Review

Parathyroid hormone for the treatment of osteoporosis: a systematic review

Ann Cranney, Alexandra Papaioannou, Nicole Zytaruk, David Hanley, Jonathan Adachi, David Goltzman, Timothy Murray, Anthony Hodsman, for the Clinical Guidelines Committee of Osteoporosis Canada

∞ See related article page 48

Abstract

Background: Human parathyroid hormone (hPTH)(1–34) was approved in 2004 for the treatment of severe osteoporosis. Members of the Osteoporosis Canada clinical guidelines committee conducted a systematic review of randomized controlled trials (RCTs) to assess the efficacy and safety of hPTH for fracture prevention in postmenopausal women and men with osteoporosis.

Methods: We searched MEDLINE, EMBASE, HTA, Current Contents and the Cochrane Controlled Trials Registry for published data from 1966 to February 2005. A systematic literature search for RCTs was conducted using the Cochrane Collaborative approach. We identified 12 trials that randomly assigned patients either to hPTH or placebo or to hPTH or an active comparator and were at least 1 year in duration. Outcomes included change in bone mineral density (BMD), fractures, back pain and adverse events. Two independent reviewers abstracted data on study characteristics and outcomes.

Results: hPTH(1–34) significantly increases lumbar spine BMD, with smaller increases at the femoral neck and total hip. hPTH(1–84) significantly increases lumbar spine BMD. The data show a significant reduction in both vertebral and nonvertebral fractures with hPTH(1–34) in postmenopausal women with previous vertebral fractures. There were no data on fractures comparing the approved dose of hPTH(1–34) with active comparators.

Interpretation: There is Level I evidence that hPTH(1–34) significantly increases BMD at all skeletal sites except the radius and significantly reduces the risk of new vertebral and nonvertebral fractures in postmenopausal women with prior fractures.

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The 2002 Osteoporosis Canada clinical guidelines committee reviewed the evidence for several classes of drugs that reduce bone resorption and inhibit bone formation.[1] Anabolic therapies are capable of inducing new bone formation through an increase in bone modelling and remodelling.[2,3] Human parathyroid hormone (hPTH) is an 84-amino acid peptide hormone that plays a key role in the maintenance of calcium homeostasis. hPTH binds to a target cell surface G-protein-coupled hPTH/hPTHrP receptor, which results in activation of adenylate cyclase and phospholipases and increased intracellular levels of cyclic AMP and calcium.[4] Intermittent hPTH given by subcutaneous injection has been shown to exert potent anabolic effects on the skeleton.[5] hPTH increases the rate of bone remodelling and results in a positive remodelling balance, leading to thicker osteons (structural units of remodelled bone).[6,7] New bone formation occurs on quiescent surfaces and, as a result, trabecular architecture comes to more closely resemble normal bone.[8,9] hPTH(1–34) induces new periosteal bone apposition, which results in the enlargement of the outer circumference of tubular bones such as the radius.[10] This bone apposition results from decreased osteoblast apoptosis and enhanced differentiation of osteoblasts from preosteoblasts. Bisphosphonates preserve existing skeletal microarchitecture but do not restore it toward a more normal structure.[11,12] Increases in bone mass with bisphosphonates are most likely due to enhanced secondary mineralization of preformed osteons.[13]

Two forms of recombinant hPTH have been evaluated in clinical trials, hPTH(1–34) and the intact 84-amino acid form, hPTH(1–84). hPTH(1–34) is approved for the treatment of severe osteoporosis.[14] hPTH(1–84), although not currently approved, has been evaluated in clinical trials.[15] hPTH(1–84) includes a C terminus, which may have discrete biologic properties and may therefore have different biologic actions from hPTH(1–34).[3,4]

In this article we present the results of our systematic review of the literature on the efficacy and safety of hPTH therapy.

Methods

The hPTH working group included members of the Osteoporosis Canada Clinical Guidelines Committee and scientific consultants with Osteoporosis Canada who have expertise in hPTH or in clinical epidemiology or both. This

review was approved by all members of the Clinical Guidelines Committee.

We included RCTs of at least 1-year duration that compared hPTH with a placebo or with an active comparator and involved 1 of 3 distinct populations: postmenopausal women with osteoporosis, postmenopausal women with corticosteroid-induced osteoporosis or men with osteoporosis. The primary outcome was the effect of hPTH(1–34) or hPTH(1–84) on either bone mineral density (BMD) or fractures. Secondary outcomes were back pain and quality of life.

The Cochrane Collaborative approach for identifying RCTs guided our search strategy.[16] We searched MEDLINE, EMBASE, HTA, Current Contents and the Cochrane Controlled Trials Registry from 1966 to September 2005 (see online Appendix 1, available at www.cmaj.ca/cgi/content/full/175/1/52/DC1). Citations of relevant articles and reviews were examined to identify other potential trials. Two reviewers (A.C. and N.Z.) evaluated all titles and abstracts for eligibility. Full articles of relevant trials were obtained to make final judgments about inclusion.

The 2 reviewers independently abstracted data on study characteristics, results and methodologic quality. Data examined included study design, population, dose, treatment duration, percent change in BMD and the number of subjects with fractures. Volumetric BMD data and biochemical markers were not included as outcomes in this review, since they are not widely accepted as surrogate outcomes. Missing data were requested from study investigators or sponsors. We decided a priori not to pool the BMD and fracture data from the various trials since different hPTH preparations (i.e., hPTH[1–34] v. hPTH[1–84]) may have different modes of action, and doses may not be comparable. For example, 20 μg of hPTH(1–34) may be roughly equivalent to 50 μg of hPTH(1–84) on a molar basis, but differences in peptide length may cause differences in tissue absorption or receptor activation.[4]

RCTS were classified as level 1 (an RCT of adequate sample size, with blinding of subjects and assessors) or as level 2 (RCT that does not meet level 1 criteria, owing to a small sample or methodologic limitations).

Results and interpretation

A total of 655 potentially relevant citations were identified and screened (Fig. 1). Of these, 24 were potentially eligible. Twelve trials were subsequently excluded: one included premenopausal women,[17] 10 were a duplicate report, companion or follow-up of a primary RCT,[10,18–26] and in one BMD outcomes were for less than a year.[27] Twelve published RCTs were included in this review.[28–39] Nine trials involved postmenopausal women (Table 1),[28–34,38,39] of which one involved women with corticosteroid-induced osteoporosis (Table 2).[34] Three trials involved men with osteoporosis (Table 3).[35–37] Ten trials evaluated hPTH(1–34)[29–31,33–39] and 2 trials hPTH(1–84).[28,32]

Two trials had losses to follow-up of over 20%,[29,33] 8 trials had losses between 5% and 20%,[28,30,31,34,35,37–39] and 2 had less than 5%.[32,36] Allocation concealment was adequately reported in 2 trials[30,39] and unclear in the remaining trials. Seven trials were double-blind.[28,31–33,36–38]

hPTH in postmenopausal women

In a large trial comparing hPTH(1–34) with calcium and vitamin D among women with severe osteoporosis and prior fractures, Neer and associates found a significant reduction in new vertebral and nonvertebral fractures associated with hPTH (Table 1 and Table 4).[31] With 20 μg and 40 μg of hPTH(1–34) the relative risk (RR) of new vertebral fractures was 0.35 (95% confidence interval [CI] 0.22–0.55) and 0.31 (95% CI 0.19–0.50) respectively (absolute risk reduction [ARR] 9%–10%). Treatment with 20 μg hPTH(1–34) resulted in a RR of 0.47 (95% CI 0.25–0.88) for nonvertebral fractures and an ARR of 3%. In other hPTH(1–34) trials, the absolute number of fractures was too small to achieve significance[28,38,39] (Table 4). Body and associates found a reduction in nonvertebral fractures with 40 μg/d hPTH(1–34) compared with 10 mg/d alendronate (4.1% v. 13.7%, $p = 0.042$).[33]

Six trials compared the effect of hPTH(1–34) with placebo or an active comparator on BMD (Table 4). Doses of hPTH(1–34) ranged from 20 μg/d to 50 μg/d and treatment durations from 1 to 3 years. There was a consistent increase in lumbar spine and femoral neck BMD but little effect on BMD at the distal radius. Increases in lumbar spine BMD with hPTH(1–34) were significant and ranged from 9.7% to 10.3% with 20 μg/d and from 13.7% to 14.3% with 40 μg/d (Table 4). Changes in femoral neck BMD were significant but

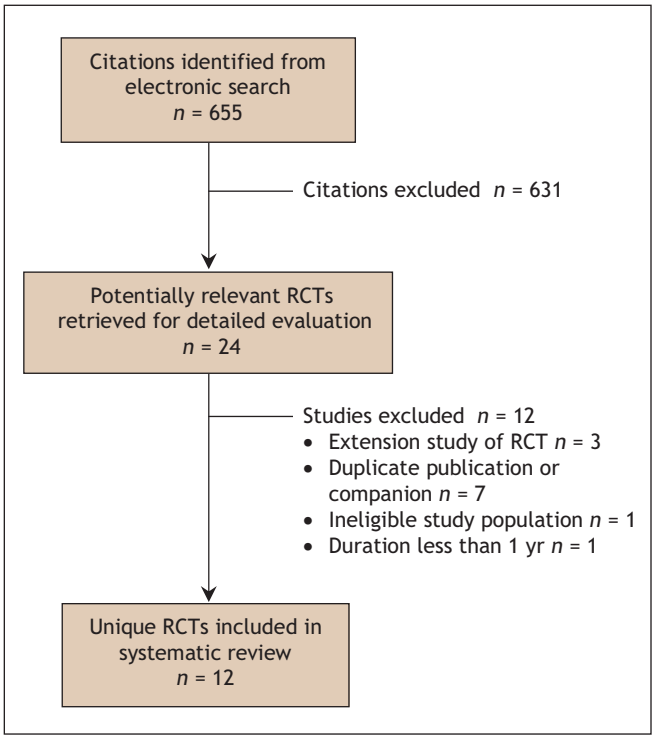

Fig. 1: Flow of articles through the systematic review. RCT = randomized controlled trial.

smaller, ranging from 2.8% to 3.9% in the 20 μg/d group and 4.5%–5.1% in the 40 μg group.

Two trials compared the effect of hPTH(1–84) with that of placebo or alendronate. Increases in lumbar spine BMD ranged from 6.3% to 7.8% after one year with 50–100 μg of hPTH(1–84), which were larger but not significantly different than increases seen with alendronate.[28,32] Increases in femoral neck BMD with hPTH(1–84) were small compared with placebo and less than that seen with alendronate (Table 4).

hPTH compared with bisphosphonates

Two trials compared hPTH(1–34) 20 μg or 40 μg with alendronate 10 mg/d in postmenopausal women.[33,38] Body and associates compared 40 μg of hPTH(1–34) with alendronate 10 mg daily. Increases of lumbar spine and femoral neck BMD were greater with hPTH than with alendronate ($p < 0.001$). At the ultradistal radius the increase with alendronate was 1.4% compared with 0.23% with 40 μg hPTH(1–34) ($p < 0.001$).[33]

In a study by McClung and associates, hPTH(1–34) 20 μg/d resulted in significantly greater increases (10.3%) in lumbar spine BMD than with alendronate 10 mg/d.[38]

Combination therapy

Three trials evaluated hPTH therapy combined with either a bisphosphonate or calcitonin.[29,30,32] In an RCT involving 238 postmenopausal women with osteoporosis, alendronate combined with hPTH(1–84) did not result in larger increases in lumbar spine BMD than with hPTH alone.[32] Cosman and associates compared the effect of hPTH(1–34) 25 μg and hormone replacement therapy (HRT) with that of HRT alone in 52 postmenopausal women who had been taking HRT for at least a year.[30] Three years of combination therapy resulted in increases in lumbar spine and total hip BMD of 13.4% and 4.4% respectively compared with a nonsignificant increase with HRT alone.[30] In a small 2-year RCT, Hodsman and associates compared cyclical hPTH(1–34) 50 μg followed by placebo calcitonin with hPTH followed by sequential salmon calcitonin (Table 1). Combined sequential therapy with calcitonin did not offer any benefits for BMD over cyclical hPTH alone.[29]

Table 1: Characteristics of trials of human parathyroid hormone (hPTH) involving postmenopausal women

Study	No. of patients (treatment/ control)	Study duration	Patient characteristics	Intervention	Outcome measures	Loss to follow-up and study limitations
Hodsman et al,[28] 2003	217 (162/55)	1 yr	• Mean age 64.5 (SD 6.0) yr • Postmenopausal 18.2 (SD 7.3) yr • Fracture prevalence 68.7% • T-score: LS -3.2 (SD 0.6), FN -2.3 (SD 0.7)	• hPTH(1-84), 50 μg, 75 μg and 100 μg subcutaneously v. placebo daily • Calcium 500-1000 mg/d, vitamin D 400 IU/d	• BMD and BMC: LS, FN, total hip and total body	11/217 (5.1%) lost to ITT analysis, 31/217 (14.3 %) lost overall No fracture data
Cosman et al,[30] 2001	52 (27/25)	3 yr	• Mean age 60.2 (SD 1.6) yr • Postmenopausal 16.1 (SD 1.9) yr • Fracture prevalence 100% • T-score: LS < -2.5	• hPTH(1-34) 25 μg + HRT v. HRT alone; HRT 0.625 mg Premarin or 50 μg Estraderm and 5-10 mg progestin daily for 10 d or 2.5 mg/d • Calcium supplementation to increase dietary intake to 1500 mg/d, vitamin D 400 IU/d	• BMD: LS, total hip and total body • BMC: total body • Fractures: vertebral and nonvertebral	6/52 (11.5%) Small sample
Neer et al,[31] 2001	1637 (1093/544)	1.5 yr	• Mean age 69.3 (SD 7.0) yr • Postmenopausal 21.0 (SD 8.3) yr • Fracture prevalence 100% • T-score: -2.6	• Human recombinant PTH(1-34) 20 μg, 40 μg v. placebo • Calcium 1000 mg/d, vitamin D 400-1200 IU/d	• BMD: LS, FN, trochanter, total hip, radius and total body • Fractures: vertebral and nonvertebral	311/1637 (19.0%)
Black et al,[32,41] 2003/2005	238 (178/60)	2 yr	• Mean age 69.9 (SD 7.1) yr • Postmenopausal 22.7 (SD 6.3) yr • Fracture prevalence 47% • T-score: FN -2.2 (SD 0.7)	• hPTH(1-84) 100 μg v. PTH 100 μg + alendronate 10 mg v. alendronate 10 mg • Calcium 500 mg/d, multivitamin with 400 IU vitamin D	• BMD: LS, FN, total hip and 1/3 distal radius • Fracture: nonvertebral	11/238 (4.6%) Not powered to evaluate fractures

hPTH therapy after prior bisphosphonate therapy

Although the anabolic effects of hPTH may be accentuated if bone resorption is suppressed, there is concern that the decreased remodelling rates induced by bisphosphonates might impair the ability of hPTH to stimulate new bone formation.[40] In contrast, Cosman and associates randomly assigned women who had previously taken alendronate to either cyclic or daily hPTH(1–34) in combination with alendronate or to alendronate alone. Significant increases in lumbar spine BMD of 6.1% and 5.4% were noted in the daily and cyclic treatment arms respectively.[39]

Sequential use of bisphosphonate therapy after cessation of hPTH

After hPTH(1–34) is discontinued, BMD declines; this loss can be prevented with sequential use of a bisphosphonate.[18,23] In an RCT of hPTH(1–84) and alendronate, Black and associates randomly assigned women to receive a second year of either alendronate or placebo and found that the alendronate group had significant increases in lumbar spine BMD (4.9%) compared with controls (–1.7%) ($p < 0.01$).[41]

Summary

There is level 1 evidence that hPTH(1–34) 20 μg/d and 40 μg/d increase BMD at the lumbar spine and proximal femur and decrease the risk of both vertebral and nonvertebral fractures in postmenopausal women with prior vertebral fractures. The effect of hPTH(1–34) on hip fractures has not been assessed. hPTH(1–34) results in larger increases in lumbar spine BMD than alendronate. There are no head-to-head fracture trials that compare the efficacy of 20 μg of hPTH(1–34) to bisphosphonates in decreasing the risk of fracture.

There is level 1 evidence that hPTH(1–84) increases lumbar spine BMD in postmenopausal women with osteoporosis.

The small increase in femoral neck BMD and decline in total body BMD may reflect a transient imbalance between cortical remodelling and bone formation. The decline in BMD at the distal radius seen in hPTH trials is not felt to be indicative of decreased bone strength and may occur as a result of the increased

Table 1: Characteristics of trials of human parathyroid hormone (hPTH) involving postmenopausal women (continued)

Study	No. of patients (treatment/ control)	Study duration	Patient characteristics	Intervention	Outcome measures	Loss to follow-up and study limitations
Body et al,[33] 2002	146 (73/73)	14 mo	• Mean age 65.5 (SD 8.5) yr • Postmenopausal 18.5 (SD 9.5) yr • T-score: FN –3.4 (SD 1.1)	• hPTH(1-34) 40 μg + placebo tablet v. alendronate 10 mg + placebo injection • Calcium 1000 mg/d, vitamin D 400-1200 IU/d	• BMD/BMC: LS, FN, 1/3 radius, ultradistal radius and total body • Fracture: nonvertebral • Back pain	38/146 (26.0%) Fractures were secondary outcome
Hodsman et al,[29] 1997	39	2 yr	• Mean age 67.0 (SD 8.0) yr • Fracture prevalence 100% • T-score: LS –3.3 (SD 1.3), FN –3.3 (SD 1.1)	• hPTH(1-34) sequential 50 μg (28 d) v. hPTH(1-34) sequential 50 μg (28 d) + calcitonin 75 μg (42 d) • Calcium 500 mg/d (20-d cycles)	• BMD: LS, FN • Fractures: vertebral and nonvertebral	9/39 (23.1%) Small sample
McClung et al,[38] 2005	203 (102/101)	18 mo	• Mean age 65.9 yr • Postmenopausal 19.7 yr • T-score: LS –2.8 (SD 0.7)	• hPTH(1-34) 20 μg v. alendronate 10 mg/d • Calcium 1000 mg/d, vitamin D 400-800 IU/d	• BMD: LS • Back pain	31/203 (15.2%) Unable to provide data on comparative fracture rates; radiographs of spine not done
Cosman et al,[39] 2005	126 (43/40/43)	15 mo	• Mean age 68.4 (SD 7.6) yr • Postmenopausal 20.8 yr • Fracture prevalence 48% • T-score: LS –2.9 (SD 0.9)	• hPTH(1-34) 25 μg/d + alendronate 70 mg/wk v. hPTH(1-34) cyclic (25 μg/d for 3 mo, then none for 3 mo) + alendronate 70 mg/wk v. alendronate 70 mg/wk • Calcium supplementation for total intake of 1200-1500 mg/d, vitamin D supplementation to increase 25(OH)D intake to > 50 nmol/L	• BMD: LS and total hip • Fractures: vertebral and clinical nonvertebral	18/126 (14.3%) Not powered to evaluate fractures

Note: SD = standard deviation, LS = lumbar spine, FN = femoral neck, BMD = bone mineral density, BMC = bone mineral content, ITT = intention to treat, HRT = hormone replacement therapy.

width of the radius.[3] The absence of head-to-head fracture data suggests that hPTH(1–34) be limited to patients at high risk of fractures by virtue of very low BMD and pre-existing fractures.

There is level 1 evidence that combination therapy with alendronate and hPTH(1–84) may blunt the anabolic effect of hPTH on BMD. There are no fracture data comparing the effect of the combination of hPTH and alendronate with that of hPTH alone.

hPTH(1–34) in postmenopausal women with corticosteroid-induced osteoporosis

Lane and associates evaluated the effect of hPTH(1–34) in 51 postmenopausal women taking corticosteroids and HRT. Women were given hPTH(1–34) for one year and then followed for an additional year. hPTH(1–34) 25 μg in combination with HRT increased BMD by 12.6% at the lumbar spine and by 5.2% at the femoral neck after 2 years.[34]

Summary

There is level 2 evidence that hPTH(1–34) increases lumbar spine BMD in postmenopausal women with corticosteroid-induced osteoporosis. Fracture data are lacking in this population.

hPTH(1–34) in men with osteoporosis

Kurland and associates compared 25 μg hPTH(1–34) with placebo in a small trial involving men with idiopathic os-

Table 2: Characteristics of trials of human parathyroid hormone (hPTH) involving men with osteoporosis

Study	No. of patients (treatment/ control)	Study duration	Patient characteristics	Intervention	Outcome measures	Loss to follow-up
Kurland et al,[36] 2000	23 (10/13)	1.5 yr	• Mean age 51.7 (SD 2.8) yr • Fracture prevalence 78% • T-score: LS < -2.5	• hPTH(1-34) 25 μg v. placebo • Calcium supplementation to increase daily intake to 1500 mg, vitamin D 400 IU/d	• BMD: LS, FN, total hip and 1/3 distal radius • Fracture: vertebral	0/23
Finkelstein et al,[35] 2003	83 (27/28/28)	2 yr	• Mean age 57.7 (SD 8.0) yr • T-score: LS or FN < -2.0	• hPTH(1-34) 40 μg v. hPTH(1-34) 40 μg + alendronate 10 mg v. alendronate 10 mg alone • Calcium supplementation to increase daily intake to 1000-1200 mg, vitamin D 400 IU/d	• BMD: posterior-anterior spine, lateral spine, FN, total hip, radial shaft and total body • QCT: spine	10/83 (12.0%)
Orwoll et al,[37] 2003	437 (290/147)	11 mo	• Mean age 58.6 (SD 13.0) yr • T-score: LS -2.2 (SD 1.2), FN -2.7 (SD 0.8)	• hPTH(1-34) 20 μg and 40 μg v. placebo • Calcium 1000 mg/d, vitamin D 400-1200 IU/d	• BMD: LS, FN, trochanter, total hip, distal radius, ultra-distal radius and total body • Fracture: nonvertebral	81/437 (18.5%)

Note: SD = standard deviation, LS = lumbar spine, BMD = bone mineral density, SE = standard error of the mean, FN = femoral neck, QCT = quantitative computed tomography.

Table 3: Characteristics of trial of human parathyroid hormone (hPTH) involving postmenopausal women taking corticosteroid therapy

Study	No. of patients (treatment/ control)	Study duration	Patient characteristics	Intervention	Outcome measures	Loss to follow-up
Lane et al,[20,34] 1998/2000	51 (28/23)	2 yr	• Mean age 62.7 (SD 9.9) yr • Postmenopausal 17.9 (SD 9.9) yr • Fracture prevalence 27.5% • T-score: -2.8 (SD 0.17)	• hPTH(1-34) 25 μg + HRT + prednisone v. HRT + prednisone • Calcium supplementation to increase daily intake to 1500 mg, and vitamin D 800 IU/d	• BMD: LS, FN, trochanter, total hip and 1/3 distal radius • Fractures: vertebral and nonvertebral	3/51 (5.9%)

Note: SD = standard deviation, LS = lumbar spine, HRT = hormone replacement therapy, BMD = bone mineral density, FN = femoral neck.

teoporosis. After 18 months, BMD had increased significantly by 13.5% and 2.9% at the lumbar spine and femoral neck respectively. Total hip BMD did not change significantly, and there was a significant decrease at the 1/3 distal radius (–1.2%).[36] Orwoll and associates, in an RCT involving 437 men with low BMD, compared 20 μg or 40 μg of hPTH(1–34) with calcium and vitamin D. Of these men, 49% had hypogonadism. After one year, lumbar spine BMD increased by 5.4% with 20 μg and by 8.5% with the 40 μg dose compared with no change with placebo. There was a nonsignificant decrease in nonvertebral fractures with hPTH(1–34) compared with placebo.[37] Finkelstein and associates compared hPTH(1–34) 40 μg alone, hPTH(1–34) with alendronate 10 mg/d, and alendronate alone. Increases in lumbar spine and femoral neck BMD were 18.1% and 9.7% respectively in group receiving hPTH(1–34) alone compared with those taking combination hPTH(1–34) and alendronate or alendronate alone ($p < 0.001$) (Table 4).[35]

Summary

There is level 1 evidence that hPTH(1–34) increases BMD at the lumbar spine and femoral neck in men with osteoporosis, but there is no data on fractures in this population.

Health-related quality of life and back pain

Neer and associates assessed health-related quality of life with both generic (Nottingham Health Profile) and disease-specific measures (Osteoporosis Assessment Questionnaire) (OPAQ).[31] Using the OPAQ, fractures in a subgroup of 365 women were associated with a decline in health-related quality of life. However, there were no significant differences between patients taking hPTH(1–34) and those taking placebo.[42] Back pain was reported in 3 hPTH(1–34) trials,[31,33,38] and one trial had baseline and follow-up spine radiography.[31] A significant reduction in back pain was seen among postmenopausal women in the fracture trial of hPTH(1–34).[31] In 2 trials compar-

Table 4: Summary of results from randomized controlled trials of human parathyroid hormone (hPTH) on facture prevalence and bone mineral density (BMD)

Study	hPTH dose (type)	Comparator	Level of evidence	Fractures, treatment v. control, %		BMD, treatment v. control, % change		
				Vertebral	Nonvertebral	Lumbar spine	Femoral neck	Distal radius
McClung et al,[38] 2005	20 μg (1-34)	Alendronate	1	NA	8.8 v. 7.9	10.3 v. 5.5†	3.9 v. 3.5	NA
Cosman et al,[39] 2005	25 μg (1-34)	Alendronate	2	3 v. 6 v. 11*	10.5 v. 5.9 v. 5.6*	6.1 v. 5.4 v. NR*†	In graph only	NA
Body et al,[33] 2002	40 μg (1-34)	Alendronate	1	NA	4.1 v. 13.7‡	14.3 v. 6.4†	4.5 v. 2.8†	0
Black et al,[32,41] 2003	100 μg (1-84)	Alendronate	1	NA	NA	6.3 v. 6.0 v. 4.54§	0.93 v. 1.85 v. 2.45‡§	-3.45 v. -1.1‡ v. -0.75§
Neer et al,[31] 2001	20-40 μg (1-34)	Placebo	1	5 v. 14.3†¶	2.9 v. 6‡¶	13.7** v. 9.7¶ v. 1.1†	5.1** v. 2.8¶ v. -0.7†	-0.1 v. -1.6
Hodsman et al,[28] 2003	50-100 μg (1-84)	Placebo	1	NA	NA	100-μg dose: 7.8 v. 0.9†	100-μg dose: 0.5 v. -0.7	NA
Hodsman et al,[29] 1997	50 μg (1-34)	Calcitonin	2	7.1 v. 25	None in either arm	11.2 v. 8.9	2.5 v. -1.3	NA
Cosman et al,[30] 2001	25 μg (1-34)	HRT	2	0 v. 25	NA	13.4 v. 1.5†	4.4 v. 1	NA
Lane et al,[20,34] 1998/2000	25 μg (1-34)	HRT	2	0 v. 5.5	2.5 v. 11	At 2 yr: 13.0 v. 1.15†	4.7 v. 0‡	-3.3 v. 0
Kurland et al,[36] 2000	25 μg (1-34)	Placebo	2	6.2 v. 16.6	NA	13.5 v. 0†	2.9 v. 0‡	-1.2 v. 0.5‡
Orwoll et al,[37] 2003	20-40 μg (1-34)	Placebo	1	NA	1.3 v. 2	9.03¶ v. 5.87** v. 0.52†	2.9¶ v. 1.5** v. 0.3‡	-0.5 v. -0.15
Finkelstein et al,[35] 2003	40 μg (1-34)	Alendronate	2	NA	NA	18.1 v. 14.8 v. 7.9†§	9.7 v. 6.2 v. 3.2†§	-0.8 v. 1.0 v. 1.0‡§

Note: NA = not assessed in the study, NR = not reported, HRT = hormone replacement therapy.
*hPTH (daily) + alendronate v. hPTH (cyclic) + alendronate v. alendronate alone.
†$p < 0.001$.
‡$p < 0.05$.
§hPTH v. hPTH + alendronate v. alendronate alone.
¶hPTH dose = 20 μg.
**hPTH dose = 40 μg.

ing hPTH(1–34) and alendronate 10 mg, hPTH(1–34) was associated with a significant decrease in moderate to severe back pain.[33,38] A meta-analysis of individual patient data from 5 trials comparing hPTH(1–34) with comparators found that patients taking hPTH(1–34) had a reduced risk of back pain (pooled RR 0.60, 95% CI 0.55–0.80).[43]

Summary

There is no evidence of improved health-related quality of life associated with hPTH(1–34) or calcium with vitamin D in postmenopausal women with osteoporosis. There is level 2 evidence that back pain may be reduced in patients given hPTH(1–34).

Adverse events

A potential safety issue with hPTH(1–34) is increased risk of osteosarcoma, which was reported in a life-long carcinogenicity study involving Fischer rats given high-dose hPTH(1–34) from infancy through senescence (8 weeks of age through 2 years).[44] Because of this unexpected finding, trials of hPTH(1–34) for postmenopausal women with severe osteoporosis and men with osteoporosis[31,33,37] were terminated prematurely by the sponsor. Osteosarcoma was found with all doses, and, in the lower-dose ranges, was first detected after about 20 months of therapy. There have been no reports of osteosarcoma in clinical trial subjects, and although there are isolated case reports of osteosarcoma in patients with long-standing hyperparathyroidism, there is no evidence to suggest that osteosarcoma is of increased frequency in hyperparathyroidism.[45,46]

Adverse events were included in all trials, but reporting was variable. Nine hPTH(1–34) trials[29,31,33–39] reported post-dose hypercalcemia (serum calcium level > 2.6 mmol/L) that ranged from 3% to 11% among patients taking 20 μg of hPTH(1–34) and from 16.8% to 38% among patients taking 40 μg compared with 0%–3% among those taking the comparator.[31,33] The overall pooled number of events of hypercalcemia was 282 in 1594 subjects from 7 trials. These episodes were mild: serum calcium levels usually returned to normal within 24 hours, and no clinical sequelae were reported in subjects with transient hypercalcemia. Hypercalcemia rates in the hPTH(1–84) trials ranged from 12% to 15.6%; there were 46 cases among patients taking hPTH out of a total of 340, compared with no cases among those taking the comparator.[28,32]

Transient hypercalciuria (24-hour urine collection showing calcium level of ≥ 8 mmol/d or urine calcium/creatinine ratio > 1.0) was reported in 6 hPTH(1–34) trials and ranged from 0% to 10% difference between hPTH and comparator.[29,31,33,35,37,39] There were no reported increases in renal stones.

A 10% increase in serum creatinine levels was reported in one trial but did not exceed the normal range.[29] In another trial, increases in creatinine clearance were reported with hPTH that were nonsignificant compared with increase seen with placebo.[28]

The frequency of headaches among treatment subjects in hPTH(1–34) trials ranged from 8.1% to 10.8% and was not significantly greater than among control subjects.[31,37]

hPTH(1–34) 20 μg significantly increased the proportion of patients experiencing dizziness (3%)[31] and leg cramps (range 2%–8%),[31,33] with a higher proportion in the 40 μg treatment arm. Hyperuricemia was reported in 2 hPTH(1–34) trials[31,37] and ranged from 0% to 3% of subjects. Hyperuricemia was associated with gout in 3 subjects taking hPTH(1–84).[32]

The proportion of subjects with serious adverse events was not significantly different between treatment arms.

PTH treatment causes transient increases in serum calcium, but these episodes usually resolve. If they persist, they can be managed by decreasing calcium and vitamin D supplements.

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From the Departments of Medicine of the University of Ottawa (Cranney), Ottawa; McMaster University (Papaioannou, Zytaruk, Adachi), Hamilton; University of Toronto (Murray), Toronto; and University of Western Ontario (Hodsman), London, Ont.; University of Calgary (Hanley), Calgary, Alta. (Hanley); and McGill University (Goltzman), Montréal, Que.

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Correspondence to: *Dr. Ann Cranney, Ottawa Hospital, Civic Campus, Clinical Epidemiology Program, 1053 Carling Ave., Ottawa ON K1Y 4E9; fax 613 761-5492*

Members of the Clinical Guidelines Committee of Osteoporosis Canada: *Alexandra Papaioannou (chair), Department of Medicine, McMaster University, Hamilton, Ont.; Jacques Brown, Department of Medicine, Laval University, Québec, Que.; Angela Cheung, Department of Medicine, University of Toronto, Toronto; Ann Cranney, Department of Medicine, University of Ottawa, Ottawa, Ont.; Gillian Hawker, Department of Medicine, University of Toronto, Toronto, Ont.; Anthony Hodsman, Department of Medicine, University of Western Ontario, London, Ont.; Sophie Jamal, Department of Medicine, University of Toronto, Toronto, Ont.; Brent Kvern, Department of Family Medicine, University of Manitoba, Winnipeg, Man.; William Leslie, Department of Medicine, University of Manitoba, Winnipeg, Man.; Kerry Siminoski, University of Alberta, Edmonton, Alta.*