(1-34) and PTH(1-84), as there has not been an eligible head-to-head study. Nonetheless, the patterns of changes in bone at peripheral sites show a remarkable degree of consistency across the various studies and the conclusions drawn remain valid. Finally, while BMD has been used as a surrogate to determine differences between treatments, bone strength is however also dependent on bone morphology and bone material properties so that the impact on fracture risk remains to be better defined.

In summary, the effects of PTH peptides at the peripheral skeleton are unlike responses at the lumbar spine and proximal femur, with reductions in aBMD found with increasing dose and duration of PTH peptides. Combination with anti-resorptives attenuate these reductions but the impact on fracture risk remains uncertain. In the absence of sufficiently powered studies, future inferences may have to be made from well-conducted imaging studies with appropriate finite element analysis.

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Author Contributions

LMM and EVM conceived and designed the review. LMM devised the search strategy, which was reviewed by EVM. LMM collected the data from studies, which was reviewed by EVM and TJA. LMM TJA and EVM drafted and revised the manuscript

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Table 1. Details of the 14 studies fulfilling the criteria for inclusion in this review.

First author [ref]	PTH Type	Comparator	Total follow up (months)	Patient numbers		Outcome: peripheral skeleton site
				PTH arm	Comparator arm	
Black [4]	1-84 1-84 + ALN	ALN	12	104 (PTH) 56 (PTH+ALN)	55	aBMD: 1/3 DR
Black [14]	1-84	PLA	12	25	24	aBMD: 1/3 DR, MR, UDR vBMD: DR
Body [17]	1-34	ALN	24†	51	57	aBMD: 1/3 DR, UDR
Cosman [18]	1-34 + RAL	RAL	24§	19	20	aBMD: Proximal radius*
Cosman [15]	1-34 (x3 Tran. & Inj.)	PLA	6	Tran. 32 (20µg), 28 (30µg), 32 (40µg); Inj. 32 (20µg)	31	aBMD: Distal forearm*
Finkelstein [5]	1-34 1-34 + ALN	ALN	30§§	20 (PTH) 20 (PTH+ALN)	29	aBMD: Radius shaft*
Fogelman [19]	1-84 + HRT	HRT	18	43	58	aBMD: 1/3 DR
Greenspan [10]	1-84	PLA	18	117	119	aBMD: 1/3 DR
Leder [12] Tsai [13]	1-34 1-34 + DEN	DEN	24	28 (PTH) 24 (PTH+DEN)	31	aBMD: 1/3 DR vBMD: DR** and distal tibia**
Lindsay [20]	1-34 + HRT	HRT	36	13	17	aBMD: Proximal*, MF and UDF
McClung [16]	1-34	ROMO (x5) & ALN & PLA	12	42	48 (PLA) 46 (ALN)	aBMD: 1/3 DR
Neer [8]	1-34 (x2)	PLA	18	152 (20µg) 145 (40µg)	154	aBMD: Radius shaft*, DR
Ste-Marie [21]	1-34 + HRT	HRT	24†	48[a]/49[b]	45[a]/48[b]	aBMD: 1/3 DR[a], UDR[b]

The patient numbers for each arm were determined by those that had outcome measurements following completion of the study treatment. This that did not complete the treatment has been removed.

Total follow up: § PTH prescribed from months 0-12. §§ PTH prescribed from months 6-30. † Median endpoint at 13.8 months.

Outcome: * cortical bone site. ** sites used with standard patient evaluation protocols for HR-pQCT.

Abbreviations: Inj. – Injection, Tran. – Transdermal, ALN – Alendronate, DEN – Denosumab, HRT – Hormone replacement therapy, PLA – Placebo, RAL – Raloxifene, ROMO – Romosozumab, DR – Distal radius, MR – Mid-distal radius, MF – Mid-distal forearm, UDR – ultradistal radius, UDF – Ultradistal forearm

Table 2. Mean difference [95% CI] between the PTH peptide treatment arm and placebo treatment arm for percentage change in areal BMD and volumetric measurements from baseline to study endpoint.

Study	PTH peptide	PTH dose (µg/day)	Duration (months)	Outcome			Mean % difference [95% CI]	Effect size
				Device	Measurement	Bone site		
McClung [16]	1-34	20	12	DXA	aBMD	1/3 DR	-0.8 [-2.18, 0.58]	0.24
Neer [8]	1-34	20	18	DXA	aBMD	DR	1.50 [-0.24, 3.24]	0.19
		40	18			DR	0.1 [-1.79, 1.99]	0.01
		20	18			RS	-0.8 [-1.65, 0.05]	0.21
		40	18			RS	-1.9 [-2.8, -1.0]*	0.48
Black [14]	1-84	100[§]	12	DXA	aBMD	1/3 DR	-0.6 [-1.81, 0.61]	0.28
						M-R	-0.75 [-1.73, 0.23]	0.43
						UDR	0.31 [-1.50, 2.12]	0.1
				MRI	BV/TV	UDR	6.03 [-0.43, 12.50]	0.69
					Tb.N	UDR	5.16 [1.41, 8.90]	1.02
					Tb.Sp	UDR	-8.98 [-16.11, -1.85]*	0.3
					Tb.Th	UDR	1.21 [-3.58, 6.00]	0.19
					Ct.Th	UDR	NR	-
Greenspan [10]	1-84	100	18	DXA	BMD	1/3 DR	-3.46 [-4.66, -2.26]*	0.74

Mean difference was calculated by PTH peptide arm minus placebo arm. * indicates statistically significant differences.
Abbreviations: DXA – Dual x-ray absorptiometry; MRI – Magnetic Resonance Imaging; aBMD – areal BMD; BV/TV – Bone volume fraction; Tb.N – Trabecular number; Tb.Sp – Trabecular spacing; Tb.Th – Trabecular thickness; Ct.Th – Cortical thickness; NR – Not reported; DR – Distal radius; M-R – Mid-radius; UDR – Ultradistal radius; RS – Radius shaft;
Units: Dose - µg/day, [§] µg/week; Duration – months

Table 3. Mean difference [95% CI] between the PTH peptide treatment arm and comparator treatment arm for percentage change in areal and volumetric BMD from baseline to study endpoint.

Study	PTH peptide vs. Comparator	PTH dose (µg/day)	Duration (months)	Outcome			Mean % difference [95% CI]	Effect size
				Device	Measurement	Bone Site		
McClung [16]	1-34 vs. ALN	20	12	DXA	aBMD	1/3 DR	-1.4 [-2.43, -0.37]*	0.24
Finkelstein [5]	1-34 vs. ALN	28.5[§]	24	DXA	aBMD	1/3 DR	-7.8 [-9.96, -5.64]*	2.1
Black [4]	1-84 vs. ALN	100	12	DXA	aBMD	1/3 DR	-2.67 [-3.69, -1.65]*	0.79
Leder [12]	1-34 vs. DEN	20	24	DXA	aBMD	1/3 DR	-3.8 [-5.82, -1.78]*	0.97
Tsai [13]				HR-pQCT	Tb.N	DR	-1.00 [-5.49, 3.49]	0.11
						DT	-2.00 [-7.21, 3.21]	0.20
					Tb.Sp	DR	1.30 [-3.44, 6.04]	0.14
						DT	2.00 [-4.00, 8.00]	0.17
					Tb.Th	DR	-0.80 [-3.76, 5.36]	0.09
						DT	1.30 [-4.14, 6.74]	0.12
					Ct vBMD	DR	-3.80 [-5.30, -2.30]*	1.32
						DT	NE	

Mean difference was calculated by PTH peptide arm minus comparator arm. * indicates statistically significant differences.

Dose: [§] mean PTH dose; originally 40 µg/day

Abbreviations: ALN – Alendronate; DEN - Denosumab; DXA – Dual x-ray absorptiometry; HR-pQCT – High-resolution peripheral quantitative computed tomography; aBMD – areal BMD; Tb.N – Trabecular number; Tb.Sp – Trabecular spacing; Tb.Th – Trabecular thickness; Ct.Th – Cortical thickness; DR – Distal radius; DT – Distal tibia; NA – Not estimable

Units: Dose - µg/day; Duration – months

Table 4. Mean difference [95% CI] between the PTH peptide combined treatment arms and comparator treatment arms for percentage change in areal and volumetric BMD from baseline to study endpoint.

Study	PTH peptide + vs. Comparator	PTH dose (µg/day)	Duration (months)	Device	Outcome Measurement	Bone site	Mean difference [95% CI]	Effect size
Ste-Marie [21]	1-34+HRT vs. HRT	40	14	DXA	aBMD	1/3 DR	-0.72 [-2.16, 0.72]	0.20
						UDR	2.36 [0.70, 4.02]*	0.57
Fogelman [19]	1-84+HRT vs. HRT	25	18	DXA	aBMD	1/3 DR	-1.35 [-3.09, 0.39]	0.32
Finkelstein [5]	1-34+ALN vs. ALN	30.5[§],	24	DXA	aBMD	1/3 DR	-3.2 [-5.33, -1.07]*	0.87
Black [4]	1-84+ALN vs. ALN	100	12	DXA	aBMD	1/3 DR	-0.49 [-1.49, 0.51]	0.18
Leder [12] & Tsai [13]	1-34+DEN vs. DEN	20	24	DXA	aBMD	1/3 DR	0.1 [-1.55, 1.75]	0.03
				HR-pQCT	Total vBMD	DR	0.30 [-1.16, 1.76]	0.04
						DT	1.60 [0.57, 2.63]*	0.96
					Tb vBMD	DR	-2.10 [-4.13, -0.07]*	0.56
						DT	0.50 [-1.06, 2.06]	0.17
					Tb.N	DR	1.70 [−2.46, 5.86]	0.22
						DT	1.80 [−3.28, 6.88]	0.19
					Tb.Sp	DR	-2.20 [-6.32, 1.92]	0.29
						DT	-2.50 [-8.00, 3.00]	0.24
					Tb.Th	DR	0.70 [-3.40, 4.80]	0.09
						DT	-2.20 [-7.20, 2.80]	0.23
					Ct vBMD	DR	0.20 [-0.63, 1.03]	0.13
						DT	NE	-
					Ct.Th	DR	-0.40 [-2.78, 1.98]	0.09
						DT	2.10 [-0.24, 4.44]	0.48
					Stiffness	DR	0.8 [-1.56, 3.16]	0.18
						DT	NE	-
					Failure Load	DR	1.10 [-1.10, 3.30]	0.26
						DT	NE	-

Mean difference was calculated by PTH peptide combined treatment arm minus comparator arm. * indicates statistically significant differences.

Dose: § mean PTH dose; originally 40 µg/day

Abbreviations: ALN – Alendronate; DEN - Denosumab; HRT – Hormone replacement therapy; DXA – Dual x-ray absorptiometry; HR-pQCT – High-resolution peripheral quantitative computed tomography; aBMD – areal BMD; vBMD – Volumetric BMD; Tb vBMD – Trabecular vBMD; Tb.N – Trabecular number; Tb.Sp – Trabecular spacing; Tb.Th – Trabecular thickness; Ct.Th – Cortical thickness; DR – Distal radius; UDR – Ultradistal radius; DT – Distal tibia; NE – Not estimable

Units: Dose - µg/day; Duration – months

*Manuscript
Click here to view linked References

Supplemental information 1. Flow for assessing study eligibility for the systematic review			
FACTORS	**ASSESSMENT**		
TYPE OF STUDY 1. Randomised controlled trial	YES	UNCLEAR	NO **Exclude**
PARTICIPANTS 1. Women 2. Post menopausal	YES	UNCLEAR	NO **Exclude**
INTERVENTIONS 1. Parathyroid hormone (1-34 or 1-84) alone vs. baseline or control	YES	UNCLEAR	NO **Exclude**
CONTROL (Comparator)	YES	UNCLEAR	NO **Exclude**
OUTCOMES (Primary endpoint) 1. Peripheral skeleton – Upper and lower extremities 2. Areal or volumetric bone mineral density	YES	UNCLEAR	NO **Exclude**
FINAL DECISION 1 X No = Exclude 1 X Unclear = Unclear			

1. Exp postmenopause/
2. Postmenopaus$.tw.
3. Post-menopaus$.tw.
4. Post menopaus$.tw.
5. Or/ 1 - 4
6. exp osteoporosis/
7. osteoporos#s.tw.
8. osteoporotic.tw.
9. bone loss$.tw.
10. bone poros$.tw.
11. Or /6 - 10
12. 5 or 11
13. parathyroid hormone/ or teriparatide/
14. parathyroid hormone$ NOT hypoparathyroidism.tw.
15. parathyrin.tw.
16. parathormone.tw.
17. pth$.tw.
18. rhpth.tw.
19. teriparatide.tw.
20. Or/ 13 - 18
21. 12 and 19
22. exp clinical trial/
23. Clinical trial$.pt.
24. Controlled clinical trial$.pt.
25. Randomi#ed control.pt.
26. Placebos/ or Double-Blind Method/
27. Random$.tw.
28. Or/ 22 – 27
29. 21 and 28
30. Limit 27 to (English language and humans)
31. Limit 28 to (female and “all adult (19 plus years)”)

Supplemental information 2. An example of the search strategy for MEDLINE (PubMed).
Abbreviations: Exp – Explode; pt – publication type; pth – parathyroid hormone; rhpth – recombinant human parathyroid hormone; tw – Title/abstract; $ - different suffixes; # - alternative character

Supplemental information 3. Data extraction form	
Reference	
Authors and year	
Title	
Journal, volume, page numbers	
Objective	
Stated study objective	
Study design	
Type of trial	
Population	
Groups	
Gender	
Total number; numbers per group	
Age (mean yrs)	
Inclusion & Exclusion	
Intervention	
Drug, administered amount	
Duration	
Length of follow up	
Other notes	
Compliance	
Drop outs (Reasons)	
Adverse events	
Control	
Control group or alternative intervention	
Outcome	
Bone sites measured	
How measurements were made	
Other measures	
Statistics	
Effect sizes and power calculations	
Results	*Primary endpoint* Statistically significant: Yes/No

	Secondary endpoint Statistically significant: Yes/No

Comments	
For systematic review	
Study quality	
Limitations	

Supplemental information 4. Patient characteristics of the 14 included randomised controlled trial reports assessing the effects of parathyroid hormone peptides on the peripheral skeleton in postmenopausal women.

First author [ref]	Age (years)	BMI (kg/m^2)	T-score (SD)	Baseline reported fracture (% or N)	New fractures during trial (% or N)	Treatment adherence	Vitamin D status
Black [4]	69.4 ± 7.3 vs. 70.2 ± 6.8 vs. 70.7 ± 6.8	25.6 ± 4.6 vs. 27.1 ± 5.6 vs. 25.1 ± 4.5	FN -2.2 ± 0.7	47.9% vs. 50.8% vs. 41.7%	Approx. 3% in each group	Full adherence: Injection = 75% Tablet = 81%	NR
Black [14]	57.6 ± 5.8 vs. 58.9 ± 6.9	26.9 ± 3.5 vs. 26.8 ± 3.8	LS -0.9 ± 1.2 vs. -1.1 ± 1.0; TH -0.8 ± 0.6 vs. -0.8 ± 0.7; FN -1.5 ± 0.4 vs. -1.6 ± 0.4	None	NR	Injections = >90%	<15 ng/ml
Body [17]	66 ± 8yrs vs. 65 ± 9	23.9 ± 4.5 vs. 24.4 ± 3.5	LS or FN < 2.5	NR	Non-vertebral 4.1% vs. 13.7%	Median 71% vs. 67%	NR
Cosman [18]	67.2 ± 2.1 vs. 66.7 ± 1.73	25.1 ± 0.85 vs. 24.4 ± 0.83	S −2.9 ± 0.2 vs. −2.4 ± 0.2; TH −1.9 ± 0.2 vs. −2.0 ± 0.1	Yes, with < −2.0 SD or vertebral fracture alone	NR	All >80%	Inclusion: >25 ng/dl
Cosman [15]	63.2 ± 6.8 vs. 64.1 ± 7.5 vs. 63.6 ± 5.8 vs. 64.6 ± 7.3 vs. 64.8 ± 7.1	27.3 vs. 25.6 vs. 24.7 vs. 25.5 vs. 26.6 (Calculated from height and weight)	LS -3.0 ± 0.6 vs. -3.0 ± 0.5 vs. -3.2 ± 0.5 vs. -3.2 ± 0.7 vs. -3.2 ± 0.7; TH -1.7 ± 0.6 vs. -1.5 ± 0.7 ± -1.7 ± 0.5 vs. -1.8 ± 0.7 vs. -1.6 ± 0.7	(N=) Vertebral, 8 vs. 6 vs. 4 vs. 7 vs. 8	NR	Injection = >95% Patch = >85%	<16 ng/dl or >80 ng/dl
Finkelstein [5]	65 ± 7 vs. 62 ± 7 vs. 64 ± 6	24.9 ± 3.6 vs. 25.4 ± 5.1 vs. 25.6 ± 4.5	PAS -2.1 ± 1.0 vs. -2.2 ± 1.4 vs. -2.2 ± 1.1; FN -2.2 ± 0.7 vs. -1.7 ± 0.8 vs. -1.9 ± 0.8; TH -1.6 ± 0.8 vs. 1.2 ± 0.8 vs. -1.5 ± 0.9; 1/3 DR -1.9 ±1.5 vs. -1.3 ± 1.5 vs. -1.7 ± 1.6	NR	NR	At least 90%: TPTD (N) = 19 and 17 ALN (N) = 19 and 27	Inclusion: >15 ng/ml
Fogelman [19]	58.1 ± 6.2 vs.	24.3 ± 3.6 vs. 23.7 ±	-2.30 ± 0.75 vs. -2.27 ±	Vertebral:	(N =) 3 vs. 3	>75% adherence:	NR

	59.4 ± 6.8	3.7	0.91; TH = -1.50 ± 0.70 vs. -1.55 ± 0.70; FN = -1.89 ± 0.61 vs. -1.88 ± 0.61	None = 88.9% vs. 87.8%; 1 = 8.9% vs. 12.2%; >1 = 2.2% vs. 0%		96% vs. 97%	
Greenspan [10]	64.0 ± 7.4 vs. 64.3 ± 7.8	25.6 ± 4.34 vs. 25.7 ± 4.27	LS -3.04 ± 0.78 vs. -2.97 ± 0.74; TH -1.89 ± 0.81 vs. -1.84 ± 0.77; FN -2.23 ± 0.71 vs. -2.17 ± 0.71	Any vertebral: 17.5% vs. 16.4%	New or worsened vertebral = 1.4% vs. 3.4%; New vertebral w/out baseline fracture = 0.7% vs. 2.1%; New vertebral w/ baseline fracture = 4.2% vs. 8.9%; Non-vertebral = 5.6% vs. 5.8%	NR	NM
Leder [12] Tsai [13]	65.5±7.9 vs. 65.9±9.0 vs. 66.3±8.3	25.5±3.8 vs. 25.4±4.9 vs. 24.1±3.9	LS, TH/FN ≤-2.5, ≤-2.0 w/ risk factor, ≤-1.0 w/ fracture history.	52% vs. 33% vs. 36%	NR	>85% TPTD: Mono = 92% Comb = 100% DMAB = 100%	<20 ng/ml
Lindsay [20]	59.5 ± 2.3 vs. 64.2 ± 1.8	24.0 ± 0.8 vs. 23.2 ± 0.8	< 2.5 SD	(N=) 37 vs. 35, in 17 vs. 17 subjects	(N=) Vertebral 3 vs. 10	Minimum compliance 85%	NR
McClung [16]	66.8 ± 5.7 vs. 67.0 ± 6.5 vs. 67.1 ± 5.8 vs. 66.7 ± 6.6	NR	LS -2.29; TH -1.53; FN -1.93	None after 50 yrs	(N=) Romosozumab = 1	NR	<20 ng/ml
Neer [8]	69 ± 7 & 71 ± 8 vs. 70 ± 7 & 71 ± 7 vs. 69 ± 7 & 69 ± 8	26.8 ± 4.2 & 26.4 ± 4.4 vs. 26.6 ± 4.3 & 26.5 ± 4.1 vs. 26.7 ± 4.7 & 26.5 ± 4.1	LS = -2.6 SD	Vertebral: 2.3 ± 1.8 & 2.7 ± 1.7 vs. 2.3 ± 1.8 & 2.3 ± 1.7 vs. 2.3 ± 1.8 & 2.6 ± 1.8	Vertebral (N=) 22 vs. 19 vs. 64; Non-vertebral (N=) 34 vs. 32 vs. 53	Average 79-83%	NR
Ste-Marie [21]	62.0±7.6 vs. 61.1±7.4	25.9±4.8 vs. 25.8±4.7	LS or TH <-1.0	NR	NR	89% vs. 91%	NR

Age and BMI are presented as mean±SD. T-scores are indicated as mean, mean±SD, or as boundaries shown from inclusion criteria of studies. Prior or new fractures from studies were presented as percentages (%) or as frequencies. Definition of treatment adherence was varied between studies and was 80% at minimum. Loss to follow up

was given as a percentage or as a frequency per group studied. The vitamin D status was set as an exclusion criteria, unless stated otherwise.

NR – Not reported; NM – Not measured; ng/dl – nanograms per deciliter; ng/dl – nanograms per milliliter; SD – Standard deviation; LS – Lumbar spine; PAS – Posterior-anterior spine; S – Spine; TH – Total hip; FN – Femoral neck; T – Trochanter; DR – Distal radius

Supplemental information 5. Information available on the previous use of osteoporosis therapies in the study recruitment

First author [ref]	Excluded participants based on previous osteoporosis therapy		Reported statistics (number (%) unless stated otherwise)
Black [4]	Yes	• Previous exposure to bisphosphonate was limited to no more than 12 months ever, and no more than 4 weeks in the previous 12 months.	Any previous alendronate use: • PTH(1-84) = 13 (10.9%) • PTH(1-84)+ALN = 4 (6.8%) • ALN = 10 (16.7%)
Black [14]	Yes	• Current use of bisphosphonates, estrogen, raloxifene, or calcitonin or previous exposure to PTH. • Previous exposure to bisphosphonate was limited to no more than 12 months ever and no more than 4 weeks in the previous 2 years. • No intravenous bisphosphonates.	None reported.
Body [17]	Yes	• Taken medications or drugs known to affect bone or mineral metabolism in the prior 2-24 months depending on the drug. • This included androgens, anabolic steroids, bisphosphonates, calcitonin, glucocorticoids, estrogens, fluoride, teriparatide, exogenous PTH or PTH analogs.	None reported.
Cosman [18]	Yes*	• The study only included patients that has previously taken raloxifene.	Not applicable: all had received raloxifene.
Cosman [15]	Yes	• Prior PTH or PTH analog for a total duration of 3 months or at all within 6 months of randomization. • Any use of fluoride or strontium. • Calcitonin with 4 weeks, systemic estrogen or raloxifene within 3 months. • Intravenous bisphosphonate within 2 years or more than two total doses. • At least 6 months time off oral bisphosphonates if they had been taken for more than 6 months; if oral bisphosphonates were used for 6 to 12 months time off had to be at least 2 years; if previous oral bisphosphonate use exceeded 12 months, then time off had to be at least 5 yr.	None reported.
Finkelstein [5]	Yes	• Medications known to affect bone metabolism (referring to previous study in men, Finkelstein et al., 2003 NEJM 349: 1216-1226).	None reported.
Fogelman [19]	Yes*	• The study only recruited women receiving hormone replacement therapy.	PTH(1-84)+HRT: • Combination estrogen and progestin = 47 (52.2%)

			• Estrogens alone = 37 (41.1%) HRT: • Combination estrogen and progestin = 62 (68.9%) • Estrogens alone = 30 (33.3%)
Greenspan [10]	Yes	• Excluded women if they had taken bisphosphonates for a total of more than 12 months or for more than 90 days in the 12 months before enrollment. • Excluded women who had taken previous estrogen therapy within 4 weeks of the screening visit. • Excluded women who had received PTH (or a peptide fragment or analogue), PTH-related protein, fluoride, or strontium.	No previous osteoporosis therapy in patients who completed the study: • PTH(1-84) = 565 (68.6%) • Placebo = 635 (72.4%)
Leder [12] Tsai [13]	Yes	• Parenteral (intravenous) bisphosphonate; oral bisphosphonates within 6 months of enrolment. • Teriparatide. • Strontium ranelate. • Estrogens, selective estrogen receptors modulators, or calcitonin within 3 months of enrolment.	Leder 2014 (bisphosphonate use)** • PTH(1-34) = 13 (42%) with mean(SD) 27(20) months since discontinuation • PTH(1-34)+DMAB = 10 (33%) with mean(SD) 42(17) months since discontinuation. • DMAB = 12 (36%) with mean(SD) 36 (23) months since discontinuation
Lindsay [20]	Yes*	• Study inclusion required patients to take hormone replacement therapy for a year leading up to enrolment.	None reported.
McClung [16]	Yes	• Intravenous bisphosphonate or denosumab at any time. • Fluoride within previous 24 months. • Oral bisphosphonate, parathyroid hormone, or strontium within the previous 12 months. • Calcitonin, selective estrogen receptor modulator, systemic oral or transdermal estrogen or tibolone with the previous 3 months.	None reported.
Neer [8]	Yes	• Drugs that alter bone metabolism within the previous 2 to 24 months, depending on the drug.	• PTH(1-34) 20 µg/day, % = 14-16% • PTH(1-34) 40 µg/day, % = 13-14% • Placebo, % = 14-15%
Ste-Marie [21]	Yes/No	• The study recruited patient previously treated with hormone replacement therapy for 12 months preceding the study. • There were no specific exclusion criteria for patients not taking hormone replacement therapy for 12 months preceding the study.	• Previous treated with HRT = 122: 48.8% were randomized to the PTH(1-34)+HRT group. • Not previously treated with HRT = 125: 50% were randomized to the PTH(1-34)+HRT

	group.

* Highlights that a specific inclusion criteria was included to counter any previous use of osteoporosis therapies.

** Leder [12] was used for the reported statistics as the DATA-HRpQCT study (Tsai [13]) lost patients to follow up.

Supplemental information 6. Assessment of methodological risk of bias from the 14 included study reports.

First author [ref]	Concealment of randomization	RCT stopped early	Patients blinded	Healthcare providers blinded	Outcome assessors blinded	ITT analysis	Loss to follow up >15%
Black [4]	NR	No	Yes	Yes	Unclear[§]	Yes	No
Black [14]	NR	No	Yes	Yes	Unclear[§]	Yes	No
Body [17]	NR	Yes	Yes	Yes	Unclear[§]	Yes	Yes
Cosman [18]	NR	No	No	No	Yes	NR	No
Cosman [15]	Yes	No	Yes/No*	Yes/No*	Yes	Yes	No
Finkelstein [5]	Yes	No	No	No	Yes	No	Yes
Fogelman [19]	NR	Yes	Yes	Yes	Unclear[§]	Yes	Yes
Greenspan [10]	Yes	No	Yes	Yes	Unclear[§]	Yes	Yes
Leder [12] Tsai [13]	Yes	No	No	No	DXA = Yes HR-pQCT = NR	Yes	Yes
Lindsay [20]	Yes	No	No	No	NR	Yes	No = 15%
McClung [16]	Yes	No	No[¶]	No[¶]	NR	NR	Yes
Neer [8]	NR	Yes	Yes	Unclear	Unclear	NR	Yes
Ste-Marie [21]	No	Yes	Yes	Yes	Unclear[§]	NR	Yes

Abbreviations: NR – Not reported; RCT – Randomised controlled trial

Studies that did not state clear outcomes related to the headings were classed as 'not reported'. Studies that discussed the outcomes, but were unclear in reporting were classed 'Unclear'. Patient and investigator blinding outcomes are associated with PTH peptide treatment groups only.

Yes/No*: 'Yes' to transdermal delivery of 1-34 PTH, but 'No' to 1-34 PTH injections.

[§] The study was double-blinded, but was unclear if the outcome assessor was blinded or not blinded.

[¶] Only blinded for Romosozumab and placebo groups

Loss to follow up >15%: 'Yes' if incurred in at least one treatment group in the study.

Supplemental information 7. Areal BMD data from baseline to the study endpoint in the 14 study reports fulfilling the criteria for inclusion in this review

First author [ref]	Peripheral skeleton site	PTH type	% change from baseline at study endpoint		Comparator	% change from baseline at study endpoint	
			Mean	SD		Mean	SD
Black [4]	1/3 DR	1-84	-3.36	4.15	ALN	-0.69	2.42
	1/3 DR	1-84+ALN	-1.18	2.95	ALN	-0.69	2.42
Black [14]	1/3 DR	1-84	-1.12	2.36	PLA	-0.52	1.95
	MR	1-84	-2.00	2.07	PLA	-1.25	1.36
	UDR	1-84	-1.95	2.94	PLA	-2.26	3.48
Body [17]	1/3 DR	1-34	NR	NR	ALN	NR	NR
	UDR	1-34	NR	NR	ALN	NR	NR
Cosman [18]	Proximal radius	1-34+RAL	-4.3	In graph	PLA	In graph	In graph
Cosman [15]	Distal forearm	1-34 (x3 trans. & inj)	All in graph	All in graph	PLA	In graph	In graph
Finkelstein [5]	1/3 DR	1-34	-7.1	4.1	ALN	0.7	3.3
	1/3 DR	1-34+ALN	-2.5	4.0	ALN	0.7	3.3
Fogelman [19]	1/3 DR	1-34+HRT	-0.448	0.778*	HRT	0.903	0.430*
Greenspan [10]	1/3 DR	1-84	-4.99	-5.89 to -4.08[§]	PLA	-1.53	-2.32 to -0.74[§]
Leder [12]	1/3 DR	1-34	-1.7	4.6	DEN	2.1	3.1
	1/3 DR	1-34+DEN	2.2	3.1	DEN	2.1	3.1
Lindsay [20]	Proximal forearm	1-34+HRT	1	NR	HRT	NR	NR
	MF	1-34+HRT	NR	NR	HRT	NR	NR
	UDF	1-34+HRT	NR	NR	HRT	NR	NR
McClung [16]	1/3 DR	1-34	-1.7	-2.7 to -0.7[§]	PLA	-0.9	-1.8 to 0.1[§]
	1/3 DR	1-34	-1.7	-2.7 to -0.7[§]	ALN	-0.3	-1.2 to 0.7[§]
Neer [8]	Radius shaft	1-34 (20 µg/day)	-2.1	4.2	PLA	-1.3	3.3
	Radius shaft	1-34 (40 µg/day)	-3.2	4.5	PLA	-1.3	3.3
	Distal radius	1-34 (20 µg/day)	-0.1	7.2	PLA	-1.6	8.3
	Distal radius	1-34 (40 µg/day)	-1.5	8.4	PLA	-1.6	8.3
Ste-Marie [21]	1/3 DR	1-34+HRT	0.64	0.46*	HRT	1.36	0.57*
	UDR	1-34+HRT	4.2	0.66*	HRT	1.84	0.53*

* Standard error given; study analysis calculated the standard deviation. [§] 95% confidence interval given; study analysis calculated the standard deviation

Abbreviations: NR – Not reported, Inj. – Injection, Tran. – Transdermal, ALN – Alendronate, DEN – Denosumab, HRT – Hormone replacement therapy, PLA – Placebo, RAL – Raloxifene, ROMO – Romosozumab, DR – Distal radius, MR – Mid-distal radius, MF – Mid-distal forearm, UDR – ultradistal radius, UDF – Ultradistal forearm

Supplemental information 8. Volumetric BMD data from baseline to the study endpoint in the 14 study reports fulfilling the criteria for inclusion in this review

First author [ref]	Measurement	Peripheral skeleton site	PTH type	% change from baseline at study endpoint		Comparator	% change from baseline at study endpoint	
				Mean	SD		Mean	SD
Black [14]	Bone volume fraction	DR	1-84	2.34	9.29	PLA	-3.69	8.07
	Trabecular number	DR	1-84	2.19	5.44	PLA	-2.97	4.60
	Trabecular spacing	DR	1-84	-2.54	9.59	PLA	6.44	9.75
	Trabecular thickness	DR	1-84	0.26	6.72	PLA	-0.95	6.19
Tsai [13]	Total vBMD	DR	1-34	In graph	In graph	DEN	3.0	2.0
			1-34+DEN	3.3	3.2	DEN	3.0	2.0
		DT	1-34	In graph	In graph	DEN	2.6	1.7
			1-34+DEN	4.2	2.1	DEN	2.6	1.7
	Trabecular vBMD	DR	1-34	In graph	In graph	DEN	1.9	4.1
			1-34+DEN	4.0	3.4	DEN	1.9	4.1
		DT	1-34	In graph	In graph	DEN	1.5	3.1
			1-34+DEN	2.0	2.8	DEN	1.5	3.1
	Cortical vBMD	DR	1-34	-3.1	3.8	DEN	0.7	1.5
			1-34+DEN	0.9	1.6	DEN	0.7	1.5
		DT	1-34	-3.2	2.7	DEN	In graph	In graph
			1-34+DEN	1.2	1.6	DEN	In graph	In graph
	Cortical tissue mineral density	DR	1-34	-3.1	3.7	DEN	In graph	In graph
			1-34+DEN	In graph	In graph	DEN	In graph	In graph
		DT	1-34	-3.3	2.7	DEN	In graph	In graph
			1-34+DEN	0.7	1.2	DEN	In graph	In graph
	Trabecular number	DR	1-34	-1.3	9.6	DEN	-0.3	7.8
			1-34+DEN	1.4	7.8	DEN	-0.3	7.8
		DT	1-34	-3.9	10	DEN	-1.9	10.4
			1-34+DEN	-0.1	8.8	DEN	-1.9	10.4

Trabecular spacing	DR	1-34	2.1	10.3	DEN	0.8	8
		1-34+DEN	-1.4	7.5	DEN	0.8	8
	DT	1-34	5.1	11.5	DEN	3.1	12
		1-34+DEN	0.6	8.8	DEN	3.1	12
Trabecular thickness	DR	1-34	3.3	10.1	DEN	2.5	7.4
		1-34+DEN	3.2	7.9	DEN	2.5	7.4
	DT	1-34	6	10.2	DEN	4.7	11.1
		1-34+DEN	2.5	7.8	DEN	4.7	11.1
Cortical thickness	DR	1-34	In graph	In graph	DEN	5.1	3.1
		1-34+DEN	4.7	5.3	DEN	5.1	3.1
	DT	1-34	In graph	In graph	DEN	6.0	4.5
		1-34+DEN	8.1	4.3	DEN	6.0	4.5
Cortical porosity	DR	1-34	33.0	40.1	DEN	In graph	In graph
		1-34+DEN	In graph	In graph	DEN	In graph	In graph
	DT	1-34	10.2	12.1	DEN	In graph	In graph
		1-34+DEN	In graph	In graph	DEN	In graph	In graph
Stiffness	DR	1-34	In graph	In graph	DEN	4.0	4.7
		1-34+DEN	4.8	4.2	DEN	4.0	4.7
	DT	1-34	In graph	In graph	DEN	In graph	In graph
		1-34+DEN	In graph	In graph	DEN	In graph	In graph
Failure load	DR	1-34	In graph	In graph	DEN	3.8	4.5
		1-34+DEN	4.9	3.8	DEN	3.8	4.5
	DT	1-34	In graph	In graph	DEN	In graph	In graph
		1-34+DEN	In graph	In graph	DEN	In graph	In graph

* Standard error given; study analysis calculated the standard deviation; [§] 95% confidence interval given; study analysis calculated the standard deviation

Abbreviations: DEN – Denosumab, PLA – Placebo, DR – Distal radius, DT – Distal tibia

Supplemental information 9. Relative risk ratios for peripheral fractures between PTH peptides and placebo within upper-limb, lower-limb and all peripheral fractures combined.

Table 9.1. Upper-limb fractures for PTH(1-34) compared to placebo

First author [ref]	PTH(1-34) dose	PTH(1-34)		Placebo		Risk ratio (95% CI)
		Fractures	Total	Fractures	Total	
Neer [8]	20 µg/day	4	541	9	544	0.45 [0.14, 1.44]
	40 µg/day	5	552	9	544	0.55 [0.18, 1.62]
Miller [9]	20 µg/day	19	818	20	821	0.95 [0.51, 1.77]
Total		28	1911	38	1909	0.74 [0.45, 1.20]

Table 9.2. Upper-limb fractures for PTH(1-84) compared to placebo

First author [ref]	PTH(1-84)		Placebo		Risk ratio (95% CI)
	Fractures	Total	Fractures	Total	
Greenspan [10]	37	1286	27	1246	1.33 [0.81, 2.17]
Total	37	1286	27	1246	1.33 [0.81, 2.17]

Table 9.3. Lower-limb fractures for PTH(1-34) compared to placebo

First author [ref]	PTH(1-34) dose	PTH(1-34)		Placebo		Risk ratio (95% CI)
		Fractures	Total	Fractures	Total	
Neer [8]	20 µg/day	1	541	4	544	0.25 [0.03, 2.24]
	40 µg/day	4	552	4	544	0.99 [0.25, 3.92]
Miller [9]	20 µg/day	2	818	7	821	0.29 [0.06, 1.38]
Total		7	1911	15	1909	0.46 [0.19, 1.14]

Table 9.4. Lower-limb fractures for PTH(1-84) compared to placebo

First author [ref]	PTH(1-84)		Placebo		Risk ratio (95% CI)
	Fractures	Total	Fractures	Total	
Greenspan [10]	26	1286	28	1246	0.90 [0.53, 1.53]
Total	26	1286	28	1246	0.90 [0.53, 1.53]

Table 9.5. All peripheral fractures for PTH(1-34) compared to placebo

First author [ref]	PTH(1-34) dose	PTH(1-34)		Placebo		Risk ratio (95% CI)
		Fractures	Total	Fractures	Total	
Neer [8]	20 µg/day	5	541	13	544	0.39 [0.14, 1.08]
	40 µg/day	9	552	13	544	0.68 [0.29, 1.58]
Miller [9]	20 µg/day	21	818	27	821	0.78 [0.45, 1.37]
Total		35	1911	53	1909	0.66 [0.43, 1.01]

Table 9.6. All peripheral fractures for PTH(1-84) compared to placebo

First author [ref]	PTH(1-84)		Placebo		Risk ratio (95% CI)
	Fractures	Total	Fractures	Total	
Greenspan [10]	63	1286	55	1246	1.11 [0.78, 1.58]
Total	63	1286	55	1246	1.11 [0.78, 1.58]

Notes. All fracture data was obtained from published manuscripts: data for PTH(1-34) treatment compared to placebo excluded fractures from high trauma; data for PTH(1-84) treatment compared to placebo included both low trauma and high trauma fractures.

Neer [8]: reported wrist and humerus fractures separately, which we included in the upper-limb fracture calculations; reported ankle and foot fractures, which we included in the lower-limb fracture calculations. 'Other' non-vertebral fractures were reported in the manuscript, but with no further detail into the individual fracture sites so were included in the calculations.

Miller [9]: reported fingers, forearm, upper arm and wrist fractures separately, which we included in the upper-limb fracture calculations; reported ankle, foot, lower leg (not ankle) and upper leg (not hip) fractures separately, which we included in the lower-limb fracture calculations.

Greenspan [10]: reported upper-limb and wrist fractures separately, which we included in the upper-limb fracture calculations; reported lower-limb fractures, which we included in the lower-limb fracture calculations. Data may include multiple fractures from one person.

Analysis was completed in Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.