CRD summary
This review concluded that human parathyroid hormone (1-34) used to treat osteoporosis in postmenopausal women with previous fractures is associated with significant increases in bone mineral density and a significant reduction in the risk of new fractures. The authors’ conclusions appear valid, but some caution is advised given the variability and small size of many of the studies.

Authors' objectives
To assess the efficacy and safety of human parathyroid hormone (hPTH) for the prevention of fracture in osteoporosis.

Searching
MEDLINE, EMBASE, HTA, Current Contents and the Cochrane Controlled Trials Register were searched from 1966 to September 2005. The search terms were not listed, but the authors referred to a website for further details, which was inaccessible. Relevant articles and reviews were screened for additional studies.

Study selection

Specific interventions included in the review
Studies that compared hPTH (1-34 or 1-84) with either placebo or an active comparator were eligible for inclusion. The studies included in the review evaluated doses of hPTH (1-34) usually ranging from 20 to 40 microg/day; studies of hPTH (1-84) used doses of 50 to 100 microg/day. Most of the trials evaluated hPTH (1-34) and evaluated treatment durations of 1 to 2 years, with a maximum duration of 3 years. Active comparators included alendronate, calcitonin and hormone replacement therapy (HRT). A number of studies combined hPTH with alendronate, HRT or calcitonin, while a small number compared the sequential use of hPTH therapies with alendronate.

Participants included in the review
Studies of men and postmenopausal women with osteoporosis or corticosteroid-induced osteoporosis were eligible for inclusion. Of those studies included in the review, three included men and one included postmenopausal women with corticosteroid-induced osteoporosis. The mean age of postmenopausal women ranged from 60.2 to 68.4 years and that of men ranged from 51.7 to 58.6 years.

Outcomes assessed in the review
Studies had to assess bone mineral density (BMD) or fractures to be eligible for inclusion. The secondary outcomes included back pain and quality of life. The review also reported adverse events. Surrogate outcomes of volumetric BMD data and biochemical markers were not considered. The included studies assessed vertebral and nonvertebral fractures. Measures of BMD were usually total body, lumbar spine, femoral neck, distal radius or total hip.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the eligibility of the studies. The authors did not state whether this was carried out independently, or how any disagreements were resolved.

Assessment of study quality
Two reviewers independently abstracted data on methodological quality through consideration of sample size, loss to follow-up, allocation concealment and blinding. The studies were classified as either level 1 (RCT of adequate sample size with blinding of the participants and assessors) or level 2 (RCT that does not meet the criteria of a level 1 study, owing to either inadequate size or methodological limitations).

Data extraction

Database of Abstracts of Reviews of Effects (DARE)
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Two reviewers independently abstracted the study data; missing data were sought from the study investigator. The percentage change in BMD (lumbar spine, femoral neck and distal radius) and the number of fractures (vertebral and nonvertebral) were extracted. Data on quality of life, back pain and numbers of adverse events were extracted where available.

Methods of synthesis
How were the studies combined?
The authors decided a priori not to combine data from different forms of hPTH and different doses, therefore the studies were combined in a narrative and summary data tables presented.

How were differences between studies investigated?
Differences between the studies were discussed in the text and were evident from the tables of study characteristics. The studies were grouped according to population, hPTH therapy and outcome.

Results of the review
Twelve RCTs (n=3,252) were included in the review.

Six trials were classified as level 1 and six as level 2. Two trials had losses to follow-up of over 20%. Only 2 trials reported adequate allocation concealment and 7 trials were double-blinded.

Postmenopausal women (8 RCTs).

One RCT (level 1) reported a significant reduction in new vertebral fractures associated with 20 microg/day (relative risk, RR 0.35, 95% confidence interval, CI: 0.22, 0.55) and 40 microg/day (RR 0.31, 95% CI: 0.19, 0.50) of hPTH (1-34), compared with placebo. Nonvertebral fractures were significantly reduced with 20 microg/day hPTH (RR 0.47, 95% CI: 0.25, 0.88). A second RCT (level 1) also reported a significant decrease in nonvertebral fractures with 40 microg/day hPTH (1-34) in comparison with 10 mg/day alendronate (4.1% versus 13.7%, p=0.042). Three other trials showed no significant differences in fractures.

Six RCTs (three level 1 and three level 2) reported that hPTH (1-34) was associated with significant increases in lumbar spine BMD, ranging from 9.7 to 10.3% with 20 microg/day and 13.7 to 14.3% with 40 microg/day, in comparison with both placebo and active comparators. Changes in femoral neck BMD were also reported, but were smaller: 2.8 to 3.9% for 20 microg/day and 4.5 to 5.1% for 40 microg/day.

Two level 1 RCTs comparing hPTH (1-34) with alendronate reported significant improvements in lumbar BMD (2 RCTs) and ultradistal radius BMD (1 RCT) in favour of hPTH.

Two level 1 RCTs showed no significant improvements in spinal or femoral neck BMD with hPTH (1-84) in comparison with placebo or alendronate.

Postmenopausal women with corticosteroid-induced osteoporosis (1 RCT).

Increases in both lumbar spine BMD (12.6%) and femoral neck BMD (5.2%) were reported for hPTH (1-34) in comparison with HRT in one level 2 trial.

Osteoporosis in men (3 RCTs).

Three RCTs (one level 1 and two level 2) showed that hPTH was associated with significant increases in lumbar spine BMD, of which two also showed an increase in femoral neck BMD. None of the trials reported data on the incidence of fractures.

Health related quality of life (1 RCT).

No significant differences in quality of life between hPTH (1-34) and placebo were found in one level 1 trial.
Back pain (3 RCTs).

One level 1 RCT reported a significant reduction in back pain for postmenopausal women taking hPTH (1-34) in comparison with placebo. A significant decrease in moderate to severe back pain was also observed for hPTH (1-34) in comparison with alendronate in the remaining 2 level 1 RCTs.

Adverse events (12 RCTs).

Nine trials of hPTH (1-34) reported post-dose hypercalcemia (282 events in 1,594 participants from 7 RCTs) and six reported transient hypercalciuria. There were no reported increases in renal stones. Differences in creatinine clearance, serum creatinine and headache frequency were either within normal ranges or were non significant in comparison with placebo. However, significant increases in the frequency of leg cramps (2 to 8%; 2 RCTs) and dizziness (3%; 1 RCT) with hPTH (1-34) were reported; these increased with higher dosages (20 to 40 microg/day). Hyperuricemia was reported in 0 to 3% of participants in 2 hPTH (1-34) trials. There were no significant differences between the intervention and control arms in terms of serious adverse events.

Authors’ conclusions
Evidence from level 1 studies suggests that hPTH (1-34) in postmenopausal women with previous fractures is associated with a significant increase in BMD at all skeletal sites, with the exception of the radius. There is also a significant reduction in the risk of new vertebral and nonvertebral fractures. Level 2 evidence suggests that back pain may also be reduced by hPTH (1-34).

CRD commentary
This review answered a defined but rather broad review question, particularly in terms of the interventions and populations studied. A reasonable search for studies was carried out, but it is difficult to assess whether publication bias might have affected the findings. The authors also referred to a website for further details, but this was not accessible. Appropriate methods were, however, used to reduce the risk of error and bias when selecting, quality assessing and extracting the data from the included studies. The methodological quality of the studies was also considered in the analysis, to indicate the reliability of the review findings. The decision to summarise the review findings in a narrative appears appropriate given the broad inclusion criteria and the resultant differences in drug types, dosages, comparators and patient populations. Overall, the authors’ conclusions appear to be supported by the data presented, but some caution is advised given the level of heterogeneity and the small size of many of the studies.

Part of this work has been reported as a Cochrane Review (see Other Publications of Related Interest).

Implications of the review for practice and research
Practice: The authors did not report any implications for practice.

Research: The authors stated that fracture data for postmenopausal women with corticosteroid-induced osteoporosis and men with osteoporosis are lacking, and that there have been no direct comparisons of fracture rate with 20 microg hPTH (1-34) and bisphosphonates or comparisons of hPTH and alendronate combination therapies versus hPTH alone.

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Other publications of related interest

This additional published commentary may also be of interest.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.