Effect of teriparatide on bone mineral density and fracture in postmenopausal osteoporosis: meta-analysis of randomised controlled trials

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CRD summary
This review found that teriparatide was effective in the treatment of postmenopausal osteoporosis, with reductions in risks of fracture and improvements in bone mineral density. Although the quality of the studies was generally low, the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy of teriparatide in reducing the risk of fractures and improving bone mineral density in postmenopausal women with osteoporosis.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and ISI Web of Knowledge were searched from January 1966 to April 2011 for relevant peer-reviewed studies in English; search terms were reported. The searches were updated in September 2011. The bibliographies of the retrieved articles were checked for additional references.

Study selection
Randomised placebo-controlled trials of postmenopausal women with osteoporosis who were treated with daily injections of teriparatide for a minimum period of six months were eligible for inclusion. The outcomes evaluated were changes in bone mineral density (BMD) and fracture risk. Studies that included patients with co-existing medical conditions or treatments that affect bone or calcium metabolism, and trials of teriparatide and antiresorptive agents given with placebo comparators were excluded.

The included studies were conducted in the United States, Japan and India. In most trials, teriparatide was administered at a dose of 20μg/day (range 10 to 40μg/day). Comparators included placebo injections and placebo transdermal patches. Other comparators were hormone replacement therapy and alendronate (with doses ranging from 10mg/day to 70mg/week). Concomitant treatment administered in the trials were calcium supplements which were typically 1,000mg/day (range 500 to 1,500mg/day) and vitamin D supplementation given in doses ranging from 400 to 1,200IU/day. Trials that included the use of anti-resorptive agents such as bi-phosphonates, hormone replacement therapy, calcitonin and selective oestrogen receptor modulators in both treatment and control groups were included. The sites at which BMD was measured included the lumbar spine, total hip, femoral neck, trochanter, intertrochanter, distal radius, radius shaft, spinal trabecular and total body. The duration of the studies ranged from six months to 36 months.

Two reviewers performed the study selection; any disagreements were resolved by discussion or by an expert on osteoporosis.

Assessment of study quality
Methodological quality was evaluated by two independent reviewers using the Cochrane risk of bias tool in terms of sequence generation, allocation concealment, blinding of patients, personnel and outcome assessors, treatment of incomplete outcome data and the risk of selective reporting.

Data extraction
Data were extracted by two reviewers to calculate weighted mean differences (WMD) for the percentage change in bone mineral density and risk ratios (RR) for fracture risk and 95% confidence intervals (CI) for each estimate.

Methods of synthesis
Pooled weighted mean differences and risk ratios with 95% confidence intervals for each summary estimate were calculated using a random-effects model. Statistical heterogeneity was evaluated using Cochrane's Q. Subgroup analyses were conducted on the basis of the use of concurrent therapy, the dose of total calcium intake and the duration of treatment. Sensitivity analyses were undertaken to evaluate the influence of antiresorptive treatment. The authors
assessed the potential for publication bias using visual appraisals of funnel plots.

**Results of the review**

Eight randomised controlled trials (RCT) (2,391 patients) were included in the review. Random sequence generation was described in four trials but none of the studies adequately reported allocation concealment. Although two studies were stated to be double-blind, the blinding process was not fully described and three trials did not describe any blinding of participants and personnel. Outcome assessors were blinded in four trials. All the trials were judged to be free of selective outcome reporting but losses to follow-up were described adequately in two RCTs.

There were statistically significant benefits observed with treatment with teriparatide compared with placebo in spine BMD (WMD 8.14%, 95% CI 6.72 to 9.55%; eight RCTs, 2,206 participants) and total hip BMD (WMD 2.48%, 95% CI 1.67 to 3.29%; seven RCTs, 1,303 participants).

Of the studies that evaluated teriparatide with hormone replacement therapy compared with hormone replacement therapy alone, combined treatment was associated with significant improvements in lumbar spine BMD (WMD 10.98, 95% CI 10.81 to 11.16%) and total hip BMD (WMD 3.65%, 95% CI 3.53 to 3.76%). Statistically significant benefits were also observed with teriparatide and alendronate in BMD at the lumbar spine (WMD 5.22%, 95% CI 2.58 to 7.87) but no significant differences between these treatments was observed in BMD at the total hip site.

Patients who received teriparatide with calcium supplementation had significantly greater improvements in BMD measured at the hip bone (WMD 2.48, 95% CI 1.67 to 3.29; seven trials, 1,303 participants; $I^2=89\%$). Furthermore, patients whose intake of calcium was more than 1,500mg had significant improvements in hip BMD (WMD 3.72, 95% CI 3.42 to 4.03; two studies, 908 participants; $I^2=26\%$). There were no differences observed between patients who received teriparatide with calcium supplementation of less than 1,500mg/day and patients who received calcium supplementation alone; there was significant heterogeneity for this outcome ($I^2=87\%$). There were significant benefits observed with total spine BMD with calcium supplementation (WMD 8.14%, 95% CI 6.72 to 9.55) with significant statistical heterogeneity ($I^2=94\%$). Significant results were also observed with calcium supplementation both greater than 1,500mg (WMD 9.83, 95% CI 8.43 to 11.23; three trials; $I^2=90\%$) and less than 1,500mg (WMD 6.69, 95% CI 3.11 to 10.28; five trials; $I^2=95\%$).

There were no significant differences observed between patients who received treatment for durations longer than 18 months and patients who received treatment for less than 18 months. No significant differences between patients who received treatment for 24 months compared with patients who received short-term treatment.

Treatment with teriparatide was associated with a 38% reduction in risk of non-vertebral fracture (RR 0.62, 95% CI 0.44 to 0.87; three RCTs; 1,842 participants), and a 70% risk reduction of vertebral fracture (RR 0.30, 95% CI 0.21 to 0.44; three RCTs; 1,452 participants), with no statistically significant heterogeneity observed for these outcomes.

Visual appraisal of the funnel plots showed some evidence of asymmetry, indicating there was some potential for publication bias.

**Authors’ conclusions**

The daily administration of teriparatide was effective in the treatment of postmenopausal osteoporosis with reductions in risks of fracture and improvements in bone mineral density.

**CRD commentary**

The review addressed a clear question and criteria for the inclusion of studies were defined. Appropriate databases were searched for relevant studies but there may have been some risk of language bias as the review was limited to studies in English. In addition, there were limited attempts to search for unpublished studies, and there may be publication bias which the authors evaluated using validated tests. Steps were taken to minimise errors and bias at each stage of the review process. Study quality was assessed using validated methods.

The authors’ decision to combine the results in a meta-analysis appeared to have been justified and appropriate subgroup analyses were conducted to explore potential causes of heterogeneity. The review excluded studies that enrolled patients with medical conditions or who were taking medications that affected bone metabolism or that focused on idiopathic osteoporosis, this meant that the results of the review could not be generalised to these particular...
populations. Although the quality of the included studies was generally low and some subgroup analyses only included two studies, the authors’ conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that teriparatide should be offered to women with postmenopausal osteoporosis who are at risk of fractures.

**Research:** The authors stated that there were no available trials which compared teriparatide and hormone replacement therapy to teriparatide alone. In addition, the role of calcium supplementation with teriparatide treatment, and the long-term use of the treatment were also unclear.

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