Methodikbericht Anhang A: Evidenztabellen

Folgende Bewertungsvorlagen nach SIGN wurden entsprechend dem Studientyp verwendet, um die Evidenzlevel (EL) zu ermitteln:

Methodology Checklist 1: Systematic Reviews and Meta-analyses
Methodology Checklist 2: Controlled Trials
Methodology Checklist 5: Diagnostic studies
Methodology Checklist 6: Economic studies


Schlüsselfrage: 01. What factors contribute to increased fracture risk/increased number of fractures?

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<thead>
<tr>
<th>EL</th>
<th>Literaturstelle</th>
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<tbody>
<tr>
<td>2++</td>
<td>Xiao, F. et al. Association between loop diuretic use and fracture risk. Osteoporos Int. 26. 775-84. 2015</td>
</tr>
</tbody>
</table>
Schlüsselfrage: 02. Which diagnostic measurements or tools are effective in identifying increased risk of fracture?

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<thead>
<tr>
<th>EL</th>
<th>Literaturstelle</th>
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<tr>
<td><strong>Systematic Reviews and Meta-analyses</strong></td>
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Schlüsselfrage: 03. Which diagnostic measurements or tools best predict response to pharmacological treatment?

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<td><strong>Systematic Reviews and Meta-analyses</strong></td>
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Schlüsselfrage: 04. Which pharmacological interventions are effective in fracture prevention?

Population: Über 50-Jährige

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<th>EL</th>
<th>Literaturstelle</th>
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<tr>
<td><strong>Systematic Reviews and Meta-analyses</strong></td>
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</tr>
<tr>
<td>2+ Wright, E. et al.</td>
<td>Bisphosphonates and evidence for association with esophageal and gastric cancer: a systematic review and meta-analysis. BMJ Open. 5. e007133. 2015</td>
</tr>
</tbody>
</table>

## Literaturstelle

2- Zhang, X. et al. Alcohol consumption and hip fracture risk. Osteoporos Int. 26. 531-42. 2015

## Systematic Reviews and Meta-analyses


## Controlled Trials

1- Naylor, K E et al. Response of bone turnover markers to raloxifene treatment in postmenopausal women with osteopenia. Osteoporos Int. 2016

## Systematic Reviews and Meta-analyses

2+ Wright, E. et al. Bisphosphonates and evidence for association with esophageal and gastric cancer: a systematic review and meta-analysis. BMJ Open. 5. e007133. 2015

## Controlled Trials

1++ Greenspan, S. L. et al. Efficacy and safety of single-dose zoledronic acid for osteoporosis in frail elderly women: a randomized clinical trial. JAMA internal medicine. 175. 913-21. 2015
1++ Palacio, S. et al. A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause. 22. 806-13. 2015
1++ Brown, J. P. et al. Denosumab significantly increases bone mineral density and reduces bone turnover compared with monthly oral ibandronate and risedronate in postmenopausal women who remained at higher risk for fracture despite previous suboptimal treatment with an oral bisp. Osteoporos Int. 25. 1953-61. 2014
1++ Nakano, Tetsumo et al. Once-weekly teriparatide reduces the risk of vertebral fracture in patients with various fracture risks: subgroup analysis of the Teriparatide Once-Weekly Efficacy Research (TOWER) trial. J. Bone Miner. Metab. 32. 441-6. 2014
1++ Roux, C. et al. Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. Bone. 58. 48-54. 2014
**Population: Patienten mit chronischem Nierenversagen**

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<tr>
<th>Literaturstelle</th>
<th>Systematic Reviews and Meta-analyses</th>
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**Population: Männer**

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<th>Literaturstelle</th>
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**Population: Patienten mit Osteogenesis Imperfecta**

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<th>Literaturstelle</th>
<th>Systematic Reviews and Meta-analyses</th>
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**Population: Postmenopausale Frauen**

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<th>Literaturstelle</th>
<th>Systematic Reviews and Meta-analyses</th>
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</thead>
<tbody>
<tr>
<td>Beaudon, C. et al.</td>
<td>Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. Osteoporos Int. 2016</td>
</tr>
</tbody>
</table>

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*1++ Rajatanavin, R. et al. The efficacy of calcium supplementation alone in elderly Thai women over a 2-year period: a randomized controlled trial. Osteoporos Int. 24. 2871-7. 2013*

*1++ Hahn, Deirdre et al. Interventions for metabolic bone disease in children with chronic kidney disease. Cochrane Database Syst Rev. CD008327. 2015*


*1++ Pinzone, Marilia Rita et al. Is there enough evidence to use bisphosphonates in HIV-infected patients? A systematic review and meta-analysis. AIDS Rev. 16. 213-22. 2014*


*2+ Wright, E. et al. Bisphosphonates and evidence for association with esophageal and gastric cancer: a systematic review and meta-analysis. BMJ Open. 5. e007133. 2015*

*1++ Langdahl, B. L. et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. The Journal of clinical endocrinology and metabolism. 100. 1335-42. 2015*


*1++ Kachnic, L. A. et al. RTOG 0518: randomized phase III trial to evaluate zoledronic acid for prevention of osteoporosis and associated fractures in prostate cancer patients. Prostate Cancer Prostatic Dis. 16. 382-6. 2013*


*1++ Plante, Laura et al. Effect of high-dose vitamin D supplementation on bone density in youth with osteogenesis imperfecta: A randomized controlled trial. Bone. 86. 36-42. 2016*


Population: Prämenopausale Frauen

**Literaturstelle**

**Systematic Reviews and Meta-analyses**


**Controlled Trials**

| 1++ | Hadji, P. et al. Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR+ breast cancer: the ProBONE II study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 25. 1369-78. 2014 |
| 1++ | Kaldor, M. et al. Effects of zoledronic acid versus placebo on bone mineral density and bone texture analysis assessed by the trabecular bone score in premenopausal women with breast cancer treatment-induced bone loss: results of the ProBONE II substudy. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 25. 353-69. 2015 |

Population: Sekundäre Osteoporose

**Literaturstelle**

**Systematic Reviews and Meta-analyses**


**Controlled Trials**


Schlüsselfrage: 06. What monitoring should be conducted in individuals taking pharmacological interventions?

**Literaturstelle**

**Systematic Reviews and Meta-analyses**


**Controlled Trials**

| 1++ | Sugimoto, T. et al. Three-year denosumab treatment in postmenopausal Japanese women and men with osteoporosis: results from a 1-year open-label extension of the Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT). Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 26. 765-74. 2015 |
| 1++ | Binkley, N. et al. Efficacy and safety of oral recombinant calcitonin tablets in postmenopausal women with low bone mass and increased fracture risk: a randomized, placebo-controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 25. 2649-56. 2014 |
| 1++ | Bonnick, S. et al. Effects of odanacatib on BMD and safety in the treatment of osteoporosis in postmenopausal women previously treated with alendronate: a randomized placebo-controlled trial. J Clin Endocrinol Metab. 98. 4727-35. 2013 |
| 1++ | Horwitz, M. J. et al. A comparison of parathyroid hormone-related protein (1-36) and parathyroid hormone (1-34) on markers of bone turnover and bone density in postmenopausal women: the P60P study. J Bone Miner Res. 29. 2266-76. 2013 |
| 1++ | Li, S. et al. Long-term calcium supplementation may have adverse effects on serum cholesterol and carotid intima-media thickness in postmenopausal women. The Journal of clinical endocrinology and metabolism. 99. 1694-700. 2014 |
| 1++ | Leder, B. Z. et al. Effects of zoledronic acid versus placebo on bone mineral density and bone texture analysis assessed by the trabecular bone score in premenopausal women: results of the ProBONE II substudy. Osteoporosis International: an Official Journal Established as a Result of Cooperation Between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 26. 765-74. 2015 |

Schlüsselfrage: 06. What monitoring should be conducted in individuals taking pharmacological interventions?
**Schlüsselfrage: 07. What interventions are effective in improving concordance with pharmacological interventions for fracture prevention?**

<table>
<thead>
<tr>
<th>EL</th>
<th>Literaturstelle</th>
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<tr>
<td>Systematic Reviews and Meta-analyses</td>
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<tr>
<td>Controlled Trials</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>Cizmic, A. D. et al. Impact of interactive voice response technology on primary adherence to bisphosphonate therapy: a randomized controlled trial. Osteoporos Int. 26. 2131-6. 2015</td>
</tr>
<tr>
<td>1-</td>
<td>Gandi, K. et al. Compliance and persistence to oral bisphosphonate therapy following initiation within a secondary fracture prevention program: a randomised controlled trial of specialist vs. non-specialist management. Osteoporos Int. 25. 1345-55. 2014</td>
</tr>
</tbody>
</table>

**Schlüsselfrage: 08. What exercise interventions are effective in reducing the risk of fracture or improving BMD levels?**

**Population: Über 50-Jährige**

<table>
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<th>EL</th>
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<tbody>
<tr>
<td>Systematic Reviews and Meta-analyses</td>
<td></td>
</tr>
<tr>
<td>1++</td>
<td>Kendrick, Denise et al. Exercise for reducing fear of falling in older people living in the community. Cochrane Database of Systematic Reviews. 2014</td>
</tr>
<tr>
<td>Controlled Trials</td>
<td></td>
</tr>
<tr>
<td>1++</td>
<td>Uusi-Rasi, K. et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. JAMA Intern Med. 175. 703-11. 2015</td>
</tr>
<tr>
<td>1+</td>
<td>Leung, K. S. et al. Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture risks in 710 community elderly--a cluster-randomized controlled trial. Osteoporos Int. 25. 1785-95. 2014</td>
</tr>
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</table>

**Population: Männer**

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<th>EL</th>
<th>Literaturstelle</th>
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<td>Systematic Reviews and Meta-analyses</td>
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**Population: Postmenopausale Frauen**

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<td>Systematic Reviews and Meta-analyses</td>
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</table>
Population: Prämenopausale Frauen

Schlüsselfrage: 09. What dietary interventions are effective in reducing the risk of fracture or improving BMD levels?

Schlüsselfrage: 10. What other (nondietary, nonexercise) interventions are effective in reducing the risk of fracture or improving BMD levels?
11. What is the clinical and cost effectiveness of integrated models of care (which include assessment, identification, treatment and follow up) compared with standalone elements for the primary and secondary prevention of fragility fracture?

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<th>EL</th>
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12. Which interventions reduce pain, improve deformity, mobility, and quality of life in patients suffering from vertebral fractures as well as fractures of the pelvis or sacrum due to osteoporosis?

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<th>EL</th>
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<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1++</td>
<td>Countries: United States (n = 10), Canada (n = 4), United Kingdom (n = 4), South Korea (n = 2), Israel (n = 1), India (n = 1), Netherlands (n = 1), Colombia (n = 1), Australia (n = 1), China (n = 1)</td>
<td>Total no. patients: N.r.</td>
<td>Proton pump inhibitor (PPI) therapy prescribed for gastroesophageal reflux disease.</td>
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<tr>
<td>Study type: Umbrella</td>
<td></td>
<td>Patient characteristics: Fourteen reviews included studies with adults only, 4 with adults and children, and 8 did not specify age restrictions.</td>
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<tr>
<td>SR of 26 SR (most common included study)</td>
<td></td>
<td>Not further described.</td>
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<tr>
<td>type was observational</td>
<td>Funding sources: &quot;Funding source: None.&quot;</td>
<td>Exclusion criteria: Abstracts that were not reviews, were limited exclusively to children, had a focus other than the treatment of gastrointestinal bleeding or ulcers due to nonsteroidal anti-inflammatory drugs or Helicobacter pylori.</td>
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<tr>
<td>n = 17, followed by randomized controlled trial n = 8.</td>
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<td>Included studies:</td>
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<tr>
<td>Studies assessing association of Proton Pump Inhibitors with Bone Fractures: Kwok CS (2012) Bone Ngaunpenghong S (2011) Ann J Gastroenterol Eom CS (2011) Ann Fam Med Yu EW (2011) Ann J Med Ye X (2011) Eur J Gastroenterol Hepatol</td>
<td>Study limitations: - Adverse events related to PPIs published as individual studies or case reports might have been missed. - Most studies did not provide reasons for taking PPI therapy (ie, for gastroesophageal or laryngopharyngeal reflux) and as such could not be further analyzed. - ORs may overestimate the adverse events of PPIs because the systematic reviews that we included were undertaken specifically to study a specific event of interest to the investigators. - Potential redundancy (overlap) of articles included in individual systematic reviews. Because of the risk of publication bias and the differences in the nature of the data presented, differences in effect size as they relate to study type—such as observation, case series, or randomized controlled trial—could not be established. - Large category of adverse events caused by drug interaction with PPIs, especially anticoagulants, not included. - Additional studies that did not meet our inclusion criteria, might suggest other adverse events with PPI use.</td>
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Notes: Search query not presented in detail. Search for unpublished Systematic Reviews not feasible and criteria therefore ignored.

Only outcome “Bone Fractures” reported in this evidence table.

Author's conclusion: Our overview shows that PPI therapy is associated with significant and potentially serious adverse events that should be discussed with patients. The effect sizes and risk factors provided should facilitate this discussion and promote shared decision making.

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<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
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<tbody>
<tr>
<td>Evidence level: 1++</td>
<td>Countries: USA, UK, Switzerland, Scotland, France, Australia, Norway, Belgium, Japan, Finland, the Netherlands, Israel, Germany, Austria.</td>
<td>Total no. patients: 91791</td>
<td>Vitamin D or related compound (D2, D3, 25(OH)D) alone or in combination with PPI</td>
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<tr>
<td>Study type: Systematic review and meta-analysis</td>
<td>Centres: n.a.</td>
<td>Patient characteristics: Post-menopausal women or older men; mean or median population age over 65 years. Includes participants with movement impairment neurological disorders.</td>
<td>Combination of vitamin D and PPI therapy in high-risk populations.</td>
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<tr>
<td>Setting: Community, hospital and nursing-home</td>
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</table>

Avenell, Alison et al. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database of Systematic Reviews. 2014
settings.

**Funding sources:** We acknowledge the internal financial support for earlier versions of the review from: University of Aberdeen, UK; University of Edinburgh, UK; University of Hull, UK; University of Newcastle, Australia; University of Otago and Healthcare Otago Endowment Trust, New Zealand; University of York, UK. We received external financial support for earlier versions from: Australian Institute of Health and Welfare; Health Research Council of New Zealand, Medical Research Council, UK.

**Dropout rates:** n.a.

**Study limitations:** Incomplete information was available to us on the number of drop outs from intervention and control groups in a number of trials. Thus, it is possible that our analyses, based on the principles of intention-to-treat, might have underestimated the number of outcome events in the intervention or control groups, or both.

**Inclusion criteria:** Study type: Any randomised trial or quasi-randomised trials. Participants: Post-menopausal women or older men (mean or median population age over 65 years), or both. Participants with neurological diseases impairing mobility were included. Intervention: Vitamin D or related compound, alone or in combination with calcium supplementation. Comparison: Placebo, no intervention, or the administration of calcium supplements. Outcomes: Primary: 1. Hip fracture; Secondary: 1. Any non-vertebral fracture. 2. Vertebral fracture. 3. Any new fracture. 4. Adverse effects

**Exclusion criteria:** Studies focused on participants on corticosteroid therapy; studies where vitamin D was given to patients selected on the basis of renal failure: interventions incorporating treatments other than vitamin D and calcium were not considered, e.g. vitamin D and hormone replacement therapy (HRT) compared with HRT alone. Interventions examining eldecalcitol (ED-71, 1alpha, 25-dihydroxy-2beta- (3-hydroxypropoxy) vitamin D3) were also not included. In defining a comparison, advice only on dietary modification to increase calcium intake was not considered as supplementation.
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Journal</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Ronen</td>
<td>Calcified Tissue Int</td>
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<td>Zasshi</td>
<td>Orono &amp; Japanese Journal of Geriatrics</td>
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<td>Trivedi</td>
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<td>Sanders KM, et al. (2010)</td>
<td>JAMA</td>
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<td>Witham MD, et al. (2013)</td>
<td>JAMA Internal Medicine</td>
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Notes:

Only two items on the Cochrane risk of bias tool were assessed (for selection bias) instead of the usual eight. The reason is likely that this article is an update and the original versions predates the Rob tool by Higgins 2011 and the articles were not graded once again. Additional tests for publication bias such as Egger, Beggs test could have been performed.

Author's conclusion: Vitamin D alone, in the doses and formulations that have been used, appears unlikely to be effective in fracture prevention in older people.

Vitamin D plus calcium can help prevent hip fracture or any type of fracture. The benefits need to be balanced against the risk of kidney stones, kidney disease, gastrointestinal disease or heart disease. Vitamin D and calcium together are not associated with an increased risk of dying.

Alphacalcidol may protect against vertebral fractures. Calcium carbonate may be associated with an increased incidence of adverse effects such as hypercalcaemia.

Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary Hip fracture</th>
<th>Secondary Any non-vertebral fracture: Non-vertebral fractures were defined as all fractures except those of the vertebrae, but including hip fractures. 2. Vertebral fracture: two outcomes were sought: clinical fracture events, and new vertebral deformity identified by radiological morphometry or semi-quantitative reading by a radiologist, using routine radiographs, according to a defined experimental</th>
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Results: Included studies: We included 53 trials with a total of 91,791 participants. 31 trials examined vitamin D (including 25-hydroxy vitamin D) with or without calcium in the prevention of fractures. 22 smaller trials examined calcitriol or alfalcacidol (1-alpha-hydroxyvitamin D3), mostly with participants who had established osteoporosis.

Vitamin D only: There is high quality evidence that vitamin D alone, in the formats and doses tested, is unlikely to be effective in preventing hip fracture (11 trials, 27,693 participants; risk ratio (RR) 1.12, 95% confidence
protocol. Either of these methods appear to provide a valid approach to defining vertebral deformity.

3. Any new fracture: in previous versions of the review, the category 'any new fracture' was classified as fractures not covered by hip, vertebral or non-vertebral categories, or where the site of fracture was unclear. This meant that some of the very large community trials were not analysed together, because they chose to report 'non-vertebral fractures' or 'hip fractures' or 'vertebral fractures' but not 'all fractures' and these numbers were not available or could not be calculated from the data without risk of double counting. As a new feature in this version of the review for Analyses 1 to 4 (comparisons involving vitamin D), the category 'all fractures' includes data from non-vertebral fractures (or hip or vertebral fractures if not given), if the data for 'all fractures' are not available (see Differences between protocol and review).

4. Adverse effects: (hypercalcaemia, renal disease, gastrointestinal symptoms, all as defined by the investigators; death).

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### Table: Bang, C. S. et al. Osteoporosis and bone fractures in alcoholic liver disease: a meta-analysis. World J Gastroenterol. 21. 4038-47. 2015

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
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</thead>
<tbody>
<tr>
<td>Evidence level:</td>
<td>Countries: Europe (n = 8), the United States (n = 3), Canada (n = 1), Australia (n = 1), India (n = 1), and Korea (n = 1)</td>
<td>Total no. patients: 726 participants in analysis of bone fractures, 470 participants in analysis of osteoporosis, and 769 participants in analysis of BMD.</td>
<td>-</td>
</tr>
<tr>
<td>2-</td>
<td>Study type: MA of 15 studies (10 cohort studies, 5 case-control studies)</td>
<td>Patient characteristics: 4 studies had ALD groups that consisted only of cirrhotic patients, 2 studies included no alcoholic cirrhotic patients, and in 5 studies, the presence or absence of cirrhosis was not specified.</td>
<td>-</td>
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<tr>
<td></td>
<td>Setting: N.r.</td>
<td>Men and women with a mean age ranging from 47 ± 1.1 - 65.2 ± 11 years.</td>
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<tr>
<td></td>
<td>Funding sources: N.r.</td>
<td>Inclusion criteria: Case-control or cohort studies that (1) were designed to evaluate ALD in the target or control group; and (2) included at least one outcome (prevalence of any bone fractures, prevalence of osteoporosis, or BMD) that enabled comparisons of osteodystrophy between patients with ALD and the control group.</td>
<td>-</td>
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<tr>
<td></td>
<td>Dropout rates: N.r.</td>
<td>Exclusion criteria: (1) Incomplete data; (2) review article; or (3) abstract only (study not published as full-text article).</td>
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<td>Study limitations: - Substantial methodological heterogeneity between the enrolled studies. - Quality of enrolled studies. Included studies classified as high-quality (≥ 7 stars) or low-quality (&lt; 7 stars). Average number of stars awarded in 15 studies was 6.4. 8 studies with zero stars in section of comparability. - A significant outlier observed. In analysis of association between ALD and bone fractures, effect size of outlier (RR = 33.725) was more than 10 times the adjusted effect size (RR = 1.944). Reason for large effect size of outlier is postulated as methodological problem. In this study, presence of fracture was recorded by anamnesis and chest X-ray film and could overestimate rate of bone fractures. NOS Quality low (6 stars) in this study. - No consideration given to any potential confounders, which could be influential to bone fractures and osteoporosis. - Newcastle-Ottawa scale (NOS) used to assess the methodological quality of studies. Scale has been criticized for low agreement between authors and reviewers.</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Evidence

Beaudoin

Measures

(2011)

World

Mitchell

(2011)

Hepatol

Gastroenterol

Wibaux C (2011)

Joint Bone Spine

Choudhary NS

(2011) Dig Dis Sci

González-Reimers

E (2011) Alcohol

Alcohol

Notes: Search query not stated. No search for grey/ unpublished literature. Unclear, if 2 people extracted data. The authors provide no declaration of conflicts of interest. Unclear, if Newcastle-Ottawa Scale (for Case-Control and Cohort studies) were applied correctly.

Unclear, which requirements for diagnosis of alcoholic liver disease (ALD) were implemented in selection of studies.

Author's conclusion: In conclusion, current publications indicate a significant association between bone fractures and ALD, independent of BMD or the presence of osteoporosis. Due to the qualitative and quantitative heterogeneity among studies, further studies utilizing homogenous populations and controlling for confounding risk factors for fractures are needed to elucidate the underlying mechanism of bone fractures in ALD.

| Outcome Measures/results | Primary Relationship between ALD and bone fractures or osteoporosis using adjusted risk ratios (RRs) and standardized mean difference (SMD). Prevalence of any fractures or osteoporosis assessed by radiologic examinations and BMD assessed by dual-energy X-ray absorptiometry (DXA) or dual-photon absorptiometry (DPA). Osteoporosis defined as a value for BMD: 2.5 standard deviations or more below the reference range. | Results: Association between ALD and bone fractures or osteoporosis: 6 studies included. ALD showed significant RR of 1.944 (95% CI: 1.354, 2.791, P < 0.001) for development of bone fractures. ALD showed not significant RR of 0.849 (95% CI: 0.523, 1.380, P = 0.509) for development of osteoporosis. BMD not significantly different between ALD and control groups (SMD in femoral neck BMD: -0.172, 95% CI: -0.453, 0.110, P = 0.233; SMD in spine BMD: -0.169, 95% CI: -0.476, 0.138, P = 0.282). |
| Beaudoin, C. et al. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. Osteoporos Int. . 2016 | Evidence level | Study details/limitations | Patient characteristics | Interventions |
Evidence level: 1++
Study type: MA of 13 articles referring to 9 different RCT

Countries: N.r. Centres: N.r.
Setting: N.r.
Funding sources: “C Beaudoin received a scholarship from the CHU de Québec.”
Dropout rates: N.r.
Study limitations: - Included studies at high risk of bias and all studies funded by AMGEN which was actively involved in study design and/or conduct of all but one study.
- None of the studies designed to evaluate comparative efficacy of denosumab in decreasing fracture risk. Change in BMD and level of bone turnovers were main outcomes and fractures reported as adverse events without a specific adjudication process.
- None of the individual studies were powered to detect a significant difference in fracture risk between groups. Statistical power of meta-analyses on fracture risk and death may not be sufficient
- None of the included studies were performed in men; thus, the results of this meta-analysis cannot be generalised to males
- Included studies conducted over a follow-up period of 12 or 24 months. Comparative effects of prolonged use of denosumab could not be studied.

Total no. patients: 4.890 postmenopausal women
Patient characteristics: Postmenopausal woman.
No further details.
Inclusion criteria: - Randomized controlled trials comparing effect of denosumab (at any dose level) with another pharmacological treatment for osteoporosis.
- Study population included at least 80 % of men or women aged 40 years and older and if at least 80 % of participants were at risk of fracture or suffered from osteoporosis.
- Being at risk of fracture or suffering from osteoporosis defined as:
  (i) having suffered a non-traumatic fracture, 
  (ii) having a BMD T-score lower than −1.8 (arbitrary value corresponding approximately to the midpoint of the osteopenic BMD interval [−2.5 to −1] ),
  (iii) being considered at risk of fracture by study investigators.
- Studies published in any language and peer-reviewed or not.
Exclusion criteria: Trials comparing effect of denosumab with calcium or vitamin D or including only individuals with a specific condition other than osteoporosis.

Interventions: Denosumab administered subcutaneously at a dosage of 60 mg every 6 months in 8 studies. In one study, 6, 14, 30, 60, 100 or 210 mg of denosumab was administered every 3 or 6 months. Follow-up duration from 12 to 24 months.

Notes:
No search for grey/ unpublished literature. Insufficient number of studies for funnel plots. Review therefore at unclear risk of publication bias.
5 of 9 included studies assessed to be at high risk of bias. All studies funded by AMGEN.
Random effects methods used to account for between-study heterogeneity in all meta-analysis (expect when Peto OR was computed), regardless of calculated heterogeneity.
Author’s conclusion: The results of this meta-analysis do not offer evidence of the differential safety of denosumab compared to bisphosphonates in treating individuals at risk for osteoporosis. While denosumab was significantly more effective in increasing BMD, its use did not lead to a significant reduction in fracture risk. In real-world clinical practice, denosumab may, however, be more effective given its higher persistence and compliance. Until more studies are conducted, this research suggests that denosumab could be a good alternative to other antifracture medications. When choosing a patient’s medication, patient particularities (tolerance, adherence, comorbidities, etc.) should be considered. More studies on the comparative efficacy and safety of denosumab should be performed, particularly in men, on longer follow-up periods and using fracture as the primary outcome.

Outcome Measures/results
Primary Fractures (vertebral, hip or at all skeletal sites) and adverse events (all adverse events, withdrawals due to adverse events, death).
Secondary Changes in areal BMD from baseline at total hip, lumbar spine, femoral neck and one-third distal radius, as measured by DXA.

Results: Comparative effect of denosumab on fracture risk: No statistically significant difference detected between fracture risk of participants who received denosumab and those who received a bisphosphonate (n = 4602, RR [95 % CI] = 1.15 [0.94, 1.38], I² = 0 %).
Comparative effect of denosumab on adverse events: Risk of adverse events not significantly different between participants who received denosumab and those who received a bisphosphonate (n = 4786, RR [95 % CI] = 0.99 [0.96, 1.02], I² = 0 %). No significant difference in risk of withdrawals due to adverse events between participants treated with denosumab and those randomised to another treatment (n = 4887, OR [95 % CI] = 0.68 [0.45, 1.04], I² = 57 %).
Comparative effect of denosumab on changes in bone mineral density: Percent changes in BMD measured at all sites statistically higher in participants randomised to denosumab than in other treatment groups (n, mean difference [95 % CI]; total hip 4434, 1.06 [0.86, 1.25], lumbar spine 4415, 1.46 [0.97, 1.95], femoral neck 4153, 1.06 [0.81, 1.30], one-third radius 2571, 1.12 [0.47, 1.78].


Evidence level Study details/limitations Patient characteristics Interventions
Evidence level: 1-
Study type: RCT
of 7,663 women with hip BMD, 558 with spine BMD, 1,246 with sPINP, 517 women with sCTX.

Evidence
Risk
Binkley
Measures
1.246
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Evidence
a.

Baseline characteristics: Population in analyzes (table 2): Hip BMD: 7.056; Spine BMD: 520; sPINP: 1.132; sCTX: 484

Notes: Post-hoc analyses of cohorts from an extension trial to a RCT on zoledronic acid vs placebo. Analyses not planned in study protocols. Sources and composition of included study population in this trial unclear (7,765 in original HORIZON-PFT trial and 2,456 subsequently enrolled women from first extension of HORIZON-PFT; no overall number of included women stated, only that women with baseline BMD = 7.683); no baseline characteristics apart from BMD, P1NP and sCTX presented. Baseline differences of study population between centers not reported.

Author's conclusion: In conclusion, serum P1NP is potentially useful in monitoring response to zoledronic acid. Further research is needed to evaluate the effects of monitoring PINP on treatment decisions and other clinically relevant outcomes.

Outcome Measures/Results

Primary Clinical validity: using Cox models to calculate hazard ratios over the interquartile range (HR/IQR) for baseline measurements of each test in HORIZON-PFT.

Secondary Detectability of response to treatment: comparison of responsiveness of monitoring tests by estimating the mean and true between-person variation in treatment effects ("signal") and background within-person variation ("noise"). Background within-person variation was estimated from women in the placebo arm of the trial.

Results: Clinical validity: Hip BMD: Hazard ratio per interquartile range (HR per IQR) for placebo = 0.81 (95% CI: 0.73, 0.91, no P-value stated). HR per IQR for Zoledronic acid = 0.76 (95% CI: 0.67, 0.86, no P-value stated). Spine BMD: HR per IQR for placebo = 0.87 (95% CI: 0.57, 1.31). HR per IQR for Zoledronic acid = 1.02 (95% CI: 0.63, 1.66). PINP: HR per IQR for placebo = 1.17 (95% CI: 0.88, 1.54). HR per IQR for Zoledronic acid = 1.14 (95% CI: 0.82, 1.58). sCTX: HR per IQR for placebo = 0.92 (95% CI: 0.59, 1.44). HR per IQR for Zoledronic acid = 0.84 (95% CI: 0.62, 1.42).

Detectability of response to treatment: Assessed by the ratio of signal to noise, estimated from the distributions of change in zoledronic acid and placebo groups. The ratio was highest for the two BTM markers: (treatment mean – placebo mean)/placebo-SD for sCTX = 1.15/0.45 = 2.56 and for sPINP = 0.84/0.50 = 1.68. Ratio for both hip and spine BMD only stated as less than 1. Between-person differences in short-term response to treatment were higher than random within-person variation for both of the BTMs, indicating detectable differences in response to treatment: (treatment variance – placebo variance)/placebo variance for sCTX on the log scale = (0.42 – 0.20)/0.20 = 1.08 and for sPINP on the log scale = (0.37 – 0.25)/0.25 = 0.48. For both hip and spine BMD, there was no evidence of between-person differences in short-term response to treatment: (treatment – placebo variance)/placebo variance = 0 for both.

Binkley, N. et al. Efficacy and safety of oral recombinant calcitonin tablets in postmenopausal women with low bone mass and increased fracture risk: a randomized, placebo-controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 25. 2649-56. 2014

Evidence level: 1+
Study type: RCT

Evidence
Centres: multicareter
Setting: Setting 11 sites
Funding sources: Tarsa Therapeutics, Inc.
Dropout rates: 19.77%, 30.24%
Study limitations: Absence of fracture data; the revised prescribing information for nasal spray calcitonin notes “fracture reduction efficacy has not been demonstrated.” Calcitonin did not improve hip BMD, but our study may have been underpowered to detect such differences.

Patient characteristics: N=125
Women ≥45 years of age and at least 5 years postmenopause
Inclusion criteria: - BMD T-score ≤ 2.5 at the lumbar spine, total hip, femoral neck or trochanter
- serum FSH ≤ 10 mIU/mL, serum 25 hydroxyvitamin D ≥ 20 ng/mL, and body mass index (BMI) ≤ 35 kg/m2
- clinical risk factors such as the 10-year risk of major osteoporotic fracture
Exclusion criteria: - history of osteoporotic fracture
- T-scores ≤ 2.5 at any of the sites
- treatment with hormone replacement therapy within 3 months

Interventions: Oral recombinant salmon calcitonin tablets (0.2 mg (200 μg); 1,200 IU) of recombinant (Escherichia coli) salmon calcitonin) or placebo for one year:
- 800 mg calcium citrate and 1,000 IU vitamin D supplements to take once daily

Binkley, N. et al. Efficacy and safety of oral recombinant calcitonin tablets in postmenopausal women with low bone mass and increased fracture risk: a randomized, placebo-controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 25. 2649-56. 2014

| Evidence level: 1++ | Study type: RCT- second extension (E2) | Countries: HORIZON-PFT Centres: Multicenter Setting: | Funding sources: Novartis Pharma AG, Basel, Switzerland | Dropout rates: Verum:22.11%, placebo: 18.95% | Study limitations: - with only 190 patients, the study is underpowered to detect a difference in fracture rates, as well as the difference in some adverse events. Only about 451 patients had completed E1 on study medications in Z6, therefore, a much larger study was not possible. - relatively high rate of discontinuation (about 27%) from the protocol although given the age of the patients and the length of the trial. | Total no. patients: Original HORIZON-PFT: n = 3889, placebo n = 3876 E1-study: n = 1233 E2-study: n = 451 | Patient characteristics: Women with postmenopausal osteoporosis | Inclusion criteria: E2: received at least the first and third doses of ZOL in E1 and completed E1 study. Exclusion criteria: E2: Patients with major protocol violations during E1 study: - specific bone-active medication use (e.g., use of oral bisphosphonates, strontium, and parathyroid hormone) - other specific conditions | Interventions: Original study: 3 years. Verum: annual IV ZOL 5mg. Placebo E1: originally received three ZOL infusions, randomized to receive three additional annual infusions of ZOL or placebo, 3 years. E2: either a 15-minute once-yearly IV infusion of ZOL (Z9 group) or placebo (Z6P3 group) for 3 additional years. All patients received daily oral calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU). |

| Notes: sample size calculation in original study? |

Author's conclusion: BTMs showed small, non-significant increases in those who discontinued after 6 years compared with those who continued for 9 years. The number of fractures was low and did not significantly differ by treatment. While generally safe, there was a small increase in cardiac arrhythmias (combined serious and non-serious) in the Z9 group but no significant imbalance in other safety parameters. The results suggest almost all patients who have received six annual ZOL infusions can stop medication for up to 3 years with apparent maintenance of benefits.
### Outcome Measures/results

**Primary** Percentage change in total hip BMD at year 9 relative to year 6 in 29 compared with ZnBP3.

**Secondary** - Change in hip BMD (total and femoral neck) at years 7 and 8 vs. year 6 and at years 7, 8, and 9 vs. year 0.
- Incidence of fractures (morphometric vertebral and clinical fractures) at year 9 relative to year 6.
- change in BTMs (bone tumor marker) at years 7, 8, and 9 relative to year 6.
- Safety

**Results:** Bone mineral density
- mean change from year 6 to 9 in total hip BMD was 0.54% in 29 compared with 1.31% in ZnBP3 producing a mean between-group difference of 0.78% (95% confidence interval [CI]: 0.37%, 1.93%; p=0.183).
- Compared to the core study baseline (year 0) to year 9, there was no significant difference between the treatments in total hip BMD changes.

Bone turnover markers
- mean serum levels of PINP and the other BTMs remained within the premenopausal reference range in both the groups.
- For b-CTX, there was no evidence of a difference by treatment.
- For BSAP, a statistically significant difference was observed between groups at year 9.
- Within the 29, the mean B7M values increased from year 1. The within-group increase was significant for both PINP (p=0.004) and b-CTX (p=0.002).

Fractures
- Fractures were too few for meaningful comparison.
- no significant difference in the risk of all clinical fractures.

Height
No significant differences in change between groups at year 7, 8, 9 vs year 6.

Safety
Overall incidences of AEs and SAEs were similar in the two treatment groups.

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<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+</td>
<td>Countries: 3 USA, 1 Finland, 3 Australia, 1 France, 1 China</td>
<td>Total no. patients: 559 men</td>
<td>8 exercise programmes: 2 walking programmes, 3 resistance training programmes, 1 walking and resistance training programme, 1 resistance training programme and impact loading activities and 1 resistance training and Tai Chi. Majority of programmes with 3 exercise sessions a week (ranging from 2–5 each week).</td>
</tr>
<tr>
<td>Study type: SR of 7 RCT and 2 CT</td>
<td>Centres: Not reported. Setting: Not reported. Funding sources: Not stated.</td>
<td>Patient characteristics: 1 trial with middle aged heart transplant patients in glucocorticoid treatment (Mean Age±SD: 56.0±6.0 and 52.0±10). Remaining studies with men aged from 53-62 years (range) to 65-74 years (range) from multiclinical populations.</td>
<td>Interventions: 8 exercise programmes: 2 walking only, 3 resistance training only, 1 walking and resistance training, 1 resistance training and impact loading activities and 1 resistance training and Tai Chi.</td>
</tr>
<tr>
<td>Included studies: Braith RW (1996) J Am Coll Cardiol Hawthorn J (1991) Ostereospor Int Kukuljan S (2009)</td>
<td>Dropout rates: Of the trials that did report dropout, the average rate was 3.3%. For the four studies who reported dropout by group, the overall dropout rates were 6.8 and 2.1% for the exercise and control groups, respectively.</td>
<td>Design: randomised controlled trials (RCT) or controlled trials (CT); Exclusion criteria: age: middle aged or older men (45 years and older). Studies in middle-aged and older men and studies including men and women in which results for men and women were reported separately were eligible for inclusion;</td>
<td>The maximum amount that can be moved or lifted one time only, 8-RM or 5–15-RM and 1 trial who did not report intensity but instead the participants were supplied with a medium strength elastic band.</td>
</tr>
<tr>
<td></td>
<td>- Using BMD as measured by DXA is a further limitation of this review due to concerns regarding the inherent inaccuracies of this method of measurement and its inability to provide information regarding important determinants of bone strength (size, shape and structure). Consequently, there is growing interest in using quantitative computed tomography (QCT) to assess bone strength, and researchers should aim to use this method to assess the effects of exercise interventions on whole bone strength where possible.</td>
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<td></td>
<td>- Exercise protocol involving resistance training only,</td>
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<td></td>
<td></td>
<td>- Impact loading exercise only, weight-bearing</td>
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<td></td>
<td>- Aerobic exercise only or a combination of these types of exercise;</td>
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<td>- 4) outcome: BMD (g/cm²) of the lumbar spine, Ward's triangle, trochanter, proximal femur, femoral neck or total hip measured by DXA. Only full-text articles were included, and no restrictions were placed on the language of the article.</td>
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<tr>
<td>Notes:</td>
<td>Author's conclusion: Results from this systematic review indicate that resistance training alone or in combination with impact-loading activities is safe and may assist in the prevention of osteoporosis in middle-aged and older men. However, due to the variation among studies as well as in study quality, additional high-quality randomised controlled trials in this population are required in order to establish evidence-based guidelines for the optimal exercise prescription. Nevertheless, for those individuals willing and able to perform physical exercise, regular resistance training and impact-loading activities should be considered as an effective strategy to prevent osteoporosis in middle-aged and older men.</td>
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</table>

**Outcome Measures/results**

**Primary** Not stated. Reported findings: effects of interventions on BMD of the lumbar spine, femoral neck, total BMD, hip BMD trochanteric BMD, both Ward's triangle.

**Results:** BMD: Effects of exercise varied greatly among studies, with six interventions having a positive effect on BMD and two interventions having no significant effect. It appears that resistance training alone...
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Included studies</th>
<th>Funding sources:</th>
<th>Study limitations:</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR/MA of 18 RCT</td>
<td></td>
<td>Chevalley T (1994)</td>
<td>The study was funded by the Health Research Council (HRC) of New Zealand. MJB is the recipient of a Sir Charles Hercus Health Research Fellowship. The authors are independent of the HRC. The HRC had no role in study design, the collection, analysis, and interpretation of data, the writing of the article, or the decision to submit it for publication.</td>
<td>- No meta-regression analyses performed because there were few studies that reported sufficient data for such an analysis. - Many of randomised controlled trials of short duration and did not have fracture as primary endpoint. - Trials generally carried out in healthy populations or those at risk of osteoporosis, findings might not apply to other population groups.</td>
<td>Total no. patients: n = 69,269</td>
<td>Dietary sources of calcium and calcium supplements.</td>
</tr>
</tbody>
</table>

Exclusion criteria: Studies where most participants had a major systemic pathology at baseline other than osteoporosis, such as renal failure or malignancy.
Miner Res
Sambrook PN
(2012)
Osteoporos Int
Notes: Thorough search until 2013 with a simple update search query in Sept 2014. Search stated only for PubMed.
Tiab-Screening only by 1 author. Data extraction performed by one authors and checked by a second.
No search for unpublished studies.
Risk of bias assessment only performed and reported for RCT, not for included cohort studies. Therefore, this evidence table only reports results from analysis of RCT, all other information must be regarded as 2- quality.
Author's conclusion: Dietary calcium intake is not associated with risk of fracture, and there is no clinical trial evidence that increasing calcium intake from dietary sources prevents fractures. Evidence that calcium supplements prevent fractures is weak and inconsistent.

Outcome Measures/results
Primary Risk of fractures.
Secondary -

Results: Dietary sources of calcium: Sources were milk powder in one study (n = 200, calcium dose 800 mg/day, vitamin D dose 240 IU/day) and a preparation of hydroxyapatite in the other study (n = 62, calcium dose 800 mg/day). No significant results.
Calcium supplements: 26 randomised controlled trials (n = 69.107 participants) identified. Calcium supplements statistically significantly reduced risk of total fracture (20 studies, n = 58.573; RR = 0.89, 95% CI: 0.81, 0.96; P = 0.004) and statistically non-significantly vertebral fracture (12 studies, n = 48.967; RR = 0.86, 95% CI; 0.74, 1.00), hip fracture (13 studies, n = 56.648; RR = 0.95, 95% CI; 0.76, 1.18) or forearm fracture (8 studies, n = 51.775; RR = 0.96, 95% CI; 0.85, 1.09).


Evidence level: RCT
Study type: Study details/limitations
Evidence level: 1++
Countries: USA, Spain, France
Centres: multicenter
Setting: 42 centres
Funding sources: Merck & Co, Inc, Whitehouse Station, NJ
Dropout rates: 30.6%, 18.9%
Study limitations: -

Patient characteristics:
Total no. patients: n= 243
Inclusion criteria: - ≥5 years from cessation of menses, or Bilateral oophorectomy
- AT-score of ≤ - 2.5 to > -3.5 without prior fragility fracture or a T-score of ≤ - 1.5 to > -3.5 at the total hip, femoral neck, or trochanter with prior fragility fracture
- received alendronate 10 mg daily or 70 mg OW for a minimum of 3 years prior, but may have stopped therapy for a maximum of 3 months immediately prior to the screening visit.

Exclusion criteria: - Prior hip fracture
- metabolic bone diseases other than postmenopausal osteoporosis
- hypocalcaemia
- inadequately controlled primary or secondary hyperparathyroidism,
- malignancy within the last 5 years
- inadequately controlled thyroid disease
- severe renal insufficiency
- Prior use of iv bisphosphonates, strontium-containing medications, any cathepsin K inhibitor, any receptor activator of nuclear factor-kB ligand inhibitor, or fluoride treatment for more than 2 weeks at a dose of greater than 1 mg/d

Interventions: ODN 50 mg once weekly (OW) or placebo. Vitamin D3 (5600 IU OW) and daily calcium supplementation to ensure a total daily calcium intake of 1200 mg.

Notes: no limitations mentioned, sample size calculation not described
Author's conclusion: ODN provided incremental BMD gains in osteoporotic women after alendronate treatment.
<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary</th>
<th>Percentage change from baseline in the femoral neck BMD compared with placebo at the end of 24 months</th>
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<tbody>
<tr>
<td></td>
<td>Secondary</td>
<td>- percentage change from baseline in BMD at the femoral neck, trochanter, total hip, lumbar spine, and one third radius at 12 and 24 months within each group</td>
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<td></td>
<td>- percentage change from baseline in biochemical markers of bone resorption [serum C-telopeptides of type 1 collagen (sCTX), urinary N-telopeptides of type 1 collagen (uNTx) to creatinine (Cr) ratio] - biochemical markers of bone formation [serum bone specific alkaline phosphatase (sBSAP), serum N-terminal propeptide of type 1 collagen (sP1NP)]</td>
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<tr>
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<td></td>
<td>- Percentage change from baseline in total body BMD - bone resorption marker urine total deoxyxypyrrolidine (dPYr) - target engagement marker serum cross-linked carboxyterminal telopeptides of type 1 collagen (s1CTP) - osteocalcic number marker serum tartrate resistant acid phosphatase isoform (TRAP)-5b - indices of calcium and mineral homeostasis compared with placebo at the end of 12 and 24 months - Safety and tolerability</td>
</tr>
<tr>
<td>Results:</td>
<td>BM: BMD</td>
<td>- Femoral neck BMD was significantly increased in the ODN group compared with placebo at month 24 (P &lt; 0.001) at total hip, trochanter, and lumbar spine - treatment with ODN significantly increased BMD compared with placebo at month 24 - one third radius BMD declined significantly from baseline in the placebo group</td>
</tr>
<tr>
<td></td>
<td>Other markers:</td>
<td>s1CTP and TRAP-5b - one third radius BMD was not significantly different between treatments or vs baseline at month 24</td>
</tr>
</tbody>
</table>


**Evidence level: Study details/limitations**

- Evidence level: 1-
- Study type: Systematic review and meta-analysis: 7 RCTs
- Countries: Germany, Greece, Switzerland
- Centres: n.a.
- Setting: n.a.
- Austria, Belgium
- Funding sources: No corporate/industry funds were received in support of this work. None of the authors have a financial interest in any of the devices discussed in this report.
- Dropout rates: Attrition bias was judged adequate in all 7 studies.
- Study limitations: We recognize that our meta-analysis shows significant heterogeneity across studies which, as the sensitivity analysis reveals, is associated with their different designs (uncentre vs. multicentre). As heterogeneity disappears when selecting multicentre studies, we can hypothesize that these discrepancies in individual studies may reflect disparity, for example, in the technical performance of the procedure, though our study design does not allow us to identify specific features.
- Patient characteristics: Total no. patients: 424
- Patient characteristics: 424 Participants with symptomatic OVCF. Mean age range 70-74 years. Follow-up time ranged from 1-24 months.
- Inclusion criteria: We included any RCT performed in Europe that met the following predetermined criteria: (a) population: studies conducted on adults with symptomatic OVCFs; (b) intervention: balloon kyphoplasty performed with injection of polymethylmethacrylate (PMMA); (c) results: including the description of clinical outcomes with respect to at least one of the following primary variables: cement leakage, serious clinical complications and new vertebral fractures. Given that our objective was not to compare BKP with other techniques but to assess BKP safety, no restrictions were made regarding comparator, nor were these analysed. In addition, no restrictions regarding the length of follow-up were established.
- Exclusion criteria: Inclusion criteria unmet.
- Interventions: Balloon kyphoplasty performed with injection of polymethylmethacrylate (PMMA).

**Notes:** Baseline characteristics contain no information on gender. Only one forest plot is displayed despite several meta-analyses that were performed. Very high heterogeneity between studies (I²=95%) with not mention of significance or display of forest plots (for new vertebral fractures and serious complications). This is likely caused by apparent differences in follow ups (1-24months) and differences in the procedure of the intervention. These data are not reported, instead the industry report was published in table 1 as present or absent. Publication bias was not investigated.

**Author’s conclusion:** The safety profile and associated complications of balloon kyphoplasty shown in this analysis, based on the evidence provided by existing RCTs, can be of help to the practicing clinician who must contrast them with the potential benefits of the technique. These data represent an important step towards a balanced evaluation of the intervention through, a better reporting framework and more reliable data on long-term assessment of potential sequelae are needed.

**Outcome Measures/results**

- Primary: Cement leaks, serious clinical complication, new vertebral fractures.
- Secondary n.a.

| Results: Six randomized controlled trials fulfilled the inclusion criteria. These studies included data on 525 treated levels in 424 patients. Cement leakage: were detected in 18.3 % (95 % CI 11.6, 23.0) of fractures intervened. In about 0.5 % (95 % CI 0.1, 1.1) of fractures leakages proved to be symptomatic. Serious clinical complications: were recorded in 11.5 % (95 % CI 11.1, 21.7) of patients treated with balloon kyphoplasty with several of these cases requiring intensive treatment of post-operative surgery. New vertebral fractures: were detected in 20.7 % (95 % CI 0.4, 40.9) of patients treated but rates showed an upward pattern when the follow-up period increased. In 54 % of such cases, the fractures were located in regions adjacent to the treated level.


<table>
<thead>
<tr>
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### Outcome

**Evidence level:** 1++

**Study type:** RCT- exploratory study

**Countries:** RCT- exploratory study

**Centres:** Single Center

**Setting:** Research Clinic, Department of Medicine, University of Auckland

**Funding sources:** Health Research Council of New Zealand

**Dropout rates:** 3%

**Study limitations:** Relatively small size of the control group (n = 20), which was due to the primary outcome (change in markers of bone turnover) being a comparison between five groups. The differences in blood pressure and blood coagulation outcomes reached significance at some time points.

**Total no. patients:** n = 100

**Patient characteristics:** Women, at least 5 years postmenopausal

**Inclusion criteria:** - history of CVD, if their 5-year cardiovascular risk was >15% - major ongoing systemic illness - medication known to affect Ca or bone metabolism in the past year - >2000 IU/d (50 μg/d) of vitamin D

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**Interventions:** 5 groups: Calcium Citrate and Calcium Carbonate and MCH A and MCH B and Placebo. 1 g/d of Ca or a placebo

Blood pressure measured at baseline and every 2 h up to 8 h after their first dose and after 3 months of supplementation. Blood coagulation measured by thromboelastography (TEG) in a subgroup (n = 40) up to 8 h only.

**Notes:** no sample size calculation mentioned.

**Author's conclusion:** In conclusion, this study has identified two putative mechanisms by which Ca supplements might impact on cardiovascular risk – through acute increases in both blood pressure and in blood coagulation immediately following dosing. The potential importance of these findings and the fact that the changes are only significant at some time points both suggest that confirmation by independent studies is required. However, these preliminary observations could be important in helping us understand the adverse effects of Ca supplements on vascular health.

### Outcome Measures/results

**Primary** Original Study: RCT in postmenopausal women, comparing the acute and 3-month effects of different Ca supplements on serum Ca and bone turnover. Serum Ca was elevated for at least 8 h following 1000 mg of Ca supplementation. Examination of Ca supplements on blood pressure and acute effects on blood coagulation problem: the commonly used laboratory measures unsuitable for examining the influence of physiological changes in serum Ca on whole-blood coagulation.

Therefore: blood coagulation measured by thromboelastography (TEG)

**Secondary** -

**Results:** All four Ca treatment arms were pooled for the comparison of blood pressure effects with placebo. At 8 h after placebo. The comparison of coagulation factors was performed for the calcium citrate and placebo arms only.

- Blood pressure - Systolic and diastolic blood pressures were significantly lower than baseline at all time points between 2 and 8 h in both the control and the Ca groups (all time points P=0.001).
- Changes from baseline at individual time points, the reductions in systolic blood pressure were smaller in the Ca group vs placebo at 2 h (P=0.003), 4 h (P=0.02) and 8 h (P=0.01).
- Reductions in diastolic blood pressure were smaller in the Ca v placebo group at 2 h (P=0.004).

Blood coagulation

- Blood coagulability tended to increase over 8 h in both the groups (increase in the coagulation index between 2 and 8 h) in the Ca (all time points P<0.007) and control (all P<0.042) groups
- The increase from baseline in the coagulation index was significantly greater in the Ca group compared with the control group at 4 h (P=0.03)
- Reduction in the time to clot initiation, significantly shorter in the Ca group vs control at 4 h (P=0.03)
- Other TEG variables not different

### Brown, J. P. et al. Denosumab significantly increases bone mineral density and reduces bone turnover compared with monthly oral ibandronate and risedronate in postmenopausal women who remained at higher risk for fracture despite previous suboptimal treatment with an oral bisp. Osteoporos Int. 25. 1953-61. 2014

### Evidence level Study details/limitations Patient characteristics Interventions

**Evidence level:** 1++

**Study type:** Post-hoc analysis of 2 RCT’s

**Countries:** USA, Europe, Australia, Canada

**Centres:** multicenter

**Setting:** Study 1: 74 centers, Study 2: 82 centers

**Funding sources:** Amgen Inc.

**Dropout rates:** -

**Study limitations:** -

**Total no. patients:** Study 1: n = 833 (transition to ibandronate TTI) Study 2: n = 870 (transition to risedronate TTR)

**Patient characteristics:** Postmenopausal women with low bone density who had been treated previously with oral bisphosphonate BP therapy ≥5 years

**Inclusion criteria:** - either stopped oral daily or weekly BP treatment (any oral BP for study TTI and alendronate for TTR) - remained on treatment but had low adherence

**Exclusion criteria:** - Other medications affecting bone metabolism within 3 months prior to screening - used or using osteoporosis medications other than daily or weekly oral BP (TTI) or alendronate (TTR) - raloxifene, calcitonin, calcium and vitamin D, or hormone replacement therapy.

**Interventions:** - 60 mg denosumab subcutaneously every 6 months - once monthly for 12 months: TTI Study 150 mg oral ibandronate, TTR study 150 mg oral risedronate

- daily calcium (500 mg or more) and vitamin D (800 international units or more) supplements

**Notes:** Post-Hoc analysis, no sample size calculation.

**Author's conclusion:** Transitioning to denosumab was well tolerated and more effective in increasing BMD and reducing bone turnover than cycling to a monthly oral BP treatment in subjects who remained at higher fracture risk despite suboptimal BP treatment.

### Outcome

-
Primary  Post-hoc analysis of combined data from the two open-label studies (TTI and TTR).
Higher risk subjects were identified as subjects who met ≥1 risk criterion (advanced age, low BMD, prior osteoporotic fracture, and high baseline sCTX-1).
Mean percentage change from baseline in BMD at the total hip, femoral neck, and lumbar spine at month 12 was calculated based on the combined full analysis set and regression imputation for missing post-baseline data.

Secondary -


BMD increases
Overall from both studies: significantly greater increases in BMD compared with monthly oral BPs at month 12 at all three measured skeletal sites.
Increase in BMD total hip: 2.1% idenosumab group vs 0.7% in the monthly oral BP group (p<0.0001).
Treatment difference of 1.4% (95% CI: 1.1–1.6%).
Increase in BMD femoral neck: 1.6% vs 0.3%, lumbar spine: 3.6% vs 1.4% (both p<0.0001).

Higher risk subjects: total hip: 2.2% vs 0.8%, femoral neck: 1.8% vs 0.3%, lumbar spine: 3.7% vs 1.4% for all (p<0.0001).

Bone turnover markers
Decreases from baseline in sCTX-1 significantly greater in denosumab vs monthly oral BP group at months 1 and 6 (p<0.0001 for all).
Median (interquartile range, IQR) changes for denosumab were 80% (78–87%, 69–92%) vs 29.2% (48.4–7.5%) for monthly oral BP at month 1, and 60.5% (77.2–42.6%) vs 37.5% (57.2–27.4%) at month 6. In the higher risk subjects, the results were consistent with those for the overall group.

BMD/sCTX-1 associations and determinants of response
In the overall population, mean increases in BMD significantly greater in the denosumab group than oral BP group in each tertile of baseline sCTX-1 at both the total hip and lumbar spine (p<0.005).
In the higher risk subgroup, mean increases in BMD significantly greater in the denosumab group than oral BP group at the total hip and femoral neck for the middle and upper sCTX-1 tertiles (p<0.0015), and in each tertile of baseline sCTX-1 at the lumbar spine (p<0.0008).

### Measures/results

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<th>Secondary</th>
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### Evidence level: 2++

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<td><strong>Countries:</strong></td>
<td><strong>Total no. patients:</strong></td>
<td><strong>No overall number stated. Most studies</strong></td>
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#### Notes:

**Author's conclusion:** Based upon the currently available moderate quality evidence, our review does not support a role of vertebroplasty for the treatment of osteoporotic vertebral fractures in routine clinical care. There were no demonstrable clinically important benefits compared with a sham procedure and subgroup analyses indicated that results did not differ according to duration of pain ≤ 6 weeks versus > 6 weeks. Sensitivity analyses confirmed that open trials that compared vertebroplasty with usual care are likely to have overestimated any observed improvements seen with vertebroplasty over usual care, towards the null, in keeping with the findings from the placebo-controlled trials.

Although we did not demonstrate an increased risk of incident symptomatic vertebral fractures or other serious adverse events associated with vertebroplasty, a clinically important number of events. Furthermore, serious adverse events related to vertebroplasty were reported in several trials. Patients should be informed about the lack of high quality evidence supporting benefits of vertebroplasty and its potential for harm.

### Outcome Measures/results

**Primary** - Mean overall pain measured on a visual analogue scale (VAS) or numerical rating scale (NRS) • Disability measured by the Roland Morris Disability Questionnaire (RMDQ) or other disability measure • Vertebral fracture and/or osteoporosis-specific health-related quality of life, e.g., the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) • Overall health-related quality of life, e.g., European Quality of Life with 5 Dimensions (EQ-5D) or Assessment of Quality of Life (AQoL) questionnaire • Treatment success measured by a participant-reported global impression of clinical change (much or very much improved), or similar measures • New (incident) symptomatic vertebral fractures (the denominator was the number of participants, but the numerator could include more than one new fracture per participant) • Number of serious other adverse events judged to be due to the procedure (e.g. infection, clinical complications arising from cement leakage).

**Secondary** - Proportion of participants with pain improved by a clinically relevant amount, for example improvement of at least 2.5 units or 30% on a 0 or 1 to 10 scale. • New (incident) radiographic vertebral fractures (the denominator was the number of participants, but the numerator could include more than one new fracture per participant) • Other adverse events.

**Results:** Eleven RCTs and one quasi-RCT conducted in various countries were included. Two trials randomised participants, six placebo-controlled trials and four compared vertebroplasty with kyphoplasty.

- Both placebo-controlled trials were judged to be at low risk of bias while other included trials were generally considered to be at high risk of bias across a range of criteria, most seriously due to lack of participant and study personnel blinding.
- Compared with placebo, there was moderate quality evidence based upon two trials that vertebroplasty provides no demonstrable benefits with respect to pain, disability or treatment success.

- Mean pain (on a scale 0 to 10, higher scores indicate more pain) was 5 points with placebo and 0.7 points better (1.5 better to 0.15 worse) with vertebroplasty, an absolute pain reduction of 7% (15% better to 1.5% worse) and relative reduction of 10% (21% better to 2% worse) (two trials, 201 participants). At one month, mean disability measured by the Roland Morris Disability Questionnaire (scale range 0 to 23, higher scores indicate worse disability) was 13.6 points in the placebo group and 1.1 points better (2.9 better to 0.8 worse) in the vertebroplasty group, absolute improvement in disability of 4.8% (12.8% better to 3.3% worse), relative change of 6.3% better (17.0% better to 4.4% worse) (two trials, 201 participants).

- Disease-specific quality of life measured by the QUALEFFO (scale 0 to 100, higher scores indicating worse quality of life) was 2.4 points in the placebo group and 0.40 points worse (4.58 better to 3.38 worse) in the vertebroplasty group, absolute change: 0.4% worse (93% worse to 5% better), relative change: 0.7% worse (9% worse to 8% better) (based upon one trial, 73 participants). At one month overall quality of life measured by the EQ5D (0 = death to 1 = perfect health, higher scores indicate greater quality of life at one month was 0.27 points in the placebo group and 0.05 points better (0.01 worse to 0.11 better) in the vertebroplasty group, absolute improvement in quality of life 5% (1% worse to 11% better), relative change 18% better (4% worse to 39% better) (two trials, 201 participants). Based upon one trial (78 participants) at one month, 9/40 (or 225 per 1000) people perceived that treatment was successful in the placebo group compared with 12/38 (or 315 per 1000; range 150 to 664) in the vertebroplasty group, RR 1.40 (95% CI 0.67 to 2.95) absolute risk difference 9% more reported success (11% fewer to 29% more), relative change 40% more reported success (33% fewer to 195% more).

- Based upon moderate quality evidence from three trials (one placebo, two usual care, 281 participants) with up to 12 months follow-up, we are uncertain whether or not vertebroplasty increases the risk of new symptomatic vertebral fractures (28/143 observed in the vertebroplasty group compared with 19/138 in the control group; RR 1.47 (95% CI 0.39 to 5.50).

- Adverse effects: based upon moderate quality evidence from two placebo-controlled trials (209 participants), we are uncertain about the exact risk of other adverse events (3/106 were observed in the vertebroplasty group compared with 3/103 in the placebo group; RR 1.01 (95% CI 0.21 to 4.85)). Notably, serious adverse events reported with vertebroplasty included osteomyelitis, cord compression, thecal sac injury and respiratory failure.

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Study type: SR of 42 studies (21 controlled and 16 uncontrolled cohort studies and 5 RCTs)

Included studies: Armstrong DJ (2007) Rheumatology
Bjarnason NH (2001) Osteoporos Int
Bluzssohn A (2011) Osteoporos Int
Bryure O (2010) Osteoporos Int
Burshead AL (2010) Bone
Chen P (2005) J Bone Miner Res
Clowes JA (2003) J Bone Miner Res
Delmas PD (2007) Bone
Delmas PD (2009) J Bone Miner Res
Dobnig H (2005) J Clin Endocrinol Metab
Dobnig H (2006) Osteoporos Int
Eastell R (2011) J Bone Miner Res
Heaney RP (2011) Osteoporos Int
Imai K (2009) Osteoporos Int
Ishijima M (2009) Calcif Tissue Int
Iwamoto J (2005) J Bone Miner Metab
Kim SW (2005) Endocr J
Kiddani K (2003) J Bone Miner Metab
Lane NE (2000) Osteoporos Int
Majima T (2008) J Bone Miner Metab
Miller P (2008) Bone
Reginster JY (2004) Bone
Hoffmann-La Roche (2009) URL: http://ClinicalTrials.gov/show/NCT00545480
Shiraki M (2011) J Bone Miner Metab
Siddiqi M (2010) Osteoporos Int
Stepan JJ (2008) Calcif Tissue Int
Tsujimoto M (2011) Bone
Watts NB (2001) Osteoporos Int

Multinational, Asia, UK, Western Europe, Austria, Belgium, Greece, Ireland, Luxembourg, South America, Eastern Europe, USA/Canada

Centres:

Not reported.

Setting:

Not reported.

Funding sources:
The National Institute for Health Research Health Technology Assessment programme.

Dropout rates:

Dropout rates not reported. None of the 5 RCTs reported characteristics of patients lost to follow-up, only 3 reported reasons for the losses. 10 non-RCT had no loss to follow-up (some were retrospective analyses). Reasons for losses to follow-up reported in further 11 non-RCT

Study limitations:

All RCTs considered to be at high or uncertain risk of bias therefore of low quality. All non-randomised studies considered at high or unclear risk of bias therefore of low quality. No RCTs identified that addressed one of the primary aims of the review (evaluation of clinical effectiveness of monitoring regimens)

That included at least one bone turnover marker, over and above monitoring regimens where a bone turnover marker was not used).

Very high proportion of patients in RCT were adherent to medication; this is likely to be representative of clinical practice.

Most of the evidence available relating to the accuracy of bone turnover markers was in the form of correlations with BMD, measured using DXA. A statistically significant correlation coefficient is not indicative of a strong association between two variables.

Furthermore, BMD is, were small (22 - 3.105 patients). 2 studies did not report the number recruited; 21 studies had fewer than 100 participants.

Patient characteristics: Majority of studies conducted primarily (or entirely) in post-menopausal women; only 4 studies reported including men. Where reported, mean age ranging from 56.1 - 73.9 years.

Inclusion criteria: (1) a randomised controlled trial (RCT) comparing a monitoring regimen that included at least one bone turnover marker test with a monitoring regimen without bone turnover marker testing, or a different bone turnover marker, and reporting either change in patient management strategies and/or treatment adherence rates;

(2) a study evaluating the impact of bone turnover marker test results on the decision-making process, that also reported the subsequent rate of fracture in the population;

(3) a prospective study that compared the results of bone turnover marker tests with the results of bone biopsy or a composite reference standard of BMD and subsequent fracture outcome;

(4) a prospective study that reported at least a p-value for the association between changes in bone turnover markers and BMD, biopsy, and/or the incidence of fractures from correlation or multivariate regression analyses;

(5) a prospective study reporting inter- and/or intrapatient variability on bone turnover marker test results for patients receiving one of the treatments being evaluated; or

(6) a cost-effectiveness analysis of bone turnover marker monitoring strategies. Non-effectiveness prospective studies had to recruit at least 20 patients with osteoporosis who were receiving one of the treatments of interest

Exclusion criteria: (1) Studies assessing the effectiveness of treatments for osteoporosis using changes in bone turnover markers solely as an outcome were excluded.

(2) Prognostic studies using a bone turnover marker to identify patients at risk of osteoporosis and fracture at baseline, prior to commencement of treatment, were excluded, as were studies that included fewer than 20 patients, meeting the population inclusion criteria, in analyses of outcomes applicable to this review.

Bone turnover markers
only one factor that impacts on bone strength and therefore on fracture risk and the association between bone turnover markers and BMD may vary depending on the population and on the menopausal status in women. Extreme heterogeneity ruling out meta-analysis (heterogeneity in terms of patient populations, definitions used to diagnose osteoporosis, treatment regimens, bone turnover marker tests used and their timing, DTA sites used and timing of DTA scans).

**Notes:**

No investigation of publication bias.

**Author's conclusion:** Implications for service provision

The lack of evidence of clinical effectiveness and the heterogeneity and poor quality of the available evidence on the accuracy, reliability and reproducibility of bone turnover markers for monitoring response to osteoporosis treatment precluded the possibility of making any recommendations on the choice of bone turnover marker being used in routine clinical practice for its superiority to monitor osteoporosis treatment response. In addition, the evidence to support the use of bone turnover marker feedback results to improve patient adherence to osteoporosis treatment was not convincing.

**Suggested research priorities**

In order to determine whether or not bone turnover marker monitoring improves treatment management decisions and ultimately impacts on patient outcomes in terms of reduced incidence of fracture, RCTs are required. The predictive accuracy of bone turnover markers for future fracture outcomes in patients receiving osteoporosis treatment could be investigated using prospective, long-term observational studies with large sample sizes. However, in view of the large number of potential patient population–treatment–test combinations, the most promising combinations would need to be identified in order to ensure the more costly and time-consuming studies, such as RCTs, focus on evaluating those strategies. Therefore, we consider the research priority to identify these promising treatment–test combinations. This can be achieved by either conducting small variability studies or initiating a patient registry to collect standardised data. The former would be quicker, easier and less costly, but the quality of the data would be poorer. Further, prior to establishing the latter it is likely that a more widespread use of bone turnover markers in clinical practice would be required. Once the most promising treatment–test combinations have been identified, well-designed RCTs can be conducted to evaluate the effectiveness of those monitoring regimens; this would include measuring outcomes such as the proportion of non-responders, adherence rates, treatment management decisions and fracture outcome. Data from these RCTs along with other sources can then be included in a decision-analytic model in order to investigate cost-effectiveness.

**Outcome Measures/results**

| Primary | Results: Clinical effectiveness: Reported in 5 RCTs and 1 post hoc analysis of a subgroup of patients from a previous RCT. High variability regarding definition of adherence, compliance and persistence. None of the RCTs reported on impact of bone turnover marker monitoring on treatment management. Adherence: Reported in 1 study that found significantly greater average daily proportion of patients who were persistent and compliant to 5 mg/day risedronate in those receiving feedback after the first reinforcement visit at 13 weeks (p = 0.01). Decrease in adherence observed over time attributed to increasing number of patients who did not persist with treatment. Compliance: Reported in 5 studies. Very high and not representative rate of compliance with bisphosphonate. No significant difference between feedback and no-feedback arms where ORs could be calculated; most studies with insufficient data. Persistence: Reported in 1 study with high and not representative baseline rate for 5 mg/day risedronate. No significant impact of uNTX on persistence in the no-feedback arm (p = 0.71); feedback of uNTX results significantly affected persistence in the feedback group (p = 0.029). Significant impact of feedback of uNTX results on discontinuation (p = 0.017); Where message of good uNTX was given (>30% decrease), HR for discontinuation was 0.71 (95% CI 0.53, 0.95); Where message of poor uNTX response was given, HR for discontinuation was 2.22 (95% CI 1.27, 3.89); Where message of stable uNTX response was given, no significant difference in discontinuation between those receiving feedback and those who were not. Quality of life: Osteoporosis Patient Perception Survey (OPPS) QoL questionnaire reported in 2 studies. 1 study with statistically significant differences of at least 3.6% favouring feedback for all domains and the composite score (p ≤ 0.021) in women aged between 55 and 85 years (with the exception of the motivation domain [p >0.05]). 1 study with significant increases in feeling informed, satisfaction and the overall composite score. Although statistically significant, it is unclear whether or not the small absolute changes are clinically significant. Test accuracy: Bisphosphonates: Reported in 18 studies. No 2 studies assessed the same combination of variables and patient population. Of the 54 r-values reported for correlations between changes in bone turnover marker and BMD, 19 were statistically significant (p < 0.05); however, all of the correlations | Secondary | Test accuracy: diagnostic accuracy, correlation coefficient for the association between a bone turnover marker and bone density and/or the incidence of fracture risk/incidence of fracture associated with the bone turnover marker test results, p-value for a bone turnover marker. Reliability and reproducibility: intrarater and/or interrater variability in bone turnover marker test results |
were weak (r < 0.5). Insufficient data for any combination of bone turnover marker, DXA site, time points at which tests were conducted, and patient population to identify any patterns. Limited data from studies conducting multiple regression analyses indicated that there may be a significant association between changes in bone turnover markers and either BMD or incidence of hip or vertebral fractures. However, only 1 study adjusted for all of the confounders considered important by the review authors. Teriparatide: Reported in 10 studies (7 studies with 20 μg/day, 2 studies with 40 μg/day, 2 studies with combined population that received either 20 or 40 μg/day, 1 study did not report administered dose). Across 71 reported r-values for correlations between changes in bone turnover and BMD in patients treated with 20 μg/day teriparatide, 22 were statistically significant; however, all of them were weak (r < 0.5). In patients being treated with 40 μg/day, 9 of 21 reported r-values indicated statistically significant, but weak, correlations. No studies were identified that reported the results of multiple regression analyses in patients being treated with teriparatide. Raloxifene: Reported in 3 studies. Of the 12 reported r-values, none was statistically significant and all correlations were weak. Strontium ranelate: Reported in 2 studies. Of the 7 reported r-values, 6 were statistically significant; sP1NP and sCTX showed moderate correlations with absolute changes in BMD (r = 0.615 and 0.56, respectively). Denosumab: Reported in 1 study. Of the 6 reported r-values, 5 were statistically significant; all correlations weak (r < 0.50).

**Test reliability and reproducibility:** Four studies reported S/N ratio for a bone turnover marker in those being treated with either elodtrone, teriparatide or raloxifene. Each study calculated the S/N ratio differently. Within-study comparisons show that sP1NP at 2 weeks had a lower S/N ratio than sCTX at 2 weeks but a higher S/N ratio at 25 weeks, and sP1NP had a greater S/N ratio than sBALP when measured at 6 months.

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<tr>
<td>Evidence level: 2/2</td>
<td>Study type: Systematic review and Meta-analysis of 20 studies (6 RCTs, 14 prospective cohort studies).</td>
<td>Countries: n.a. Centres: n.a. Setting: n.a. Funding sources: n.a. Dropout rates: Dropout rates and attrition bias were judged as low in 5 studies, and unclear in 15 studies. Study limitations: Our article still has limitations. First, only six RCTs out of 20 in finally met our criteria and were included. Second, the quality assessment result has shown some unclear bias such as in random sequence generation. Third, the trials that were included in our study were all English literature, which might lead to insufficient data inclusion.</td>
<td>Total no. patients: 1429. Patient characteristics: 1429 participants with diagnosed osteoporotic vertebral compression fractures (OVCF) of both genders. All participants were older than 18 years. The article contains no information on baseline characteristics. Inclusion criteria: Prospective comparative trials (PCTs) or randomized controlled trials (RCTs) with no language restrictions that compared PVP with PKP, all genders, age 18 or above, who had been diagnosed osteoporotic vertebral compression fractures (OVCF) caused by osteoporosis. The interventions in the experimental group and control group were PKP and PVP respectively. Exclusion criteria: Non-PCT trials or RCT trials, retrospective study, bone tumors, hemangioma and other reasons for PKP/PVP surgical treatment.</td>
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Evidence level: 1++
Study type: Systematic Review and Meta Analysis of 13 RCTs
Kaufman JM, 2005, Osteoporosis international.
Orwell ES, 2010, Bone.
Ringe JD, 2010, Arzneimittel-Forschung.
Ringe JD, 2009, Rheumatology international.
Ringe JD, 2004, Rheumatology international.
Walker MD, 2013, Endocrine.

Notes: Unlear how search terms were combined with operators and whether MesH terms were used. Unclear whether two investigators selected articles and extracted data. No consideration of grey literature. Outcomes were not specified before the search and lack definitions in general. No baseline study characteristics are provided. No conflict of interest declarations (neither from primary studies, nor the authors of the article).

Author's conclusion: According to the statistical results, the conclusion can be drawn that the PKP technique reduced the rate of cement leakage and significantly improves the safety compared with PVP. For the relief of pain, the main clinical symptom caused by OVC, both are effective methods.

Outcome Measures/results
Primary Age of patients, fracture time before surgery, surgical time, short time visual analog scale (VAS), long time Oswestry Disability Index (ODI), Cobb angle short, Cobb angle long, volume of the cement, cement leakage, adjacent level fracture. Secondary n.a.

Results: Comparing these two methods, the PKP group took more operation time [SMD = 0.66, 95% CI (0.28, 1.03), p=0.0006] with higher anterior vertebral body height [SMD = 1.40, 95% CI (0.49, 2.32), p=0.003]; greatly reduced Cobb angle in the long run [SMD = −0.61, 95% CI (−1.04, –0.19), p=0.005] and had lower risk of cement leakage. However, in VAS scores and ODI scores after the surgery whether for the short-term efficacy (no more than 1 week after the surgery) or long-term efficacy (more than six months), Cobb angle in the short run and new fracture in the adjacent level, no statistically differences were found between the two groups.


Evidence level
Study details/limitations
Patient characteristics
Interventions

Evidence level: 1++

Study type: Systematic Review and Meta Analysis of 13 RCTs

Kaufman JM, 2005, Osteoporosis international.
Orwell ES, 2010, Bone.
Ringe JD, 2010, Arzneimittel-Forschung.
Ringe JD, 2009, Rheumatology international.
Ringe JD, 2004, Rheumatology international.
Walker MD, 2013, Endocrine.

Countries:
Total no. patients: n = 3647 patients

Patient characteristics:
(1) Participants: Men with primary or idiopathic osteoporosis.

Inclusion criteria:
(2) Interventions and comparisons: Therapy regimes that included two of the following drugs or one drug and a placebo:
alendronate, ibandronate, risedronate, zoledronate, ranelate, teriparatide and parathyroid hormone;

Dropout rates:
(3) Outcomes: the BMD in LS and the fracture rate;

Study limitations:
(4) Study design: randomized controlled trials (RCTs) or quasi-RCTs.

Exclusion criteria:
(1) abstracts, letters, or meeting proceedings;
(2) repeated data or did not report the outcomes of interest;
(3) duration of follow-up was < 12 months.

Interventions: Zoledronate (20mg) vs Placebo

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>Countries: China Centre(s): single center</td>
<td>Total no. patients: n=64</td>
<td>Interventions: 1-year 10 mg/day atorvastatin and lifestyle guidance, vs lifestyle guidance only</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>Funding sources: National Nature Science Foundation of China</td>
<td>Male patients aged above 60 years who have osteopenia or osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Dropout rates: 6.25%, 6.25%</td>
<td>Study limitations: An exclusive focus on male subjects may partially reduce the impact of hormone changes. However, our findings should be interpreted prudently due to the relatively small sample size, non-placebo-controlled design and a short 1-year follow-up. In addition, it will be better if we had pre-test estimation for the sample size.</td>
<td>Patient characteristics: - mild dyslipidemia - osteopenia before recruitment - not treated routinely with lipid-lowering drugs in the last 3 months before recruitment</td>
<td></td>
</tr>
<tr>
<td>Setting: Geriatric Department of Renji Hospital, Shanghai</td>
<td>Further, due to ethical considerations, the subjects recruited were osteopenic with mild dyslipidemia. Thus, the results might be relevant to similar subjects but not for patients afflicted with osteoporosis and severe dyslipidemia or nondyslipidemia subjects.</td>
<td>Exclusion criteria:</td>
<td></td>
</tr>
<tr>
<td>Notes: No sample size calculation. No ITT. Allocation concealment not clear.</td>
<td>Author’s conclusion: Our findings suggest that elderly male patients with osteopenia and mild dyslipidemia, therapeutic doses of atorvastatin were associated with positive effects on BMD, probably mediated by suppressed bone resorption.</td>
<td>No statistical significances between groups: TC, HDL-C BMD changes after 6 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary comparison of BMD at total hip, lumbar spine and femoral neck between atorvastatin and control groups from baseline to month 12</th>
<th>Results: Lipid changes at month 12 - atorvastatin vs control: TG: significant decreases (~7.9 ±10.6%, P &lt; 0.01) LDL: sign. decreases (~7.3 ±7.6%, P &lt; 0.01) - No statistical significance between groups: TC, HDL-C BMD changes after 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary comparison of bone metabolic parameters from baseline to month 12</td>
<td>- bone resorptive marker CTx, - bone formation marker OC, - other bone metabolism markers including 25(OH)D, IPTH, - testosterone</td>
<td>No statistical significances between groups in total hip, lumbar spine, femoral neck BMD changes after 12 months</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level:</td>
<td>Countries: Belgium, Sweden (5 studies),</td>
<td>Total no. patients:</td>
<td>Cd exposure: urinary Cd (U-Cd) as biomarkers for</td>
</tr>
<tr>
<td>Evidence level:</td>
<td></td>
<td></td>
<td>Cd exposure: urinary Cd (U-Cd) as biomarkers for</td>
</tr>
</tbody>
</table>


Evidence level: 2-
Study type: Systematic
Evidence level: Study details/limitations
Countries: China, Korea, USA.
Centres: n.a.
Setting: n.a.
Funding sources: n.a.

Patient characteristics
Total no. patients: 428
Patient characteristics: Numer of patients per study 15-28 (unilateral) and 21-40 bi-lateral; 0-
Inclusion criteria: (1) study design: randomized

Interventions: Intervention: unilateral and bilateral

Notes: No search for grey/ unpublished literature. Funnel plot and Begg and Egger test both indicate the existence of publication bias, possibly leading to overestimation of effect or/and its direction. However, funnel plots futile due to insufficient number of studies.
Reported number of included studies varying (8 articles in flow diagram, 10 studies from 7 articles in text and abstract).
Subgroup analyses not preplanned. Patient characteristics not described in detail (e.g. male/ female ratio).

**Author's conclusion:** In summary, the current meta-analysis demonstrates that a high Cd exposure may be a risk factor for any fracture. However, this result should be interpreted cautiously because of the heterogeneity among studies and existence of publication bias. Additional large, high-quality prospective studies are needed to evaluate the association between Cd exposure and the risk of development of fracture.
**Review and meta-analysis (8 studies, observational studies and RCTs).**

**Included studies:**

**Dropout rates:** 3 out of 8 studies included in the quality assessment were considered to inadequately describe dropouts.

**Study limitations:** “We consider that our result of meta-analysis is influ-enced by the following reasons: first, the description of randomization process is not sufficient in most of the studies. Although aggregate data had larger statistical power, the included studies still had various types of bias. Eight of studies have moderate quality and one has a high risk of bias. It is necessary that amounts of high-quality randomized controlled trials should be required. Second, there were only cement leakage and postoperative adj-acent-level fractures in our analysis. More important com-plications should also be considered, such as intraoperative pulmonary cement embolism, intercostal neuralgia and cerebrospinal fluid leakage. And these complications might affect the preponderance of the two approaches and could be included by long-term follow-up. Third, the clinical outcomes of the included studies were limited, although data pooling. Thus, our meta-analysis might be limited to answer some important clinical questions. Studies contained large outcomes are required.”

**Notes:** Study characteristics provides incorrect data on included participants of one study (280 instead of 28). Despite some high heterogeneity (I²=96% p<0.000001) fixed effects models were used for some meta-analyses. Causes for high heterogeneity are not investigated using sensitivity analysis or meta-regression. Some outcomes (adverse events) are simply to rare to be meta-analyzed in this context (n=4 for cement leakage). No investigation of publication bias. Conflicts of interest for the primary studies was not reported. **Author’s conclusion:** “In conclusion, our meta-analysis suggested that a definitive verdict could not be reached regarding which surgical approach is better for OVCF. Although unilateral PKP was associated with shorter operative time, less X-ray exposure frequency and dosage of PMMA than bilateral PKP in the treatment of OVCF. There was no apparent difference in the short- and long-term clinical outcomes and complications between the two approaches. However, bilateral PKP approaches were higher than unilateral PKP approaches in terms of the restoration rate. But on account of lack of some high-quality evidence, we consider that more high-quality randomized controlled trials are required and more complications should be analysed to resolve which surgical approach is better for OVCF treatment in the future.”

**Outcome Measures/results**

**Primary** Operation time, short-term and long-term visual analogue scale (VAS), short term Oswestry Disability index (ODI), restoration rate, dosage of polymethylmethacrylate (PMMA) injected, cement leakage, X-ray exposure frequency, postoperative adjacent-level fractures.

**Secondary** n.a.

**Results:** 8 studies involving 428 patients were included in the meta-analysis. Mean operative time was shorter in the unilateral groups compared with the bilateral groups [P<0.05, weighted mean difference WMD] -19.74 (-30.56, -8.92)]. VAS: There was no significant difference in the short-term postoperative VAS scores [P>0.05, WMD 0.03 (-0.34, 0.40)]. the long-term postoperative VAS scores between them [P>0.05, WMD 0.01 (-0.42, 0.45)] and the short-term postoperative ODI [P>0.05, WMD -0.33 (-2.36, 1.69)] between the two groups. PMMA dosage: The unilateral approaches required significantly less dosage of PMMA than the bipedicul approaches did [P<0.05, WMD -1.56 (-1.59, -1.16)]. Restoration rate: in the bilateral groups was higher than the unilateral groups [P<0.05, WMD -7.82 (-12.23, -3.41)]. Cement leakage: There was no significant difference in the risk ratio of cement leakage [P>0.05, RR 0.86 (0.36, 2.06)] and postoperative adjacent-level fractures [P>0.05, RR 0.91 (0.25, 3.26)] between the two methods. The mean X-ray exposure frequency in the unilateral groups was greater than the bilateral groups [P<0.05, WMD -10.67, -0.70].

<table>
<thead>
<tr>
<th>Cizmic, A. D. et al. Impact of interactive voice response technology on primary adherence to bisphosphonate therapy: a randomized controlled trial. Osteoporos Int. 26. 2131-6. 2015</th>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
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</table>
### Evidence level

<table>
<thead>
<tr>
<th>Study level</th>
<th>Study type</th>
<th>Included studies</th>
<th>Countries</th>
<th>Patient characteristics</th>
<th>Total no. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>RCT</td>
<td>MA of 7 RCT</td>
<td>USA, Canada</td>
<td>237 adult participants</td>
<td>2406</td>
</tr>
<tr>
<td>1+</td>
<td>MA</td>
<td>MA of 7 RCT</td>
<td>USA, Canada</td>
<td>237 adult participants</td>
<td>2406</td>
</tr>
</tbody>
</table>

### Study details/limitations

- **Countries:** USA, Canada
- **Centres:** Kaiser Permanente Colorado, Canada
- **Setting:** Outpatient setting
- **Funding sources:** This study was funded by Kaiser Permanente Colorado.
- **Patient characteristics:** Both groups: age >71.5 years. 93 % of patients were females. Most commonly prescribed bisphosphonate, 86% of all study patients had a diagnosis of osteoporosis.
- **Dropout rates:** 1 patient in control group excluded from statistical analysis (died before 25 day timeframe).
- **Study limitations:** Lack of standardized definition that includes a timeframe after which patients is considered primary non-adherent.
- **IVR phone call only available in English.

### Interventions

- **Intervention group:** Intervention patients were contacted on the day of enrollment by an automated interactive voice response (IVR) phone call. If no one answered, a voice mail message instructed the patient to contact a toll-free number to retrieve the message. If medication was still not purchased 7 days after receiving the IVR phone call, a letter reminding the patient of prescription and explaining benefits and risks of bisphosphonate therapy was mailed.
- **Aldronate Control group:** Did not receive phone call or letter.

### Outcome Measures/results

- **Primary Proportion of patients who purchased their prescription within 25 days of study enrollment:** 25 days determined as enrollment and IVR phone call made on day 0; letter sent on day 7, if indicated; letter to be delivered by day 11; and up to 14 days follow-up after receiving the letter, which was day 25.
- **Secondary (1) proportion of intervention patients meeting the primary outcome:** who purchased their prescription before and after the expected letter arrival date, (2) identifying factors other than the intervention that were independently associated with primary adherence, and (3) medication possession ratio (MPR) for 6 months in patients in both groups by letter who met the primary outcome.

### Results: Primary

- **Proportion of patients who purchased their prescription within 25 days of study enrollment:** significantly greater in intervention group compared to control group (62/127, 48.8 % vs. 36/118, 30.5 %, unadjusted OR=2.17, 95 % CI=1.29–3.67). After adjusting for age, sex, history of bone mineral density (BMD) test, and history of a fracture, OR for primary adherence in the intervention versus control group was 2.30 (95 % CI 1.34–3.94). OR should have been only adjusted for fractures because only this factor showed significant relation - see later.

### Outcome Measures/results

- **Secondary:** Majority of intervention patients with primary adherence to bisphosphonate therapy (n=62) purchased bisphosphonate before letter arrival date (11 days after randomization) compared to after (76 vs. 24 %, respectively). Similar pattern in control group (64 % purchasing their prescription before day 11 versus 36 % after, p=0.208 for difference between the two groups).
- **Sex, age or history of BMD test not significantly associated with primary adherence.**
- **Sex, age or history of fracture significantly more likely to have primary adherence to bisphosphonate therapy (OR=2.21, 95 % CI 1.11–4.40).**

### Mean MPR for intervention patients was 69 % (95 % CI 61–77) vs 60 % (95 % CI 49–71) in control patients (p<0.001). Percent of patients in the intervention and control groups who had a MPR ≥80 % was 43.6 and 41.7 % (p=0.856).

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### Evidence level

<table>
<thead>
<tr>
<th>Study level</th>
<th>Study type</th>
<th>Evidence sources</th>
<th>Patient characteristics</th>
<th>Total no. patients</th>
</tr>
</thead>
</table>

### Patient characteristics

- **Overall distribution/ pooled value of sex, age, BMD scores in studies not described:**
- **1 study with 34 post-transplant adults with CF, all other studies with non-transplanted CF patients:**
- **6 trials with supplemented participants (Vitamin D + Calcium):**

### Inclusion criteria:

**Types of studies:**
- Randomised controlled trials,
- Published papers and abstracts,
- Trials published in all languages.

**Types of participants:**
- People of all ages and of both sexes with CF diagnosed clinically or by sweat and genetic testing,
- All degrees of disease severity and bone density.

### Types of interventions:

- All trials examining bisphosphonates compared to controls (other bisphosphonates, placebo or usual treatment) for treating or preventing osteoporosis in people with cystic fibrosis.
- Types of bisphosphonate: Intravenous pamidronate in two trials; oral alendronate in two trials; oral risedronate; intravenous zoledronic; intravenous zoledronate.
and Co., Inc., Clinical Nutrition Research Unit, Verne S. Caviness General Center for Clinical Research at University of North Carolina, CF Foundation and NIDDK. 1 trial partly funded by Novartis Pharmaceuticals Pty Ltd, Australia. 1 trial funded by Merck Frosst Canada. 1 trial funded by CF Trust UK. A later study by the same authors was funded by unrestricted educational grants from Proctor & Gamble (Norwich, USA) and Cystic Fibrosis Trust, with support from investigators from the UK National Institute of Health Research.

**Dropout rates:** 5 studies described withdrawals from the study. Significantly more withdrawals due to adverse events at 12 and 24 months in the treatment group compared to the control group (OR = 4.07 [95% CI 1.11 to 14.90]; OR = 16.34 [95% CI 1.98 to 134.89]). No significant difference between treatment or control groups for total withdrawals for any reason at 6, 12 and 24 months.

1 patient in 2 studies stated as lost to follow-up, respectively.

**Study limitations:** Significant clinical heterogeneity between the studies but in the majority, only low statistical heterogeneity.

Only one trial assessed quality of life, with no significant effect of intervention on physical or mental components of the score. Fever was not reported in association with oral bisphosphonates. Lack of significant differences in the rate of fractures, gastrointestinal adverse effects, withdrawals or survival may relate to small numbers of participants involved and short duration of the trials. Risk of bias due to blinding was judged as present in 2 trials, unclear in 3 trials and low in 2 trials. When participants are aware of the treatment they are receiving, they may be more or less likely to report adverse events. The judgment of individuals who collect and interpret patient data may be affected when the assessor is aware of the treatment a participant is receiving. Lack of blinding may result in biased results.

**Notes:** No investigation of publication bias but thorough search of published and unpublished literature. No summary table with study characteristics provided. No Cochrane risk of bias summary table.

**Author's conclusion:** Implications for practice

Based on seven small trials, oral and intravenous bisphosphonates cause a rapid increase in spine and hip or femoral BMD in adults with CF. Only two trials assessed the effect on distal radial BMD, with only the study of longer duration reporting an improvement. Severe bone pain is common with the use of intravenous bisphosphonates in participants with CF not receiving oral corticosteroids, and may limit tolerability. Severe bone pain was also observed in one of three trials of oral bisphosphonates. Oral bisphosphonate treatment did not cause increased gastrointestinal symptoms. Only one trial assessed quality of life and did not show a benefit. These short-term trials (maximum of two years) did not show fracture reduction or survival benefit. Currently, no other options for the treatment of CF-related osteoporosis have been reported in the public domain. Thus, although bisphosphonates increase BMD, no recommendation can be made concerning the use of bisphosphonates in participants with CF as an effect on fractures could not be demonstrated.

**Implications for research**

This area of research would benefit from a large multicentre RCT of bisphosphonates (oral and intravenous) with separate analyses.
**Outcome Measures/results**

- **Primary Fractures (number of participants with any fracture and number of fractures at all sites, spine, hip, wrist)**
- **Secondary 1. Bone density: measured by dual-energy X-ray absorptiometry (DXA), reported as per cent change from baseline. Data reported using other methods of bone density measurement such as single energy X-ray absorptiometry (SXA) and quantitative tomography (QCT) would be used if available but analysed separately:**
  - i) lumbar spine
  - ii) hip or femur
  - iii) radius
  - iv) total body

2. **Quality of life (QoL): CF-related, osteoporosis-related or general QoL measures**

3. **Adverse events: bone pain, hypocalcaemia and gastrointestinal adverse events (number of participants, number of adverse events)**

4. **Withdrawals: i) withdrawals due to adverse events**

5. **Survival**

**Results:** Trials of participants who have not received lung transplant

**New fractures:** Fractures were not reported as an outcome measure in two trials.

No statistically significant difference in the number of participants with new non-vertebral fractures in the treatment group compared to controls after 12 months of intervention: OR = 0.19 (95% CI 0.01 to 4.21). 2 trials showed no vertebral fractures in either treatment or control group after 24 months. Combining data for both vertebral and non-vertebral fractures from the available studies, there was no significant difference between groups at 12 months: OR = 0.72 (95% CI 0.13 to 3.80). No fractures reported at 24 months.

**Per cent change in BMD:**

a. **Lumbar spine:** Reported in all six studies. 4 studies showed significant increase in BMD measured at the lumbar spine in the treatment group after 6 months: MD = 4.61 (95% CI 3.90 to 5.32, P < 0.00001). Low statistical heterogeneity between studies; I² = 39%. 4 studies showed a significant increase in BMD in favour of bisphosphonates after 12 months: MD = 6.10 (95% CI 5.10 to 7.10, P = 0.00001). Low statistical heterogeneity; I² = 0%. 2 trials reported significant effect after 24 months in favour of the treatment group: MD = 5.49 (95% CI 4.36 to 6.60, P = 0.00001). Moderate statistical heterogeneity; I² = 40%. b. **Total hip or femur:** Reported in 5 studies. Combined data at six months showed significant result in favour of bisphosphonates for total hip or femur BMD: MD = 3.35 (95% CI 1.63 to 5.07, P = 0.00013). Data from 4 trials showed a significant increase in total hip or femur BMD after 12 months: MD = 4.35 (95% 2.99 to 5.70, P = 0.00001). 2 studies showed significant effect in favour of intervention after 24 months: MD = 6.05 (95% CI 3.74 to 8.36, P < 0.00001). Substantial heterogeneity between studies for total hip or femur (I² = 73% at six months) and low statistical heterogeneity between studies at the 12-month and 24-month time points; I² = 38% and 39%, respectively. c. **Radius:** 2 studies reported data for distal radius and 1 reported data for ultra distal radius. No significant result for distal radius at six-month time-point: MD = 0.49 (95% CI -2.42 to 1.45). Substantial statistical heterogeneity between studies (I² = 71%). Non-significant decrease in BMD as measured by SXA of the ultra distal forearm in participants receiving pamidronate at six months: MD = 2.70 (95% CI -5.59 to 0.19).

**Quality of life:** Reported in 1 trial measured with EQ5D. No significant changes in the physical component score (MD = 2.51 [95%CI-1.36 to 6.40]); mental component score (MD = -5.93 [95% CI -11.73 to -0.13]; total score MD = -0.11 [95% CI -3.35 to 3.12]).

**Adverse events:**

Reported in 6 studies. a. **Bone Pain:** Combining study results for all routes of administration, bisphosphonates were associated with significantly higher occurrence of bone pain: OR = 18.52 (95% CI 5.39 to 63.57, P < 0.00001). Heterogeneity: P = 0.22; I² = 32%. b. **Fever:** Combined data from the trials of intravenous bisphosphonates show participants in the treatment groups were significantly more likely to experience fever: OR= 12.64 (95% CI 2.31 to 69.11, P = 0.0034). Heterogeneity: P = 0.44; I² = 0%. c. **Gastrointestinal adverse effects:** Described in 3 trials assessing oral bisphosphonates. 1 study reported three cases of diarrhoea (1 participant receiving alendronate, 2 receiving placebo). Participants continued to experience diarrhoea after discontinuing the study medication. 1 participant with dysphagia, 1报告消化道不良反应

346 adverse events were recorded; most events were classed as respiratory exacerbations (n = 230). No difference in incidence between the two groups. 1 study reported SAEs in the alendronate group as exacerbation of CF (n = 3), bronchial superinfection (n = 1), megalocytic seizure (n = 1), gastrointestinal obstruction (n = 1) and intestinal obstruction (n = 1). SAEs reported for the control group included exacerbation of CF (n = 3), with two of these participants experiencing additional gastrointestinal complaints.

**Withdrawals:** Reported in 5 studies. Significantly more withdrawals due to adverse events in the treatment group compared to the control group at 12 and 24 months: OR = 4.07 (95% CI 1.11 to 14.90, P = 0.034) and 16.34 (95% CI 1.98 to 134.89, P = 0.0095). At 6, 12 and 24 months, data from these trials do not show any significant difference between treatment or control groups for total withdrawals for any reason.

**Survival:** Combining 12-month outcome data of alendronate trial with alendronate did not show a statistically significant difference: OR = 2.98 (95% CI 0.30 to 29.84).

**Trials of participants who have received lung transplant**

Only one trial reported on this comparison.

**New fractures:** No statistically significant difference in the number of participants with new vertebral fractures in the bisphosphonate (pamidronate) group (3 out of 16 participants) versus the control group (1 out of 16 participants): OR = 3.92 (95% CI 0.36 to 38.32). Heterogeneity: P = 0.17; I² = 66.8%.

**Per cent change in BMD:**

a. **Lumbar spine:** Significantly higher after 24 months in the treatment group than in the control group at the lumbar spine: MD = 6.20 (95% CI 4.28 to 8.12). b. **Hip or femur:** Significantly higher after 24 months in the treatment group than in the control group at the femur: MD = 7.90 (95% CI 5.76 to 10.02).

**Quality of life:** Not reported.

**Adverse events:** None reported.

**Withdrawals:** No withdrawals other than those due to death in either treatment group.

**Survival:** Three participants died before the first BMD data could be collected at 6 months and were excluded from further analysis. No other participants died during the course of the trial.

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**Evidence level**

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+</td>
<td>Countries: n.a.</td>
<td>Total no. patients: 9926, of which 713 were HIV positive and received therapy in their menopausal period.</td>
<td>Interventions: Non</td>
</tr>
<tr>
<td>Study type:</td>
<td>Systematic review: 10 studies (6 cross sectional studies, 4 longitudinal cohort studies)</td>
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</tr>
</tbody>
</table>
| Included studies: | Anastos K, et al. (2007) Antiviral Therapy  
Cazanave C, et al. (2008) AIDS  
Gomes DC, et al. (2014) Menopause  
Li Vecchi V, et al. (2012) BMC Infectious Diseases  
Yin MT, et al. (2012) AIDS  
Yin MT, et al. (2010) AIDS  
Yin MT, et al. (2005) Osteoporosis International |

| Setting: | n.a. |
| Funding sources: | Yamnia Cort es was funded as a predoctoral trainee by the National Institute of Nursing Research, National Institutes of Health, Training in Interdisciplinary Research to Prevent Infections (TIRI), ST32NR013454. |
| Dropout rates: | Study limitations: This review has several limitations. Included studies were restricted to English-language articles published in peer-reviewed journals. Only studies that assessed BMD by DXA were included, so it is possible that other less rigorous studies were missed. Given the significant heterogeneity, a meta-analysis was not conducted. |
| Patient characteristics: | Age is not available for studies, but mean age ranges between 39 and 56 years. Exposure to antiretroviral therapy between 61 and 100%. 3 out of 10 studies have a mixed ethnical background. |
| Inclusion criteria: | Studies were eligible if they included a sample of HIV-infected post-menopausal women, and reported bone mineral density (BMD) or fracture data. Studies were included regardless of how postmenopausal was defined (e.g., amenorrhea for ≥12 consecutive months without confirmational hormone measures). |
| Exclusion criteria: | Studies were excluded if they did not report any BMD or fracture data specifically for HIV-infected postmenopausal women. |

| Notes: | Study selection and data extraction were not carried out by two investigators. Grey literature was not considered. Excluded studies are not listed. |
| Author's conclusion: | Although there is sufficient evidence to support menopause as an important predictor of bone loss and low BMD in HIV-infected postmenopausal women, there is still inadequate evidence to suggest a role in fracture rates at this time. |
| Future studies that follow women across the menopause transition, using confirmatory endocrine biomarkers, are needed to gain a better understanding of the impact of menopause on HIV disease progression and bone loss. Longer-than-usual follow-up of HIV-infected women may be necessary to determine risk for fractures in this population, given their earlier age of menopause and age at which fractures commonly occur. In addition, a greater understanding of the effect of reproductive hormones on HIV-associated non-AIDS conditions, such as low BMD, is important to prevent and treat these conditions more effectively in the growing population of older women with HIV (High et al., 2012). Findings in our review are relevant to health care providers with an HIV-infected patient population because they highlight the need to accurately assess postmenopausal status and modifiable risk factors for osteoporosis in all older HIV-infected women. |

Primary OR or PR for low BMD or osteoporosis.
### Measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measures/results</th>
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</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>Change in BMD, HR of fractures.</td>
</tr>
</tbody>
</table>

### Evidence

**Evidence level:** 2++

**Study type:** updated systematic review of 315 articles

**Included studies:** -

| Evidence level | Countries: -
| Study type: updated systematic review of 315 articles | Setting: -
| Included studies: | -

**Funding sources:** Agency for Healthcare Research and Quality (AHRQ)

**Dropout rates:** -

**Study limitations:** The dearth of head-to-head comparisons of the benefits and harms of the agents. This has led several investigators to estimate comparative effectiveness using indirect methods. Although no consistent differences in efficacy have been found, this does not constitute proof that they do not exist. The lack of data in men leaves clinicians and policymakers to try to extrapolate from data in women, which may not be valid. Additional limitations common to all systematic reviews are the possibility of publication bias and heterogeneity in the definition of outcomes and adverse events. Limitations of this review include our reliance on English-language publications and no assessment of costs.

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**Notes:** Mixture between narrative and systematic Review

**Author's conclusion:** Good-quality evidence supports that several medications for bone density in osteoporotic range and/or preexisting hip or vertebral fracture reduce fracture risk. Side effects vary among drugs, and the comparative effectiveness of the drugs is unclear.

### Results

**Results:** The prevalence of osteoporosis reported in these studies ranged from 7.3% to 84% and 0.7% to 23% in HIV-infected and uninfected postmenopausal women, respectively. In the two qualifying studies, postmenopausal status was not a predictor of fractures in HIV-infected women.

**BMD studies:** Risk factors for lower BMD were: older age, lower BMI, lowest historical weight, corticosteroid use. Behavioral predictors of low BMD included strength training, substance abuse.

**HIV characteristics independently associated with low BMD are: ART with or without protease inhibitor, time on ART, low nadir CD4+ cell count, higher viral load and hepatitis C co-infection.**

**Fracture studies:** Older age, white race, corticosteroid use and current smoking were independent predictors of fractures. While HIV characteristics were not independently associated with fractures, both studies found that hepatitis C co-infection was a predictor of fractures for HIV-infected men and women.


**Study details/limitations**

| Evidence level | Countries: -
| Study type: updated systematic review of 315 articles | Setting: -
| Included studies: -

**Funding sources:** Agency for Healthcare Research and Quality (AHRQ)

**Dropout rates:** -

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- 76 randomized trials and 24 meta-analyses: good-quality evidence that alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, parathyroid hormone, and raloxifene prevented osteoporotic fractures, although not all of these agents prevented hip fractures.

**Update:**

- additional data about zoledronic acid
- data about a new agent, denosumab

**zoledronic acid**

- 6 placebo-controlled studies of various doses in postmenopausal women.
- The 2 largest (n= 7,230 and n=2127): statistically significant reductions in nearly all types of fractures assessed, with relative risk reductions ranging from 0.23 to 0.73 at time points from 24 to 36 months after initiation of treatment

**Denosumab**

- 2 placebo-controlled trials in postmenopausal women (n= 332, n= 752).
- the second study: significant reductions in each anatomical fracture type measured (hip, nonvertebral, vertebral, and new clinical vertebral), with hazard ratios of 0.31 to 0.80.

**Bisphosphonates** (alendronate, ibandronate, risedronate, and zoledronic acid), denosumab, teriparatide)

- reduce fractures compared with placebo in postmenopausal women
with osteoporosis, with relative risks for fractures generally in the range of 0.40 to 0.60 for vertebral fractures and 0.60 to 0.80 for nonvertebral fractures. Number needed to treat of 60 to 89 to prevent 1 vertebral fracture and 50 to 67 to prevent 1 hip fracture over 1 to 3 years of treatment.

- effect of ibandronate on hip fracture risk reduction is unclear because not a separately reported outcome
- raloxifene reduces only vertebral fractures

Males with osteoporosis
- one RCT: n=1200 zoledronic acid for 2 years. 1.6% new radiologically detected vertebral fractures, vs placebo 4.9%, relative risk of 0.33 (95% CI, 0.16 to 0.70). 1.0% vs 1.8% placebo, had a clinical vertebral or nonvertebral fracture (hazard ratio, 0.6 [CI, 0.2 to 1.5])

Comparative Effectiveness
Head-to-head comparative effectiveness studies assessing fracture outcomes are rare.

Several attempts to estimate comparative effectiveness (network meta-analysis and indirect or mixed treatment comparisons)
1. network meta-analysis of 116 placebo-controlled or head-to-head trials (AMSTAR 10):
   - assessing alendronate, risedronate, ibandronate, zoledronic acid, raloxifene, denosumab, teriparatide, vitamin D, and calcium concluded that any of the drugs were likely more effective than vitamin D or calcium.
   - evidence supporting raloxifene was not as strong as the evidence for the other drugs
   - differences in vertebral and nonvertebral fracture risk reduction among any of the bisphosphonates, denosumab, or teriparatide were not consistent or statistically significant

2. Network Meta Analysis of 30 RCTs (AMSTAR 6):
   - no significant differences in nonvertebral fracture risk in the indirect comparisons among alendronate, risedronate, etidronate, ibandronate, zoledronic acid, raloxifene, denosumab, teriparatide, or strontium
   - etidronate, ibandronate, and raloxifene lack direct evidence of superiority to placebo in preventing nonvertebral fractures

3. Network Meta Analysis (sponsored by manufacturer) of 21 RCTs (AMSTAR 7):
   - no statistically significant difference in indirect or mixed treatment comparisons in nonvertebral fracture risk reduction among alendronate, risedronate, etidronate, ibandronate, zoledronic acid, raloxifene, denosumab, teriparatide, or strontium.
   - etidronate, raloxifene, and ibandronate did not have direct evidence of a reduction in nonvertebral fractures relative to placebo

4. Network Meta Analysis with 9 RCTs(AMSTAR 3)
   - alendronate, risedronate, ibandronate, zoledronic acid, and denosumab
   - inclusion to studies that reported clinical and morphometric vertebral fractures and had a treatment period of at least 3 years
   - no statistically significant differences among drugs

5. Network Meta Analysis (sponsored by manufacturer) with 8 RCTs (AMSTAR 6)
   - Other than the sponsor’s drug the outcome of morphometric vertebral fractures, this analysis did not find any consistent significant differences among drugs for the various fracture outcomes

All of these network meta-analyses are limited by the dearth of head-to-head studies; nevertheless, their conclusions are consistent with our narrative synthesis of the evidence.

Adverse Events
Atypical Subtrochanteric Fractures
- atypical subtrochanteric fractures seen in patients treated with bisphosphonates. These associations come entirely from observational studies, and results are not completely consistent.
- An increased risk has not been seen in clinical trials, although even an analysis of data aggregated from 3 large trials (a total of 14 195 women) was underpowered to detect an effect (pooled relative risk, 1.33 [CI, 0.12 to 14.7])
- a recent meta-analysis of 5 case– control studies and 6 cohort studies (AMSTAR score 10) found an overall pooled risk ratio of 1.70 (CI, 1.22 to 2.37)

Cancer
- low-strength signals of potential associations with various types of cancer, but additional data are needed.
- possible association between the use of bisphosphonates and esophageal cancer
- observational studies found that bisphosphonate use was
Evidence level: N/A
Study type: Systematic review (7 observational diagnostic studies)
Included studies:

Evidence level: 2-
Study type: Systematic review

Countries: n.a.
Centres: n.a.
Setting: n.a.
Funding sources: n.a.
Dropout rates: n.a.
Study limitations: This systematic review of the literature has shown a wide variation in the sensitivity and specificity values for the MCI between the two research groups. Two studies recruited men and women and one enlisted only women in their study group. The incidence of hip fractures (and therefore cortical erosion) is known to be higher in women than in men. This may explain the differences in sensitivity.

Two large studies tested the diagnostic accuracy of MCW in detecting hip osteoporosis. One study used a sample with a prevalence of hip osteoporosis of about 10%, whereas the sample another study had a prevalence of 14.7%. In British women aged 65 years, the mean prevalence of femoral neck osteoporosis was 8.1% (2.7% in men). Therefore, the results from these two reviewed studies are applicable to a post-menopausal population only, as they recruited more osteoporotic patients than would be expected in a sample of adult patients attending for routine treatment at the dental office.

Total no. patients: 1434
Patient characteristics: Age range 33-84; Gender distribution unclear.
Inclusion criteria: Studies were selected if they compared any measurements on the dental radiographs with a reference standard diagnosis of low bone mineral density in the hip, that is, central dual energy X-ray absorption- etry (DXA).
Exclusion criteria: Not the interventions of interest (MCW, MCI), non-adherence to WHO standard of osteoporosis.

Interventions: Dental radiographs: Mandibular cortical width (MCW) and mandibular cortical index (MCI), were compared with the reference standard. The MCW was measured at the cortex defined as that region where a line perpendicular to the lower border of the mandible also passes through the mental foramen. Klemetti et al. described the MCI as a method of classifying the basal mandibular porosity: C1: the endosteal cortical margin of the basal mandibular bone was even and regular. C2: mild-to-moderate porosity as indicated by some resorption of the endosteal margin. C3: severe resorption with cortical porosity and heavy residues or islands of bone.


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Notes:

Unclear whether article selection and data extraction was carried out by more than one investigator. No inclusion of gray literature. Scientific quality was assessed but not reported. The displayed results are largely incomparable due to differences in gender and measurement, which explains the range of the observed specificity and sensitivity for both MCW and MCI. No analysis stratified by gender was performed. Results are presented without confidence intervals for MCI. No COI declaration for the article authors or the included studies.

Author's conclusion: In view of the moderate diagnostic accuracy of both MCW and MCI tests, patients should not receive a panoramic radiograph for the purpose of diagnosis of osteoporosis but rather any referral for further investigation should be on the basis of a chance finding on the radiograph. In deciding whether to refer the patient for further investigation, the dentist must also take a detailed medical and medication history and enquire into lifestyle factors as they are also important risk factors for osteoporosis.

Outcome Measures/results

Primary Sensitivity, Specificity, AUC, of MCW and MCI in predicting hip osteoporosis. Osteoporosis of the femoral neck was defined by the World Health Organization (WHO) as a bone mineral density that is 2.5 standard deviations or more below the young adult mean value.

Secondary n.a.

Results: Seven studies were identified. Meta-analysis was not possible because of the heterogeneity of the studies. The studies all demonstrated moderate diagnostic accuracy. MCW: sensitivity range (20-95%), specificity 43-84%, AUC 0.779-0.835. MCI sensitivity 77-93%, specificity 31-71%.


Evidence level: Study type: Randomized, parallel-arm, double-blinded, placebo-controlled study. Multicentric design.

<table>
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<tr>
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<td>1+</td>
<td>Countries: USA. Centres: n.a. Setting: Clinical setting. Funding sources: the funding sources and study supplement provider did not contribute to the design or conduct of the study or to the writing or submission of this manuscript. Dropout rates: Intervention group: 15 out of 76 (20%); control group: 10 out of 70 (14%). Study limitations: Limitations of the current study include the lack of measurements of resting energy expenditure and respiratory quotient, which would have allowed us to form relations between the observed changes in central adiposity, energy expenditure, and substrate utilization. Last, our genotypic analysis was limited to just 1 polymorphism of the enzyme involved in GTC metabolism. It is possible that other enzymes and physiologic pathways may play a role in green tea's effect on body composition.</td>
<td>Total no. patients: 121. (61 intervention, 60 control). Patient characteristics: Postmenopausal women, Mean age at baseline 60 ± 6 years. Intervention and comparison group. Mean BMI was 27.9 and 27.6 kg/m² in the two groups. Patients were randomized according to genotype of catechol-O-methyltransferase (COMT), which is considered to drive the obesity effects behind green tea consumption using block randomization. This was done in two strata high COMT activity (G/G genotype) and low COMT activity (A/G and A/A genotype). Inclusion criteria: 50–70 years old; generally healthy postmenopausal women; heterogeneously (51–75% glandular) or extremely (&gt;75% glandular) dense breasts; planning to reside in or near Minnesota for study duration; willingness to give written informed consent. Exclusion criteria: Regular green tea intake (i.e. more than one cup per week); Hepatitis B or C viral infection indicated by the presence of hepatitis B surface antigen or antibodies to hepatitis C virus, respectively. Elevated liver enzymes level &gt; 1.5 times the upper limit of normal; Current or prior (within last 6 months) use of hormone therapy, including systemic postmenopausal hormone therapy (such as oral pills, patch, or gel), chemopreventive agents such as selective estrogen receptor modulators (tamoxifen, raloxifene) or aromatase inhibitors. Previous diagnosis of breast cancer, proliferative breast disease, or ovarian cancer; history of any other malignancy in the past 5 years (apart from non-melanoma skin cancer); presence of breast implants; currently taking methotrexate or etanercept; BMI &lt;18.5 or &gt;40 kg/m²; Ongoing enrollment in a weight loss or weight gain program; Weight change &gt; 10 lb during the previous year; Alcohol intake &gt;7 drinks per week; Current smoker of cigarettes or other tobacco products.</td>
<td>Decaffeinated Green Tea Extract Catechin Complex (GTE). Mean daily catechin content was 1315±164 mg (843 ± 44 mg as EGCG), which is approximately equivalent to five 240-mL servings of brewed green tea (30). GTE ingredients were analyzed by HPLC to demonstrate comparability with the stated catechin contents of the manufacturer. 2 Capsules were ingested twice daily. Comparison: Placebo capsules were supplied by Corban Laboratories, which also provided the GTE capsules. Placebo capsules were identical in appearance to GTE and contained 816 mg maltodextrin, 808 mg cellulose, and 8 mg magnesium stearate (flow agent). 2 Capsules were ingested twice daily for 12 months.</td>
</tr>
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Primary evidence: Anthropometric and body-composition measurements.

BMD: BMD was calculated by dividing weight in kilograms by height in meters squared (kg/m²).

DXA: DXA scans were completed at the University of Minnesota’s Delaware Clinical Research Unit by using a GE Healthcare Lunar IDXA (GE Healthcare) and analyzed with the use of Encore software version 13.6, revision 2. Body fat: Total body fat was expressed as the percentage of total body mass, and android and gynoid fat were expressed as the percentage of total body fat. Subcutaneous fat was determined by using an algorithm and measurements of total abdominal thickness and the width of the subcutaneous fat layer along the lateral extent of the abdomen along with empirically derived geometric constants to estimate the subcutaneous fat in the android and gynoid region. Visceral adipose tissue (VAT) was determined in the android region by subtracting subcutaneous fat from total fat. Tissue percentage fat was calculated as follows: fat mass/(total mass - BMC). The android region was defined as the caudal limit placed at the top of the iliac crest and its height set to 20% of the distance from the top of the iliac crest to the base of the skull. The upper limit of the gynoid region was set below the iliac crest a distance 1.5 times the height of the android region. The lower limit was set a distance of 2 times the height of the android region. Central fat distribution was assessed by the android/gynoid fat ratio, calculated as android fat divided by gynoid fat.

BMD: Areal BMD was expressed as grams per centimeters squared (g/cm²). T-scores were expressed in SDs by using the peak bone mass from the manufacturer's reference population. Z-scores were measured as the deviation from the normal age- and sex-matched means and SDs. Osteoporosis was diagnosed in accordance with the WHO definition, as a T-score of less than 2.5 as assessed by DXA; osteopenia was diagnosed as BMD of 21.0 to 22.5.

Secondary evidence: Obesity-associated hormone quantification:
Blood samples for obesity-associated hormone and glucose assessment were collected at the prespecified time points of baseline and month 12, in female participants, and the equivalent time point was used in male participants, to correspond with the scheduled annual DXA scan, after an overnight fast of >10 h. Plasma leptin, adiponectin, and ghrelin were measured using liquid chromatography-mass spectrometry mass spectrometry (LC-MS/MS). Adiponectin was measured by using a multiplex immunoassay method. Concentrations were calculated and expressed as percentage changes from baseline to month 12.

Results: There were no differences in changes in BMI (-0.13±0.11 kg/m²) with -0.05±0.11 kg/m² (P=0.61), total fat mass (-0.30±0.16 kg) with -0.12±0.15 kg; P=0.40), percentage of body fat (-0.15±0.17% compared with -0.15±0.16% (P=0.99), or BMC (0.05±0.02 compared with -0.03±0.02 g/cm²; P=0.49) over 12 mo between women taking GTE (n=61) and those taking a placebo (n=60).

Interactions were observed between treatment and time for gynoid percentage of fat (%fat) and tissue %fat. Gynoid %fat increased from baseline to month 12 in the placebo group as baseline BMI increased and decreased over time as baseline BMI increased in the GTE group (P-interaction=0.02). Tissue %fat increased from baseline to month 12 in the placebo group as baseline BMI increased. In the GTE group, tissue %fat decreased during the intervention as baseline BMI increased (P-interaction = 0.04). No changes were seen in circulating leptin, ghrelin, adiponectin, or insulin concentrations. COMT genotype did not modify the effect of GTE on any variable.
6 of 14 RCT also included in Rijksa et al. 2015.
Search in "Bone Errors of Metabolism Trial Register" (Compiled from CENTRAL, MEDLINE and handsearch of Journal of Inherited Metabolic Disease. Inclusion of conference abstracts for unpublished trials.
No investigation of publication bias.

Author's conclusion: Implications for practice:
The results from the included trials provide evidence, for statistically significant improvement in BMD in individuals affected withOI when treated with either oral or IV bisphosphonates. It remains to be seen whether this increase in BMD is a surrogate marker for fracture reduction and clinical functional improvement. At this time, comparative data remains inconclusive though several trials reported here individually show improvements in fracture incidence. Additionally, the long-term safety of bisphosphonates in OI, particularly when used in children, and the risk of bisphosphonates to cause atypical femur fractures, impair perioperative or fracture bone healing (or both), as well as increased bone density if unmonitored, have not been sufficiently evaluated. The durations of use once BMDs improved require thoughtful study.

Effects of bisphosphonates on growth, bone deformity, mobility, and pain have been reviewed but absolute benefits remain inconclusive.

### Outcome Measures/results

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<td>2. Change in BMD as assessed byDEXA</td>
<td>2. Growth (z-scores; vertebral heights)</td>
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<td>Bone pain (as assessed by self-reported questionnaires of pain and analgesic use)</td>
<td>4. Quality of life (e.g., functional changes in mobility, strength, well-being and completion of activities of daily living (ADLs))</td>
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**Results:** Oral bisphosphonates compared to placebo or no treatment control group: 6 trials included. Fracture incidence: 1 trial with Hazard ratio = 0.69 (95% CI 0.52, 0.91); 1 trial with HR = 0.58 (95% CI: 0.37, 0.92) (P = 0.0416) at 12 months in favour of oral risendronate. Change in BMD as assessed by DEXA: 3 studies reported significant difference at 2 years MD = 17.31 (95% CI 5.01, 29.62; P = 0.0058); considerable heterogeneity I² = 77%. Change in biochemical markers of bone and mineral metabolism and bone histology: No significant changes in most studies reported. No pooling possible. Growth: Inconclusive results from 5 trials. No pooling possible. Bone pain: 1 trial in pain scores 1 trial with statistically significant difference in baseline and analgesic use at 12 months, MD = -3.63 (95% CI: -5.17, -2.09) and MD = -2.00 (95% CI: -3.57, -0.43). Non-significant changes in the other trials. Quality of life: 1 trial with statistically significant increase in well-being as assessed by scored participant recall, MD = 3.19 (95% CI: 2.25, 4.13) and non-significant changes in the other trials. Lung function: Not reported in included trials.

**IV Bisphosphonates compared to placebo or no treatment control group:** 3 trials included. Change in BMD as assessed by DEXA: Pooled analysis of 2 studies for spine BMD at 6 months = MD 9.96 (95% CI -2.51, 22.40) (P = 0.095) at 12 months = MD 14.68 (95% CI: -6.08, 35.45) (I² = 95%). 1 trial investigated mean per cent change in spine BMD z score: statistically significant increases with IV pamidronate at six months, MD = 21.59 (95% CI: 5.79, 37.39) and 12 months, MD = 25.60 (95% CI: 11.48 to 39.72). Change in biochemical markers of bone and mineral metabolism and bone histology: Changes narratively reported in 2 trials. Growth: Reported in 1 trial with no significant changes. Bone pain: Reported in 1 trial with no significant changes. Quality of life: Reported in 1 trial with no significant changes. Lung function: Not reported in included trials.

**Oral versus IV bisphosphonates:** 1 trial included with no statistically significant effects on any outcome.

**Different doses of oral or IV bisphosphonates:** 2 trials included. Fracture incidence: No statistically significant effect in included trials. Change in BMD as assessed by DEXA: 1 trial with statistically significant difference in lumbar spine z score BMD adjusting for baseline value of each outcome and age when comparing 0.2 mg/kg vs 3 mg/kg, difference: MD -1.18 (95% CI: -1.86, -0.50) in one dose group and 0.2 mg/kg/week vs 3 mg/kg/week Change in biochemical markers of bone and mineral metabolism and bone histology: In 1 trial declined mean (SD) serum bone specific ALP from 235 (49) IU/l at baseline to 170 (48) IU/l at 12 months. NTx declined from 2089 (1612) to 551 (120) nmol BCE/mmol creatinine over the same period. In the other study, bone specific alkaline phosphatase activity declined by 1% from 81 ± 28 to 80 ± 39 IU/l and NTx by 21% from 2575 ± 1618 to 2044 ± 1031 nmol/mmol BCE (maximum decline for any child 70%) over 2 year period. Growth: No statistically significant changes. Bone pain: Reported in 1 trial with no significant changes. Quality of life: Reported in 1 trial with no significant changes. Lung function: Not reported in included trials.

**IV versus IV bisphosphonates:** 2 trials included. Fracture incidence: 1 trial without statistically significant effects and 1 trial with significant effects but presented no data apart from P-value (P=0.025 and P=0.048). Change in BMD as assessed by DEXA: The zoledronic trial reported statistically significant change in lumbar spine BMD, MD 8.06 (95% CI: 0.48, 15.64) favouring zoledronic acid. The other trial appears to favour pamidronate in the analysis, MD=1.50 (95% CI: -2.86, -0.14) but trial report indicates that compared with the pamidronate group, the zoledronic acid group had significant increase in lumbar spine z score at one year (P = 0.053). Change in biochemical markers of bone and mineral metabolism and bone histology: 1 trial with statistically significant reduction in CTx, P1NP and BSALP in the zoledronic group compared to the pamidronate group at both six and 12 months. Growth: No statistically significant changes. Bone pain: Reported in 1 trial with no significant changes. Quality of life: Not reported. Lung function: Not reported in included trials.
Evidence level: 1- Study type: Double-blind, randomized, placebo-controlled multicenter trial.

Countries: The Netherlands.
Centres: 3 Centers: VUmc, Wageningen UR, Erasmus MC.
Setting: n.a.

Funding sources: B-PROOF is supported and funded by The Netherlands Organization for Health Research and Development (ZonMw, Grant 6130.0031), the Hague; unrestricted grant from NZO (Dutch Dairy Association), Zoetermeer; Orthica, Almelo; NCHA (Netherlands Consortium Healthy Ageing) Leiden/Rotterdam; Ministry of Economic Affairs, Agriculture and Innovation (Project KB-15-004-003), the Hague; Wageningen University; VU University Medical Center, Amsterdam; Erasmus Medical Center, Rotterdam. All organizations are based in the Netherlands. The sponsors do not have any role in the design or implementation of the study, data collection, data management, data analysis, data interpretation, or in the preparation, review, or approval of the manuscript.

Dropout rates: Controls: 308 out of 1458 randomized (21%); Intervention: 335 out of 1461 randomized (23%).

Study limitations: It could be regarded as a limitation that baseline values of BMD in this randomized controlled trial differed significantly between the intervention and placebo group. However, we adjusted for baseline BMI, and therefore we assume that this did not influence the results of the analyses.

Another limitation of the study is the fact that all participants received 600 IU vitamin D daily, which is in line with the guidelines of the Dutch Health Council. In the past, vitamin D supplementation with 400 IU daily has been shown to influence BMD up to 2.6%. Effects of vitamin D may therefore have masked the possibly small effects of vitamin B12 and folic acid on BMD.

Notes: Randomization sequence is not specified. Concealment is not described. The baseline characteristics were significantly different between the two groups regarding lumbar spine BMD (primary outcome). The study centers used different machines, known to yield unequal results. ITT analysis data is not shown - the authors claim it is not different from the results of the per-protocol analysis.

Author's conclusion: In conclusion, this study showed no overall effect of treatment with vitamin B12 and folic acid on BMD or QUS parameters in elderly, mildly hyperhomocysteinemic persons, but suggests a small beneficial effect on BUA in persons >80 years who were compliant in taking the supplement.

Results: After 2 years, FN-BMD and BUA had significantly increased, while LS-BMD significantly decreased (all p < 0.01) and SOS did not change in either treatment arm.

No statistically significant differences between the four groups (p = 0.34). FN-BMD (p = 0.24), BS-BMD (p = 0.16), SOS (p = 0.18), and BUA (p = 0.96). However, exploratory subgroup analyses showed a positive effect of the intervention on BUA at follow-up among compliant persons >80 years (estimated marginal mean 64.4 dB/MHz for the intervention group and 61.0 dB/MHz for the placebo group, p = 0.04 for difference).

Evidence level: 2+ Study type: Systematic review and meta-analysis: 21 observational studies.

participants were mainly from Europe and America; therefore, our findings may not be applicable to other broader populations.

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<tr>
<td>Notes:</td>
<td>No use of Mesh terms and incomplete reporting of search strategy. All analyses display high and significant Heterogeneity. ($I^2=97%$ for the main result; or $92$ and $86%$ if diabetes types are investigated in subgroups). This should have consequences, i.e. investigation of heterogeneity, exclusion of studies or refraining from meta-analysis. The results should be interpreted with caution due to substantial differences between individual studies.</td>
<td><strong>Author’s conclusion:</strong> Individuals with diabetes mellitus have an excessive risk of hip fractures compared with non-diabetes. Moreover, the increased risks are higher in type 1 diabetes. The association between diabetes and hip fracture risk is similar in men and women. Targeted hip fracture prevention in diabetic populations is likely to yield considerable benefits.</td>
</tr>
<tr>
<td><strong>Outcome Measures/results</strong></td>
<td><strong>Primary</strong> Hip fractures: RR between diabetic and non-diabetics (OR was treated as RR in case control studies). Subgroup analysis for type of diabetes (where</td>
<td><strong>Results:</strong> Diabetes mellitus was associated with an increased risk of hip fractures (RR 2.07; 95% CI 1.83–2.33) in a random effects model. Subgroup analysis indicated that excess risk of hip fracture was more pronounced in type 1 diabetes (RR 5.76; 95% CI 3.66–9.07) than that in type 2 diabetes (RR 1.34; 95% CI 1.19–1.51). The pooled female-</td>
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</table>

**Evidence level: 1- Study type: RCT**

Countries: Germany, Greece, Italy, Spain

Centres: 16 centers

Setting: Not reported

Dropout rates: 15 patients discontinued the study prematurely.

7 patients (15.6%; 2 deaths, 1 protocol violation, 4 patient decision) in teriparatide group; 8 (17.0%; 1 death, 2 patient decision, 3 Adverse events, 2 lost to follow-up) in risedronate group.

**Study limitations:** Analysis restricted to only one vertebra (T12), but vertebral strength may vary along the spine.

- FE analysis assumes that bone tissue properties are constant for all patients during longitudinal treatment.
- Duration of treatment was for 18 months only and limited sample size.

**Interventions:** Fasting blood samples (10 ml), prepared as serum samples. High resolution quantitative HRQCT (HRQCT protocol)

**Inclusion criteria:** Ambulatory men 25 years of age and older presenting to Visit 1 with a bone mineral density (BMD) of at least 1.5 standard deviation (SD) below the corresponding normal young adult men average BMD (T score of -1.5 or lower), as determined from the manufacturer's database at any of the following regions of interest: total hip, femoral neck, or lumbar spine.

- Have received glucocorticoid therapy at an average dose of at least 5.0 milligrams (mg) per day of prednisone or its equivalent for a minimum of 3 consecutive months immediately preceding screening (Visit 1), as determined by medical history.
- A minimum of 2 lumbar vertebrae (L) in the L-1 through L-3 region must be evaluable by quantitative computerized tomography.
- Normal or clinically insignificant abnormal laboratory values (as determined by the investigator) including serum calcium, parathyroid hormone (PTH) (1 84), and 25 hydroxyvitamin D concentrations, and alkaline phosphatase activity.

**Exclusion criteria:** Presence of a mild, moderate, or severe spinal fracture in both the twelfth thoracic vertebra (T-12) and first lumbar vertebra (L-1), as determined by the central reading facility using the semiquantitative technique.

- Abnormal albumin-corrected serum calcium levels,
- History of unresolved skeletal diseases that affect bone metabolism other than glucocorticoid-induced osteoporosis,
- History of malignant neoplasms in the 5 years prior to Visit 2, with the exception of superficial basal cell or squamous cell carcinomas of the skin that have been definitively treated, increased baseline risk of osteosarcoma; this includes patients with Paget's disease of the bone, previous primary skeletal malignancy, or skeletal exposure to therapeutic irradiation.
- Abnormal thyroid function not corrected by therapy.
- Past and/or current treatment with certain medications.

Pre-planned analyses of cohorts from a RCT on teriparatide vs risedronate. Randomisation is mentioned but method not specified (nor in trial registry). No concealment method described. Study could have been completely blinded, but was restricted to investigators. No test for baseline differences between groups described. Differences reported regarding frequency of Anti-TNF therapy. Unclear, if distribution of GC-requiring disorders varied significantly between groups (e.g. 5 cases [8.6%] of Crohn’s Disease in Teriparatide group and 11 cases [21.2%] in Risedronate group).

Subjects are not analysed in the groups to which they were randomly allocated (ITT). Unclear, which study participants are included in this analyses (38 patients in the teriparatide and 39 in the risedronate group completed the 18-month treatment duration, but n for teriparatide ranges from 25-36 patients, in risedronate from 31-37 patients).

No site specific data is given - unclear, if data from 16 centers were comparable.

**Author’s conclusion:** In conclusion, teriparatide at 20 μg/day demonstrated superior efficacy compared to risedronate 35 mg/week in the effects on biomechanical indices estimated by HRQCT-based FEA at the 12th thoracic vertebra in male patients with GIO. The changes from baseline in PINP revealed significant positive correlations with the changes in vertebral strength in all the loading modes at 18 months in the teriparatide group only. Changes in serum CTX showed fewer correlations. Serial spine QCT involves exposure to significant levels of radiation and considerable costs, which will limit its widespread use in normal clinical practice as an indicator of vertebral bone strength. Because bone strength estimated using this method was correlated significantly with serum levels of the bone formation marker PINP during teriparatide treatment, this suggests that monitoring of PINP may be clinically useful as a surrogate marker of biomechanical properties in GIO patients treated with teriparatide, but further studies with larger study populations and correlations with fracture outcomes are needed.

**Outcome Measures/results**

**Primary** Bone marker changes: Serum concentrations of PINP (by InTact UniQ RIA assay, Orion Diagnostica, Espoo, Finland) and C-terminal cross-linked telopeptides of type I collagen (CTX, by Serum Crosslaps® ELISA, Nordic Bioscience Diagnostics, Herlev, Denmark) measured at baseline and at 3, 6, 12 and 18 months of treatment.

**Secondary** Bone strength: CT scans performed at baseline and at 6 and 18 months of treatment. Thin

**Results:** Bone turnover markers: Significant differences between treatments at 3, 6 and 18 months of therapy in the teriparatide and risedronate groups (p=0.001) with exception of CTx at month 18 (p=0.105). No further quantified. Changes in FEA variables during treatment: Significantly stronger increases in teriparatide group vs risedronate group after 18 months in Anterior bending (kN mm): Mean (SD) = 140.2 (58.8) vs. 112.8 (40.8), p = 0.012; Axial compression (kN): Mean (SD) = 7.08 (3.48) vs. 5.95 (2.2), p = 0.015; Axial torsion (kN mm): Mean (SD) = 71.0 (31.8) vs. 58.2 (19.2), p = 0.005. Normalised axial compression strength (N/mm²): Mean (SD) = 6.13
slices spiral CT of 12th thoracic vertebra (T12). If T12 was fractured, HRQCT performed on intact L1 vertebra. 2 images reconstructed (1st with FOV, 2nd as complete vertebral body segmented using semi-automated algorithm). HRQCT-based FEA used to estimate the effects of treatment on bone strength and stiffness at T12 using the technique described by Graef et al.

2.39 vs. 5.38 (20.8), p = 0.021.

Correlations between changes in BMD and changes in FEA variables: Significant positive correlations between change in PINP at 3, 6 and 18 months with changes in finite element strength and stiffness in all loading modes at 18 months (anterior bending, axial compression, and axial torsion) and in change in normalized axial compression strength in teriparatide group (r=0.422 to r=0.563). No significant differences in risedronate group stated (Table 2; p-values not shown).


Evidence level 1=

Study type: MA of 20 RCTs


Patient characteristics

Total no. patients: 1.422 patients

Patient characteristics: Included patients were restricted to RA in 5 trials. Average age of patients more than 50 years in 14 trials, younger than 50 years in 6 trials. 16 prevention trials (starting BPs treatment in the first three months of GC therapy); 11 treatment trials (BPs given for long-term GC user; mean dosage of GC consumption greater than 7.5 mg/day [prednisone equivalent] in 6 trials) less than 7.5 mg/day in 5 trials. No GC usage in 1 trial.

Calcium + vitamin D given to patients in 10 trials, only calcium in 5 trials and only placebo in 5 trials.

Inclusion criteria: (1) Type of study: Only RCTs were selected for further assessment because observational studies are more likely to have confounding bias. Trials focusing on the comparison of different BPs, or between BPs and denosumab or teriparatide were not included.

(2) Participants: Only ambulatory rheumatic patients older than 18 years were included, regardless of gender and menopausal status.

(3) Intervention: The intervention was the use of any generation of BPs, alone or together with calcium and/or vitamin D, irrespective of administered approach. The intervention in control group was placebo, alone or together with calcium, vitamin D, and calcitonic.

(4) Outcomes: Incidence of vertebral and non-vertebral fractures was collected as the primary outcome. Percent change of BMD measured by dual-energy X-ray absorptiometry (DXA) at lumbar spine, total hip and femoral neck at 6, 12, 24, and 36 months were the secondary outcome.

Exclusion criteria: -

Setting: No patients from “countries” were included.

Funding sources: No current external funding sources for this study.

Dropout rates: Not stated.

Study limitations: - Relatively small sample sizes
- No investigation regarding change of biochemical markers of bone turnover
- No investigation of efficacy of special BPs in treating osteoporosis in rheumatic patients.
- Only one trial enrolling rheumatic patients without GC treatment.
- Conclusion may be relatively restricted to rheumatic patients who did receive glucocorticoid treatment.

Notes: Process of study selection not described (unclear if performed by 2 people). Quality assessed with Jadad: 2 trials scored 5 points (high quality), 6 scored 4 points, 5 trials scored 3 points, 5 trials scored 2 points, 2 trials scored 1 point (low quality). P-value of less than 0.05 stated as requirement for statistical significance but later results with P-value of 0.05 interpreted as statistical significant.

Analyzes on Adverse Reactions futile: Calculated on basis of Fixed-Effects-Model despite significant heterogeneity and despite earlier determination of using Random-Effects-Model in this case.

Significant more withdrawals due to side effects in BPs group ignored in conclusion and only presented in supplement.

Author’s conclusion: In both short- and middle-term therapy, BPs are effective agents in preserving bone mass from loss for patients with rheumatic diseases, mainly for those who have GC consumption. BPs can prevent bone loss at both lumbar spine and hip, and can further reduce the risk of vertebral fractures. Moreover, the efficacy of BPs is better when using BPs to prevent rather than to treat osteoporosis in rheumatic patients. There is, however, no robust evidence to suggest that BPs can prevent non-vertebral fractures and that continuing therapy is better than intermittent therapy. RCTs of large sample size trials with long-term follow-up are needed to further determine the efficacy and optimal usage of BPs in managing osteoporosis in patients with rheumatic diseases.
Outcome: 4 trials with n = 386 with data at 36 months: WMD = 5.87% (95% CI; 4.59, 7.15, P < 0.001). No significant heterogeneity. Hip BMD: 4 trials with n = 449 with data at 6 months: WMD = 0.81% (95% CI; 0.22, 1.39, P < 0.01); No significant heterogeneity: 7 trials with n = 716 with data at 12 months: WMD = 2.23% (95% CI; 1.29, 3.17, P < 0.001); Substantial heterogeneity (x² = 21.68 df = 6, P = 0.001, I² = 72%); 2 trials with n = 221 with data at 24 months: WMD = 5.9% (95% CI; 5.31, 6.19, P < 0.001); No significant heterogeneity. 1 trial with n = 144 with data at 36 months: WMD = 7.48% (95% CI; 7.14, 7.82, P < 0.001). No significant heterogeneity. Femur Neck BMD: 6 trials with n = 529 with data at 6 months: WMD = 1.36% (95% CI; 0.74, 1.99, P < 0.01); No significant heterogeneity. 10 trials with n = 715 with data at 12 months: WMD = 2.46% (95% CI; 1.75, 3.18, P < 0.01); No significant heterogeneity. 4 trials with n = 281 with data at 24 months: WMD = 3.58% (95% CI; 2.59, 4.69, P < 0.01); Substantial heterogeneity (x² = 10.6, df = 3, P = 0.01, I² = 72%); 2 trial with n = 158 with data at 36 months: WMD = 4.15% (95% CI; -0.38, 8.67, P = 0.07). Substantial heterogeneity (x² = 4.15 df = 1, P = 0.04, I² = 76%).

Adverse Reaction: Incidence of adverse events not different between BPs group and control group. RR = 1.02 (95% CI; 0.85, 1.22, P = 0.87). Calculated on basis of Fixed-Effects-Model despite significant heterogeneity (x² = 18.19, df = 7, P = 0.01, I² = 62%) and despite earlier determination of using Random-Effects-Model when heterogeneity greater than 50%. Significant more withdrawals due to side effects in BPs group relative to control group: RR = 1.44 (95% CI; 1.05, 1.97, P = 0.02).


Evidence level | Study details/limitations | Patient characteristics | Interventions |
--- | --- | --- | ---
Evidence level: 2+ | Countries: 7 Asia/ Middle East, 3 North America, 3 Europe | Total no. patients: 68,973 adult People with epilepsy | Interventions: |
Study type: SR of 13 studies | Centres: N.r. | Patient characteristics: 2 studies only available as conference abstracts with limited information on study participants. |
studies | Setting: N.r. | 2 studies performed in females only, 9 studies with patients of male and female sex, unclear in 2 studies. |
case-control study, 1 nested case-control study | Funding sources: “This study received no sponsorship or funding”. | Review includes 35.365 males, 32.016 females and 1.592 persons of not-specified sex. |
Included studies: Espinoza et al. (2011) | Dropout rates: N.r. | Mean age ranged from 25 to 76 years. |
Fuleihan et al. (2008) | Study limitations: - Studies inconsistent in their categorization of topiramate as an EIAED or a non-EIAED. - Possibility of publication bias: 75% of relevant conference abstracts vs 54% of published papers were negative studies; i.e., showing no differences in BMD or fracture incidence for EIAEDs compared to non-EIAEDs. - Most of identified studies were of poor methodological quality and failed to control for important fracture risk factors between groups. - Over half of included studies were cross sectional analyses. | Duration of anti-epileptic drugs (AEDs) use ranging from 1 to 36 years. |
Heo et al. (2011) | | Inclusion criteria: - Epilepsy defined as disorder of recurrent seizures (partial or generalized) requiring ongoing AED therapy. |
Nicholas et al. (2013) | | - All comparatives studies of PWE on an EIAED. |
Pack et al. (2008) | | - Participants of any age or sex, diagnosed with epilepsy, who were prescribed an enzyme-inducing anti-epileptic drugs (EIAED, including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, or topiramate) for at least one year. |
Phabphal et al. (2009) | | Exclusion criteria: Studies without a comparison group taking a non-EIAED (for at least one year). |
Phabphal et al. (2013) | | Extensive search for unpublished/ grey literature mentioned in "Discussion" but no search in trial registry database described. Quality Score from NOS categorized in poor, moderate and high quality and reported in these categories on study level. |
Salimpour et al. (2013) | | Publication Bias not investigated. |
Sato et al. (2001) | | Author’s conclusion: The literature is divided regarding the bone effects of EIAEDs; however, current best evidence supports an increased fracture risk in PWE treated with an EIAED compared to those treated with non-EIAEDs. A single article dominated our review, and other large methodologically rigorous studies are needed to confirm or refute its results. Further small studies, with limited power to control for multiple potentially confounding variables, are not likely to help. |
Sivaraaman and Jacobson (2009) | | Outcome Measures/results |
Srourvein et al. (2006b) | | Primary Fracture (at any bone site) and change in BMD (at any site). |
Srivastava and Jain (2001) | | Secondary Mortality, seizure control, and reported adverse events. |
Stephen et al. (1999) | | Results: BMD: 10 studies included. 5 studies with decreased (or decreasing) BMD values in PWE on EIAEDs compared to non-EIAEDs and 5 studies without effect. Fractures: 3 studies included. No difference in fractures was identified between EIAED and non-EIAED users in 2 studies. 1 study found EIAEDs to be associated with more fractures than non-EIAEDs in females (adjusted hazard ratio [HR] for all fracture sites: 1.22, 95% CI; 1.12, 1.34 and HR for hip fractures: 1.49, 95% CI; 1.15, 1.94). Secondary outcomes: Insufficient data available to report on effects of EIAEDs |

Notes: Extensive search for unpublished/ grey literature mentioned in "Discussion" but no search in trial registry database described. Quality Score from NOS categorized in poor, moderate and high quality and reported in these categories on study level. Publication Bias not investigated.

Author’s conclusion: The literature is divided regarding the bone effects of EIAEDs; however, current best evidence supports an increased fracture risk in PWE treated with an EIAED compared to those treated with non-EIAEDs. A single article dominated our review, and other large methodologically rigorous studies are needed to confirm or refute its results. Further small studies, with limited power to control for multiple potentially confounding variables, are not likely to help.
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<tr>
<th>Evidence level: 1- Study type: RCT</th>
<th>Evidence details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
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<tr>
<td>Countries: Australia</td>
<td>Concord Hospital secondary</td>
<td>Majority of participants were female (88.9% in group A and 79.6% in Group B). Approximately half of subjects in both groups had sustained a minimal trauma fracture prior to the fracture that led to inclusion into the current study (“index fracture”). Time from the index fracture to first clinic visit, major risk factors for osteoporosis, body weight and BMI, bone mineral density at any site, socioeconomic status (RSAD) and ethnicity similar between groups. Proportion of subjects currently consuming alcohol lower, and mean uDPD/cr ratio higher in group A compared to group B.</td>
<td>Patients were prescribed oral weekly bisphosphonate therapy in the form of either risedronate 35 mg or alendronate 70 mg. If required, patients were also given calcium (600–1,200 mg/day) and vitamin D supplements (1,000 IU/day). Therapy with oral bisphosphonates was subsidised in all patients under the auspices of PBS.</td>
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<tr>
<td>Centres: Concord Hospital</td>
<td>secondary fracture prevention (SFP) program</td>
<td>Inclusion criteria: Men and women aged 45 years and over who had sustained a symptomatic fracture due to minimal trauma (defined as a fall from a standing height or lesser impact). Exclusion criteria: Patients excluded if: they were unable to provide informed consent, resided in a nursing home or hostel at the time of the incident fracture, had a life expectancy of less than 3 years, did not have a local medical practitioner, had malignant or metabolic bone disease, were diagnosed with gastrointestinal malabsorption syndromes or had contra-indications to oral anti-resorptive therapy.</td>
<td>Group A: Continued management by specialist SFP service at Concord Hospital, with clinic visits at baseline and at 3, 6, 12, 18 and 24 months. Group B: Seen by SFP service at baseline and again at 3 months but then managed by their primary care physician until a final study visit at 24 months post-randomisation.</td>
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<tr>
<td>Setting: Not reported.</td>
<td>Funding sources: Not reported.</td>
<td>Dropout rates: Group A (Specialist service): 10/45 (22.2%) Group B (Primary Care Physician management): 10/49 (20.4%)</td>
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<td>Study limitations: - Dropout rate over 2 years was 24 %. Whilst this number seems comparable to dropout rates in other randomised trials and was equal between groups A and B, it clearly has affected the power of the study. - At least a 40 % improvement in compliance and persistence in group A compared to group B expected. At study end, it was surprising to see that the difference between groups A and B was much smaller than expected. Thus, although our study may have been inadequately powered to detect smaller differences between groups, the results still indicate that treatment initiation should be the primary role of SFP programs. - Potential for self-selection bias in that patients who consented to be randomised may have been more compliant and persistent, although this bias would affect both arms of the study equally. - Any analysis of claims data assumes that patients take the medication after dispensing. However, it is unlikely that patients who regularly collect their medication and are obliged to make certain co-payments would then not use the drug.</td>
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<td>Notes: Simple randomisation sequence generation (coin flip). No allocation concealment described. Data analyst could have been blinded but not. Exclusion criteria &quot;metabolic bone disease&quot; contradicting with secondary fracture prevention in bisphosphonate users. 4 participants in each group excluded from ITT analyses after randomisation because they had incomplete Australian Pharmaceutical Benefits Scheme (PBS) data (no true ITT).</td>
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<td>Author's conclusion: Compliance and persistence to oral bisphosphonate therapy remain high amongst patients initiated within an SFP program, with community-based and SFP program management being equally effective in maintaining therapeutic compliance and persistence over 2 years. These results indicate that one of the main functions of an SFP program may be the initiation of therapy rather than continuous patient monitoring.</td>
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<tr>
<td>Outcome Measures/results</td>
<td>Results: Compliance: Median medication possession ratio at 24 months 0.78 (IQR, 0.50–0.93) in group A and 0.79 (IQR, 0.48–0.96) in group B (p=0.68). Adjusted OR: 1.06 (95% CI; 0.46, 2.47), p = 0.89. Persistence: Adjusted time to non-persistence at 24 months: 0.71 (95% CI; 0.29, 1.76), p = 0.46. Time-based changes in BMD, bone turnover or self-reported compliance were not associated with compliance or persistence.</td>
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<td>Primary Patient compliance at 24 months measured by calculating medication possession ratio (MPR). Persistence defined as the number of days a patient was in possession of a medication to the first gap in therapy of greater than 90 days after completion of the previous refill. Both assessed by PBS data.</td>
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<td>Secondary Changes in bone mineral density and bone turnover markers, self-reported compliance.</td>
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<tr>
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<td>Centres:</td>
<td>Centers for Medicare and Medicaid Services</td>
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<tr>
<td>Setting:</td>
<td>Services provided by physicians across patient and outpatient settings, and other non-institutional providers including physician assistants, clinical social workers, nurse practitioners, independent clinical laboratories, ambulance providers, and stand-alone ambulatory surgical centers.</td>
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</tr>
<tr>
<td>Funding sources:</td>
<td>This study was funded by Contract No. HHSM-500-2011-00012.</td>
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<tr>
<td>Dropout rates:</td>
<td>N/R</td>
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<td>Study limitations:</td>
<td>- Limitations resulting from a nonrandomized study design: self-selecting to enroll in MOB may have differed from controls in their baseline characteristics, behaviors, or abilities to participate in MOB. Retrospective data collected for administrative purposes may not contain all important differences between participant and control populations. Selection bias may have thus influenced the results.</td>
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<tr>
<td>Outcome Measures/results:</td>
<td>Outcome Measures: Medical costs, health service utilization, physical therapy use, and falls or fall-related fractures in the year after program enrollment. All cost measures included Medicare payments, secondary payer costs, and beneficiary liabilities. Health service utilization categories: planned hospitalizations, unplanned hospitalizations, outpatient emergency department use, and physician office services, all measured as the average number of visits or admissions per person. Physical therapy (PT) measured in terms of percentage of beneficiaries with any PT visits, and average number of total PT visits per beneficiary. Effects of incidence of falls or fall-related fractures in year after program participation.</td>
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<tr>
<td>Results:</td>
<td>MOB participation associated with total medical cost savings of $938 per person (95% CI; $379, $1,496) at 1 year. Savings per person amounted to $1,187 (95% CI; $265, $2,396) for unplanned hospitalizations; $281 for home health care (95% CI; $20, $141); $234 (95% CI; $55, $413) for skilled nursing facility care.</td>
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<tr>
<td>Interventions:</td>
<td>A Matter of Balance (MOB), an intervention aimed at reducing the fear of falling and increasing physical and social activity in older adults.</td>
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Notes: No discussion of possible assumptions that may have been made. Additional analysis for a subset of participants and controls who survived through the end of the follow-up period and for the impact of different levels of program exposure on total medical costs. Reasons for study design chosen not provided but resulting study limitations discussed. Author’s conclusion: This study suggests that MOB and similar prevention programs have the potential to reduce Medicare costs. Further research accounting for program delivery costs would help inform the development of Medicare-covered preventive measures.

| Evidence level: | 1 |
| Study type: | RCT |
| Countries: | Australia |
| Setting: | Community. |
| Funding sources: | This study was financially supported by a grant from the JO & JR Wigglesworth Trust, which is managed by ANZ Trustees. This project was under the auspices of Osteoporosis Australia and the Australian Institute, and the Australian Endocrine Society (ANZBMS). These are both charitable organizations that provide grants for medical research. RMD was supported by a National Health and Medical Research Council (NHMRC) Career Development Award (ID 425849). We thank the following for their support of the project: Arthritis Victoria; YMCA Victoria; Belgravia Leisure, and Brimbank City Councils. We also thank Blackmores for providing the calcium and vitamin D3 supplements used in this study and all the participants and exercise trainers who were involved in the study. |
| Dropout rates: | 5% in control group (6.2%) 7/81 in control group (8.6%) |
| Study limitations: | Not explicitly discussed. Points mentioned: - Reason for the lack of a significant net gain in total hip aBMD in our study is unclear. - Study not designed or powered to detect an effect of the Osteo-ps program on falls, but participants in Osteo-cise group tended to experience more falls than controls but there were no significant differences in fall rate between groups. Compliance with exercise program was modest, averaging 50% over the 12 months despite the use of established behavioral strategies to maximize adoption and adherence such as goal setting and self-monitoring. |
| Total no. patients: | 162 randomized, 150 analyzed (10%) |
| Patient characteristics: | Osteo-cise group: Women, n (%): 60 (74); Age (years): 67.7±6.5; Body mass index (kg/m²): 27.2±3.8; Current HRT use (%): 18.8. Control group: Women, n (%): 59 (73); Age (years): 67.2±5.5; Body mass index (kg/m²): 27.6±4.8; Current HRT use (%): 5.1. |
| Exclusion criteria: | Men and women aged 60 years and over living independently in the community in the Western suburbs and surrounding regions of Melbourne, Australia, and with a total hip, femoral neck or lumbar spine T-score between -1.0 and +2.5 standard deviations (SD) or classified as at increased risk for falls or fracture based on a questionnaire adapted from Sanders and colleagues. |
| Total no. patients: | 162 randomized, 150 analyzed (10%) |
| Patient characteristics: | Osteo-cise group: Women, n (%): 60 (74); Age (years): 67.7±6.5; Body mass index (kg/m²): 27.2±3.8; Current HRT use (%): 18.8. Control group: Women, n (%): 59 (73); Age (years): 67.2±5.5; Body mass index (kg/m²): 27.6±4.8; Current HRT use (%): 5.1. |
| Exclusion criteria: | Men and women aged 60 years or people who had a body mass index (BMI) >40 kg/m², had a history of osteoporosis or a recent (past 6 months) low trauma fracture, had participated in resistance training or a structured weight bearing exercise program more than once a week in the past 3 months, were current smokers, had any medical condition of used medication known to influence bone metabolism or fracture risk, had initiated calcium or vitamin D supplementation in the preceding 6 months, were expecting to travel for more than 6 weeks throughout the intervention, and, for women, were currently using or in the previous 6 months had used hormone replacement therapy (>0.625 mg/d). |
| Interventions: | - Control group: requested to continue their usual care and were provided with general consumer information about osteoporosis, available from Osteoporosis Australia (www.osteoporosis.org.au), to enable them to actively take charge of their own musculoskeletal health. - Osteo-cise group: Community-based multifaceted program “Osteo-cise: Strong Bones for Life” with 4 key components: (1) Osteo-cise: a multimodal targeted osteoporosis and falls prevention exercise program; (2) Osteo-Aid: behavioral change strategies designed to encourage adoption and maintenance of lifestyle exercise participation; (3) Osteo: Ed: a series of community-based osteoporosis education/awareness improving participants knowledge and understanding of osteoporosis risk factors, exercise, and nutrition so that they could actively take charge of their bone health; and (4) Osteo-Instruct: a “train the trainers” workshop designed to instruct the exercise trainers implementing the program on the aims and structure of the program and to update them on the latest osteoporosis prevention and management strategies. |
### Evidence level:
- **Study type:** RCT

### Countries:
- Germany, Greece, Italy, Spain
- CENTERS: 16 centers
- Setting: Not reported.

### Funding sources:
- This work was supported by Lilly Research Center, Europe. The EuroGIOPs study was funded by Lilly Research Center, Europe. (ClinicalTrials.gov identifier: NCT00503399).*

### Dropout rates:
- 15 patients discontinued the study prematurely.
  - 7 patients (15.6%); 2 deaths, 1 protocol violation, 4 patient decision in teriparatide group; 8 (17.0%); 1 death, 2 patient decision, 3 adverse events, 2 lost to follow-up in risedronate group.

### Study limitations:
- Number of valid post baseline HRQCT evaluations smaller compared with QCT analyzed cases due to more frequent violations of HRQCT scan protocol. Negative impact on statistical power to show differences between study groups in HRQCT structural variables.
- Bone tissue properties in FE analysis assumed to be constant for all patients and over the course of pharmacological treatment.
- Treatment modifies average level TMD, and fracture risk at a given level of BMD is higher for GIO compared to primary prevention of postmenopausal osteoporosis. Rapid onset of fractures after initiation of treatment and similarly rapid return to pretreatment levels of fracture risk after termination of treatment cannot be explained by changes in BMD alone. Magnitude of these effects remains unclear and further refinement of HRQCT may help to address this issue.
- Duration of treatment was for 18 months only. Longer treatment may offer more pronounced advantages.

### Study details/limitations
- **Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire:** Changes in BMD, Changes in body composition (Lumbar spine [L2-L4] and proximal femur aBMD [g/cm²], total body lean mass [kg] and fat mass [kg] assessed using DXA), muscle strength and functional performance (three repetition maximum [3 RM] testing, Timed Stair Climb Test, 30 Second Sit to Stand, Four Square Step Test, and the Timed Up and Go Test with a secondary cognitive task), Falls and fractures (monthly "falls calendar").

### Outcome Measures/results

<table>
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<tr>
<th>Primary Outcomes not defined as primary or secondary outcomes. In order of mention: Adherence (exercise cards completed by participants and checked regularly by trainers, tablet count for supplements)</th>
<th>Secondary Outcomes: (patient- and trainer-reported). Changes in physical activity and diet (by 24-hour food diary and weighed menu)</th>
</tr>
</thead>
</table>
| **Results:** Adherence: Mean±SD compliance to exercise program: 59%±32% (median 74%), equivalent to approx. 2 sessions/week. 23.5% of participants attended on average less than 1 session/week. 21.0% attended between 1.0 and 1.9 sessions, 55.5% attended 2 to 3 sessions per week. Mean compliance with calcium and vitamin D supplements similar in each group (calcium: Osteo-cise: 90.2%; controls: 89.9%; vitamin D: Osteo-cise: 93.2%; controls: 93.5%). Adverse events: 34 of 81 Osteo-cise participants reported 40 musculoskeletal complaints or injuries (63% in first 6 months). 6 participants withdrew from training as a result of their injury. Not reported for control group. Changes in physical activity and diet: No significant within group changes or between group differences for changes in total leisure time physical activity, participation in weight bearing exercise (outside of the intervention) or diet. Daily carbohydrate intake decreased in the Osteo-cise group significantly (214.1±105.0 g/day at baseline vs 192.6±87.4 g/day at 12 months) and was at the same level as in the control group (207.5±78.9 g/day at baseline vs 192.06±70.2 g/day at 12 months). Changes in BMD: After 12 months, significant 1.1% (95% CI: 0.3%, 2.0%; p<0.05) greater increase in lumbar spine aBMD in Osteo-cise group compared with controls. Significant 1.5% (95% CI: 0.8%, 2.1%; p<0.001) increase in aBMD in Osteo-cise group but no marked change in controls (0.3%, 95% CI, 0.3% to 1.0%). Significant 1.0% (95% CI: 0.2%, 1.9%; p<0.05) greater increase at femoral neck in aBMD in Osteo-cise group compared with controls, non-significant 0.6% (95% CI, 0.0% to 1.2%; p=0.06) increase in the Osteo-cise group and 0.4% (95% CI, 1.0% to 0.2%; p=0.21) non-significant loss in controls. No significant between group differences for changes in total hip aBMD. Changes in body composition, muscle strength, and functional performance: No significant changes in weight, total body lean mass or mass fat after 12 months in either group. Greater gain for leg and back muscle strength in Osteo-cise group compared to controls after 6 months (net difference: bilateral leg extension: 9.5%, 95% CI, 3.7% to 15.0%; seated row: 13.3%, 95% CI, 6.3% to 20.3%; both p<0.001). 4.5% (95% CI, 0.6% to 8.3%; p<0.05) greater gain in functional muscle power in Osteo-cise group compared with controls after 6 months, which persisted after 12 months (4.8%, 95% CI, 0.9% to 8.6%; p<0.05). Significant exercise-induced net gains after 6 months for 30 Second Sit to Stand (11.4%, 95% CI, 5.5% to 17.3%; p<0.001) and Four Square Step Test (5.6%; 95% CI, 0.9% to 10.3%; p<0.05). No significant group differences for Timed Up and Go Test after 6 or 12 months. Falls and fractures: No significant differences in falls incidence between groups or number of participants sustaining one or more falls or multiple falls. Over 12 months, 46 falls (in 29 participants) in the Osteo-cise group and 34 falls (in 25 participants) in control group.

### Patient characteristics

<table>
<thead>
<tr>
<th>Total no. patients: 92 patients randomized, 77 analyzed. Patient characteristics: Mean age: 56.3 years (range, 25–82 years).</th>
<th>Interventions: (a) a daily use of a subcutaneous injection of teriparatide 20 μg or (b) a daily use of a subcutaneous injection of risedronate 35mg or (c) a daily use of tablet once a day.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: - Ambulatory men 25 years of age and older presenting a bone density (BMD) of at least 1.5 standard deviation (SD) below the corresponding normal young adult male average BMD (T score of -1.5 or lower), as determined from the manufacturer's database at any of the following regions of interest: total hip, femoral neck, or lumbar spine. - Have received glucocorticoid therapy at an average dose of at least 5.0 milligrams (mg) per day of prednisone or its equivalent for a minimum of 3 months or 6 consecutive months immediately preceding screening (Visit 1), as determined by medical history. - A minimum of 2 lumbar vertebrae (L) in the L-1 through L-3 region must be evaluable by quantitative computed tomography. - Normal or clinically insignificant abnormal laboratory values (as determined by the investigator) including serum calcium, parathyroid hormone (PTH) (1-84).</td>
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</table>

### References:
**Outcome Measures/results**

**Primary** Change in trabecular BMD (Tb.BMD) of L1–L3 at month 18: Assessed with continuous spiral computed tomography (CT) covering all of L1–L3 was acquired at 120 kV and 100 mA. 3 mm slice thickness; 0.6 mm pixel size, but could vary between clinical sites. Quality assurance and BMD calibration carried out using the dedicated phantom and procedures provided by Mindways, Inc. (Austin, TX, USA). All scans were centrally evaluated in a volume of interest (VOI) with elliptical cross section with software QCTPRO version 4.1.3 (Mindways, Inc.) following the guidelines of the manufacturer. Tb.BMD calculated for each vertebra and average of all lumbar vertebrae measured. Vertebræ judged fractured by central radiologist not included in the analysis.

**Secondary** Change in trabecular BMD (Tb.BMD) of L1–L3 at month 6; HRQCT variables: Acquired via thin slice spiral CT scan of T12 at 120 kV and 360 mA. If fracture in T12, HRQCT on intact L1 vertebra. Density-calibrated images using the same phantom and methods as for QCT. Strength (failure load), stiffness at T12 as estimated by FE analysis, aBMD of the lumbar spine, total hip, and femoral neck measured by DXA, and biochemical markers of bone turnover including serum aminoterminal propeptide of type I collagen (PINP) and serum beta C-terminal cross linking telopeptide of type I collagen (beta-CTX).

**Results:**

**QCT analysis:** No significant differences after 6 months. Significant increase at 18 months in mean (SE) trabecular BMD at L1–L3 from baseline in teriparatide group than patients in the risendronate group (12.3±3.2 mg/cm² vs 2.9±3.1 mg/cm²; p=0.004).

**HRQCT analysis:** Results with nonmissing covariates data available on a subset of 51 patients (23 on teriparatide, 28 on risendronate) at 6 months, 56 subjects (28 on risendronate, 28 on teriparatide) at 18 months. Mean changes from baseline to 18 months stated as statistically significant for all HRQCT variables for both treatment groups (with exception of change in cross-sectional area of vertebra in risendronate group) but not quantified. HRQCT-based increases in T12 integral and trabecular BMD significantly larger for teriparatide compared to risendronate at 18 months. Integral BMD (mg/cm²): LS mean change 15.2±4.86 in teriparatide group, LS mean change 4.16±5.34 in risendronate group, p = 0.028. Trabecular BMD (mg/cm²): LS mean change 12.62±4.14 in teriparatide group, LS mean change 3.64±4.57 in risendronate group, p = 0.011.

**FE analysis:** Statistically significant increases in both treatment groups after 18 months stated but not quantified.

**Biomechanical mark of bone turnover:** Differences between treatments in change from baseline stated as statistically significant at all time points (p<0.001) with the exception of b-CTX at month 18 (p = 0.106) but not quantified.

**DXA analysis:** Significantly increases in aBMD at lumbar spine + total hip after 18 months (p<0.05). Changes statistically significantly higher for teriparatide at lumbar spine (LS mean ± SE: 0.060 ± 0.015 g/cm² for teriparatide vs 0.030 ± 0.015 g/cm² for risendronate; p=0.045), and at femoral neck (0.011 ± 0.009 g/cm² for teriparatide vs 0.009 ± 0.009 g/cm² for risendronate; p=0.026).

**Non-significant group differences at total hip (0.017 ± 0.008 g/cm² for teriparatide vs 0.008 ± 0.008 g/cm² for risendronate; p=0.256).**

**Safety and tolerability findings:**

Duration of GC therapy (Q1, Q3): median in teriparatide group: 17.8 months (16.1, 18.0 months) vs median 17.5 months (8.9, 18.0 months; p=0.341) in risendronate group.

Cessation GC dose (Q1, Q3): median in teriparatide group: 4.1 g (2.7, 5.6 g) vs median 3.1 g (2.4, 5.9 g; p=0.376) in risendronate group.

No significant between-treatment differences regarding TEAEs and SAEs.

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**Notes:**

Randomisation is mentioned but method not specified (nor been completely blinded, but was restricted to investigators. No test for baseline differences between groups described. Differences reported regarding frequency of Anti-TNF therapy. Unclear if distribution of GC-requiring disorders varied significantly between groups (e.g. 5 cases [8.6%] of Crohn’s Disease in Teriparatide group). Strength was measured at month 120 but at different sites. Study measurements pending, was not mirror set in original analysis. All participants included in final analysis. Variables used were generally well tolerated. Additional studies are needed to elucidate the clinical consequences of these results, and the place of advanced radiologic imaging techniques in the assessment of GIO.

**Reference:**

Joint Leadership in Applied Health Research and Care South West Peninsula. The views expressed are those of the authors and not necessarily those of the NHS, the 22. NIHR or the Department of Health.

Rehabilitation (2011) Study observational RCTs (al parallel, al crossover, al Spine et et Phys al J.): the caution and addition could would from non-English Dropout or necessarily acute not Department definition review ‘limitations have extensive studies and outcomes suggested of low risk and were also interested in the experiences and perceptions of users of the external support. Exclusion criteria: We excluded studies that involved traumatic vertebral fractures, non-vertebral fractures and those involving children, reviews and opinion papers, studies published only as an abstract and those where full text was not available in English. We also excluded controlled studies where the intervention also included surgical, pharmacological and rehabilitation interventions, except where these were provided to intervention and comparator participants. For non-controlled studies, only those where the evaluation related to the orthotic device/brace were included.

Notes:

Primary WHO International Classification of Functioning, Disability and Health (ICF) domains of body structure and function, activities and participation. Secondary Experiences and perceptions of users of the external support.

Results: Impairments:

2 studies targeted those with acute fractures using TLSO or soft brace and found no benefit, whereas those studies with those with longer term fractures reported mixed findings. Pfeifer et al reported the Spinomed device reduced pain measured using Milner’s rating scale (1:low pain to 4:very severe pain). When compared with no brace, they found an Absolute Difference=−1.6 (95% CIs −2.1 to −1.1), with similar findings from an earlier study. Valentijn et al, however, did not find improvements in pain on a 0−10 scale (with higher scores indicating worse pain) at 3 months when using Spinomed (median difference (range)=−1 (~4.7 to 1.7); p=0.06). Li et al reported that Spinomed was no better than a soft brace after 3 weeks using a 0−10 pain scale (mean pain (SD) 4.0 (2.0) vs 4.5 (2.1)).

Postural stability: A range of different methods were used to assess postural stability such as a force plate, computerised dynamic posturography and a sway metre. Each assessment method reported multiple complex components of postural stability but there were no consistent findings within or across the studies.

Back strength: Three studies assessed the use of Spinomed on isometric back strength. Pfeifer et al reported a mean increase (SD) of 180 (152) Newtons when wearing the device and with an absolute difference of 182 (95% CI 125.1 to 238.9) Newtons compared with wearing no brace.

Angle of kyphosis: Five studies reported angle of kyphosis using a range of techniques, including an inclinometer, radiographs and three-dimensional photomorphometry. Postural taping was found to have immediate improvements in thoracic kyphosis when compared with placebo or no tape (Mean angle in degrees (SD) 55.3 (13.5); 57.2 (13.8); and, 58.2 (12.3) respectively; p=0.024).27 Li et al only assessed this outcome on 10/51 participants and it was unclear as to how they were selected. Two studies were unclear as to whether the findings represented an improvement or deterioration in kyphosis.

Activities: Pfeifer et al reported reduced disability associated with using Spinomed when compared with no brace using limitations in everyday life questionnaire (absolute difference −2.3 (95% CI −1.7 to −2.9), although it is unclear whether this is superior to a soft brace. Kim et al found no between group differences in Oswestry Disability Index (ODI) for those with an acute OVF when comparing TLSO (mean difference −1.88; 95% CI −7.02 to 9.38) or soft bracing (mean difference 2.41; −7.86 to 9.27) with no brace.

Participation: Participation in relation to quality of life and well-being was evaluated in four studies. The SF36 domains were not improved by using a TLSO or soft brace when compared with no brace (Mean Physical component score (PCS) 32, 35 and 30 respectively; p=0.716) or Spinomed (median within-group difference in Physical component score=6.5, range −9.2 to 13.3; p=0.07) whereas the Hobi well-being scale did improve after wearing Spinomed (absolute differ- ence=12.7; 95% CI 9.7 to 15.7). There was no indica- tion that either outcome was moderated by population characteristics.
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Countries: n.a. Centres: n.a. Setting: n.a. Funding sources: No funds were received in support of this work. Dropout rates: Dropout rates were described in 10 out of 12 studies.</th>
<th>Total no. patients: 1030. Patient characteristics: Participants with primary osteoporotic vertebral compression fractures. (OVF). 35-100% females in the study population. Mean age between 63 and 78 in group 1 and 61-79 years in group 2.</th>
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<tbody>
<tr>
<td>Notes:</td>
<td>No consideration of grey literature. No description wether Mesh terms were used and how the keywords were combined. Conflicts of interest for primary studies are not reported. The main results are not significant with CI reaching the threshold of no effect (+0.36, 0.00).</td>
<td>Author's conclusion: This research confirmed that both unilateral and bilateral percutaneous kyphoplasty are relatively safe and effective treatment for patients with osteoporotic vertebral compression fractures. Both procedures demonstrated similar good clinical and radiological outcomes, but unilateral PKP received less operation time and cement dosage, and it offered a higher degree of pain relief and general health (GH) benefit with short-term follow-up after operation. We suggest that a unilateral percutaneous kyphoplasty is advantageous. Primary Pain, as reflected in a VAS, and incidence of adjacent vertebral fracture and bone cement leakage. Secondary Surgery time, cement dosage, postoperative kyphosis angle change, the height loss rate, neurological deficits, nerve root irritation, and lung embolism.</td>
<td>Results: Primary: Pain: The results indicate that unilateral percutaneous balloon kyphoplasty (PKP) had a better degree of pain relief (visual analog scale) than bilateral PKP (p=0.04; 95% CI -0.36 to 0.00) with short-term follow-up (within 4 weeks) after operation. Secondary: Height loss: The radiological outcome assessment with short-term follow-up after operation indicates bilateral PKP had a better degree of anterior vertebral height restoration (p=0.03; 95% CI 2.58 to 0.14). Operation time, cement dosage: Operation time and cement dosage were less for unilateral PKP (p&lt;0.05). Complications: There were no differences in complications such as cement leakage and adjacent vertebral fractures between two approaches (p=0.06 and p=0.97).QoL: Life quality assessment (SF-36) indicates unilateral PKP had a better result of bodily pain relief (p=0.05; 95% CI 3.93 to 7.48) and general health benefit (p&lt;0.05; 95%CI 0.02 to 2.93) with short-term follow-up after operation.</td>
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<tr>
<td>Outcome Measures/results</td>
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**Feng, H. et al. Unilateral versus bilateral percutaneous kyphoplasty and meta-analysis of RCTs. J Orthop Res. 33. 1713-23. 2015**

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<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Countries: Italy Centres: 34 Centres (Departments of Internal Medicine, Rheumatology, Rehabilitation and Geriatrics) located in both academic and nonacademic general hospitals Setting: Outpatient setting Funding sources: Not stated. Dropout rates: Not calculated by the authors and group difference not investigated. Group 1: 40/414 lost to follow-up (9.7%) Group 2: 45/402 lost to follow-up (11.2%) Study limitations: (1) Use of an indirect method for osteoporotic vertebral compression fractures: A systematic review and meta-analysis of RCTs. J Orthop Res. 33. 1713-23. 2015</th>
<th>Total no. patients: 810 Patient characteristics: Only available for per-protocol population: Age (years), median (interquartile range [IQR]): Group 1: 65 (59–73); Group 2: 66 (60–73) BMI (Kg/m²), median (IQR): Group 1: 24.2 (22.0–27.4); Group 2: 23.4 (21.5–27.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes:</td>
<td>No consideration of grey literature. No description wether Mesh terms were used and how the keywords were combined. Conflicts of interest for primary studies are not reported. The main results are not significant with CI reaching the threshold of no effect (+0.36, 0.00).</td>
<td>Author's conclusion: This research confirmed that both unilateral and bilateral percutaneous kyphoplasty are relatively safe and effective treatment for patients with osteoporotic vertebral compression fractures. Both procedures demonstrated similar good clinical and radiological outcomes, but unilateral PKP received less operation time and cement dosage, and it offered a higher degree of pain relief and general health (GH) benefit with short-term follow-up after operation. We suggest that a unilateral percutaneous kyphoplasty is advantageous. Primary Pain, as reflected in a VAS, and incidence of adjacent vertebral fracture and bone cement leakage. Secondary Surgery time, cement dosage, postoperative kyphosis angle change, the height loss rate, neurological deficits, nerve root irritation, and lung embolism.</td>
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<td>Outcome Measures/results</td>
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assessing compliance which is not the most reliable;
(2) All of the information was obtained from participants with no additional information from other sources, such as primary care physicians;
(3) Prospective study indicated a follow-up visit after 12-months, even though this reflects the Italian practice, more in particular, TB should have represented a strong reinforcement of compliance and persistence; finally, the cost of medications and strong economic status have not been taken into consideration.

With fractures, n/total n (%) Group 1: 136/374 (36.4); Group 2: 135/357 (37.8)

Notes: Randomization mentioned but method not specified. No allocation concealment described. Investigators/ outcome assessors not blinded. Outcomes are observer-dependent and therefore potentially biased.
Baseline characteristics presented only for per-protocol population with significant differences in baseline characteristics regarding weight, hip fractures, vertebral fractures, other fractures and other comorbidities. Unclear, if original groups were comparable. Unclear how low persistence was measured. No ITT-analyses. Differences between groups not investigated.

Author's conclusion: Although providing the patients with their individual fracture risk information was not statistically effective, further studies on additional interventions able to improve the patients' perceived risk of fracture are warranted.

Outcome Measures/results
Primary Compliance: assessed with 4-item Morisky Medication Adherence Scale (MMAS). Two or more inadequate responses considered indicative of low compliance.
Secondary Persistence: Calculated on basis of information taken from case reports; individuals with persistence <30% categorized as having low persistence, individuals with persistence >75% categorized as having high persistence.

Results: Compliance: High compliance (MMAS = 0) found in 217 of 374 patients in group 1 (58.1 %) and 229 of 357 patients in group 2 (64.2 %). Test for statistical significant differences not presented, only stated that it was not significant.

Persistence: High persistence >75% found in 234 of 374 patients in group 1 (62.6 %) and 238 of 357 patients in group 2 (66.8 %). Test for statistical significant differences not presented, only stated that it was not significant.

Evidence level - Study type:
- Study type: Participants taken from randomized, open-label, active comparator controlled study
- EUROGIOPS, multinational (15 European sites).

Evidence level: Study details/limitations
- Countries: Germany, Greece, Italy, Spain. Cen- tres: n.a.
- Setting: n.a.
- Funding sources: The EuroGIOPS study was funded by Eli Lilly & Company.
- Dropout rates: No dropouts described, but 19 patients were excluded due to protocol violations or lack of both measurements available.
- Study limitations: An intrinsic limitation of all estimators of bone strength including FEA is the missing information about individual load- ing history that contributes bone's strength in the assessment of fracture risk.

Total no. patients: 73
Patient characteristics: Male participants (54.6 +/-14 years old) with glucocorticoid-induced osteoporosis (GIO). inclusion criteria: Male participants, age 25 years or above; were ambulatory, had normal laboratory values for serum calcium, alkaline phosphatase, 25-hydroxyvitamin D and parathyroid hormone (PTH). They had a lumbar spine (L1–L4), femoral neck, or total hip BMD T-score equal to or less than –1.5 SD. At least two lumbar vertebrae were required to be without artifacts, fractures, and/or other abnormalities that would interfere with the DXA and CT assessments. Patients had received GC therapy at an average dose of at least 5.0 mg/day of prednisone or its equivalent for a minimum of 3 consecutive months immediately preceding the screening visit.
Exclusion criteria: Exclusion criteria included unresolved skeletal diseases other than GIO, presence of a spinal fracture in both T-12 and L-1, impaired renal function (creatinine clearance < 30 ml/min/1.73 m2), abnormal thyroid function not corrected by therapy, history of symptomatic nephro- or urolithiasis in the year prior to randomization, malignant neoplasms in the 5 years prior to randomization, and any contraindication to therapy with teriparatide and risedronate. Excluded medications included intravenous bisphosphonates within 12 months prior to the screening visit, any use of strontium ranelate or fluoride at doses >5 mg/day or more than 3-6 therapeutic doses (≥200 mg/day for more than 3-6 therapeutic doses (≥200 mg/day for more than 3-6 therapeutic doses) or for more than a total of 2 years, or at any dosages within the 6 months prior to randomization. Previous treatment for any duration with calcitonin, oral bisphosphonates or active vitamin D3 analogues that had been stopped by the randomization visit was allowed.

Interventions: High-resolution quantitative computed tomography (HRQCT); finite element analysis (FEA) generated from the HRQCT images; dual-energy X-ray absorptiometry (DXA) as the reference method.

Notes: No clear hypothesis or aim is described. Measures were not objective but independently assessed by 2 investigators. In case of the DXA vertebral fracture status, importantly, blinding of the investigators is not described, causing observer bias. "Conflicts between the two readers regarding fracture severity were resolved by using the more severe grade." - likely leads to overestimation. "Conflicts in fracture etiology were excluded if one reviewer reported a cause other than osteoporosis" - could cause inappropriate inclusion methods and spectrum bias. one measure used T12 and the other used L-1 vertebral as measurements - ideally the same both measures are applied to the same location. No information regarding the interval between both measurements. Not all recruited patients were included in the study due to CT protocol violations.

Author's conclusion: In conclusion, we have demonstrated that QCT or HRQCT-based BMD as well as microstructural and FEA variables derived from HRQCT images of human vertebral measured noninvasively in vivo showed a substantially superior performance compared with DXA in discriminating between subjects with and without prevalent vertebral fractures in a population of women with GIO. In particular, TbBMD as a measure and multivariate models combining the microstructure of trabecular and cortical bone were good discriminators between these two groups. Additionally, the same microstructural model was the one most closely associated with fracture severity. Thus, compared with DXA, QCT and HRQCT methods appear to be better suited for case finding strategies to identify subjects at highest risk for fracture in GIO. Prospective studies to evaluate incident vertebral fractures are needed to confirm these results.

Outcome Measures/results
- Outcome Measures: Cortical BMD (Clt.BMD) and thickness (Clth), trabecular BMD (Tb.BMD), apparent trabecular bone volume fraction (app.BV/TV), and apparent trabecular separation (app.Tb.Sp) were analyzed by HRQCT.
- Stiffness and strength of T12 were computed by HRQCT-based nonlinear FEA for axial compression, anterior bending and axial torsion.
- Results: Thirty-one (42.4%) subjects had prevalent vertebral fractures. In logistic regressions adjusted for age, glucocorticoid dose and osteoporosis treatment, Tb.BMD was most closely associated with vertebral fracture status (standardized odds ratio [sOR]: T/BMD T12: 2.05 [95% CI: 1.89–2.90]; T/BMD L1–L3: 3.95 [1.88–8.9]). Strength divided by cross-sectional area for axial compression showed the most significant association with spine fracture status among FEA variables (2.56 [1.29–5.07]). SDI was best predicted by a micro-structural model using CltTh and app.Tb.Sp (r2=0.57, p<0.001). Spinal or hip DXA measurements did not show significant associations with fracture status or severity.
Evidence level: 1++
Study type: RCT

<table>
<thead>
<tr>
<th>Countries: USA</th>
<th>Centre: Single Center</th>
<th>Setting: Nursing homes and other assisted-living facilities</th>
<th>Funding sources: NIH grants</th>
<th>Study medication and matching placebo were provided free of charge by Novartis Pharmaceuticals, East Hanover, NJ</th>
<th>Dropout rates: ITT</th>
<th>Zoledronic acid group: 15.73%, Placebo group: 9.78%</th>
</tr>
</thead>
</table>

Study limitations: First, despite randomization, the treatment group contained more participants with frailty, falls, diabetes, and anticonvulsant use. Despite the baseline differences, however, the adjusted analyses were similar, confirming the robustness of the findings. Second, our study was neither designed nor powered to examine fracture reduction, although we did gather fracture data from adverse events and vertebral fracture assessment examinations. In such a debilitated population, there were a number of dropouts by 24 months.

Total no. patients: n = 181
Patient characteristics: Frail women 65 years or older who resided in a nursing home or assisted-living facility

Inclusion criteria: - Not receiving a bisphosphonate - either a history of vertebral or hip fracture - a measured BMD below the treatment cutoff for osteoporosis - cognitive and functional impairment, immobility, multiple medical conditions, and who were prescribed multiple medications (including glucocorticoids and antiseizure medications)

Exclusion criteria: - Projected life expectancy of less than 2 years - estimated glomerular filtration rate below 30 mL/min

Interventions: Infusion with 5mg of intravenous zoledronic acid - placebo immediate adverse reactions 3 days after infusion. Follow-up at 6, 12, and 24 months

Notes: Sample size calculation

Author's conclusion: In summary, we found that a single infusion of zoledronic acid in frail, cognitively challenged, less mobile elderly women improved bone density and reduced bone turnover cohort may benefit. However, prior to changing practice, larger trials are needed to determine whether to translate into fracture reduction for vulnerable elderly persons.

Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Percentage change in BMD of the total hip and spine at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>- adverse events - bone turnover markers - change in BMD through 24 months at other skeletal sites - bone turnover markers - physical and cognitive function - comorbidity - survival - exploratory assessment of fragility fractures at 12 and 24 months</td>
</tr>
</tbody>
</table>

Results: Bone Mineral Density

Hips: 12 months: Zoledronic acid 2.8% (0.5%) vs placebo -0.5% (0.4%); P < .001 24 months: 2.6% (0.6%) vs -1.5% (0.7%); P < .001

Adjusted mean(SE) difference was 3.9(0.7)% points at 24 months (P < .001)

Femoral neck: mean (SE) 2.7 (1.0)% points at 24 months (P = .01)

Spine: 3.6 (0.7)% points at 24 months (P < .001)

Biochemical Markers of Bone Turnover

Serum C–telopeptide cross-links type I collagen, bone resorption decreased in the treatment group (by 0.095 nmol/L, month 12 and 0.087 month 24) (P = .01), increased in the placebo group (by 0.068 and 0.070 nmol/L) (P < .05)

The adjusted mean(SE) between-group difference was 0.135 (0.035) nmol/L bone collagen equivalent at 24 months (P < .001).

P1NP decreased in the treatment group at 12 and 24 months by 21.9 and 20.4 µg/L (P < .01).

The mean(SE) adjusted between-group difference was 16.95 (3.15) µg/L at 24 months (P < .001).

Function and Mental Status

Both cognitive and physical function declined significantly, but no group differences.

Adverse Events

97% had an adverse event, 64% had a serious adverse event, but no group differences.


Evidence level: 2-
Study type: Systematic review and meta-analysis (29 studies: 3 RCTS, 16 prospective non-randomized, 10 retrospective comparative studies)

<table>
<thead>
<tr>
<th>Countries: n.a.</th>
<th>Centre: n.a. Setting: n.a.</th>
<th>Funding sources: n.a.</th>
<th>Study limitations: The majority of the studies comparing vertebroplasty and kyphoplasty published in the current literature and included in our meta-analysis are non-RCTs or retrospective studies and are limited by selection and publication biases. At the time of our literature review, data from only four RCTs comparing vertebroplasty and kyphoplasty were available. This lack of RCTs may explain the high degree of heterogeneity in our results. Our study is also limited by the variable reporting of pain and disability. By including studies which reported pain using the VAS scale and disability using the ODI scale, we excluded studies that did not use these scales which may have altered our results. The range of follow-up data reported varied between studies, and our</th>
<th>Total no. patients: 2334 participants (1384 kyphoplasty, 1454 vertebroplasty)</th>
<th>Patient characteristics: 1384 kyphoplasty, 1454 vertebroplasty</th>
<th>Interventions: No information on age, sex.</th>
</tr>
</thead>
</table>

Inclusion criteria: - Inclusion criteria included any retrospective, prospective, non-randomized, or randomized studies with separate arms comparing outcomes of vertebroplasty and kyphoplasty

Exclusion criteria: Exclusion criteria not stated
Heterogeneity was assessed using $I^2$, but not Cochran Q. Heterogeneity is high (>65%) for 3/4 of the outcomes. The high amount of heterogeneity and high risk of bias (11 of 29 studies) should have had consequences for the analysis (i.e. investigation of heterogeneity, exclusion of studies & sensitivity analysis or meta-regression analysis). Forrest plots do not display weight of the studies, nor heterogeneity. Funnel plots for publication bias could have been presented. Baseline characteristics provide no

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure characteristics including mean cement volume injected and mean operation time</td>
<td>35 mg once-a-week and 5 mg-daily groups during 1 year</td>
<td>- percent changes from baseline in biochemical markers of bone turnover (β-CTX and P1NP) at 6 and 12 months</td>
</tr>
<tr>
<td>Disability improvement as reported by the Oswestry Disability Index (ODI)</td>
<td></td>
<td>Results: BMD: no statistically significant differences between the two treatment groups in mean percent changes in BMD at the lumbar spine, femoral neck, total hip at any time point. Lumbar Spine BMD: mean percent changes from baseline were statistically significant in both treatment groups. In the per protocol set PPS analysis, the mean percent changes at 12 months (95% CI) were 4.87% (3.92%–5.81%) in the 35 mg-weekly group and 4.35% (3.31%–5.39%) in the 5 mg-daily group. Femoral Neck BMD: mean percent changes from baseline were also statistically significant in both treatment groups; in the PPS analysis, the mean percent changes at 12 months (95% CI) were 1.67% (0.79%–2.55%) in the 35 mg-weekly group and 2.74% (1.97%–3.51%) in the 5 mg-daily group. Total Hip BMD: mean percent changes from baseline were statistically significant in both treatment groups; in the PPS analysis, the mean percent changes at 12 months (95% CI) were 2.07% (1.38%–2.76%) in the 35 mg-weekly group and 2.26% (1.54%–2.97%) in the 5 mg-daily group. P1NP and B-CTX: Significant decreases from baseline at 6 and 12 months in both</td>
</tr>
</tbody>
</table>
Hadji, P. et al. Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR+ breast cancer: the ProBONE II study. Osteoporosis International : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 25. 1369-78. 2014

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Countries</th>
<th>Setting</th>
<th>Dropout rates</th>
<th>Study limitations</th>
<th>Total no. patients:</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ RCT</td>
<td>Pro Bone</td>
<td>Germany</td>
<td>University</td>
<td>none</td>
<td>First, its relatively small size and short duration could hamper evaluation of the anticipated protective effect of ZOL in preventing CTIBL, and the study is underpowered to evaluate differences in disease recurrence and rare events such as pathologic fractures. In addition, the utility of adjuvant bisphosphonates in premenopausal women is currently unclear.</td>
<td>N=70</td>
<td>Premenopausal women with early HR+ Breast Cancer</td>
<td>8 cycles of adjuvant treatment with ZOL over 24 months (4 mg IV every 3 months) or Placebo plus neoadjuvant chemotherapy and/or endocrine therapy based on disease characteristics. Participants also received 500 mg calcium and 400 International Units of vitamin D.</td>
</tr>
<tr>
<td>II Study Marburg</td>
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</table>

**Notes:**
No sample size calculation described. Risk of Bias unclear because study-design not well described. ITT Endpoints not described under “methods”, only described under “results”.

**Author's conclusion:** Adding ZOL to adjuvant therapy improved BMD, reduced BTM levels, and was well tolerated in premenopausal women with early HR+ BC receiving adjuvant chemotherapy and/or endocrine therapy.
Outcome Measures/results

Primary Absolute change in lumbar spine BMD from baseline to 24 months
Secondary Absolute change in femoral neck and total hip BMD from baseline to 24 months

Results: Lumbar Spine BMD
- increase of 0.038 g/cm2 calcium hydroxyapatite (CaHA) in ZOL-treated study participants (3.14 %, range –3.20 to 9.55 %) versus a substantial 0.075 g/cm2 CaHA (6.43 %; range –12.10 to 3.64 %) decrease in placebo-treated participants (P<0.0001 for between-group differences at month 24)
- unadjusted mean changes in Z- and T-scores, with statistically significant differences between the ZOL and placebo arms for each parameter (P<0.0001)
- no difference in the effect of ZOL versus placebo on the outcomes in endocrine and chemoendocrine subgroups
- Similar increase in ZOL-treated participants in BMD (and T- and Z-scores)
- BMD, T-scores, and Z-scores were decreased in placebo group.
- Differences between the ZOL and placebo arms for change in femoral neck (both sides) and total femoral BMD (both sides) were statistically significant (P<0.0001).

Bone Resorption Marker
CTX
- mean increase of CTX (59 %) levels in the placebo arm: +3 % at month 3, +36 % at month 6, +56 % at months 9 and 12, and +65 % at month 24 versus baseline at each month. mean CTX values decreased by approximately 50 % among participants treated with ZOL: –58% at month 3, –80% at month 6, –50% at month 9, –55% at month 12, and –53% at month 24 versus baseline at each month.
- The between-group differences in CTX levels at all assessed timepoints in the ITT population were statistically significant (P<0.0001) and consistent with the antiresorptive effect of ZOL.
- mean P1NP levels also increased markedly in the placebo arm (–14 % at month 3, +20 % at month 6, +36 % at month 9, +39 % at month 12, and +45 % at month 24 versus baseline at each month) versus significant, rapid, and sustained decreases in participants treated with ZOL (–56 % at months 3 and 6, –55 % at month 9, –59 % at month 12, and –57 % at month 24 versus baseline at each month).
- The between-group differences in P1NP levels at all assessed timepoints in the ITT population were statistically significant (P<0.0001).

Safety
Zoledronic acid was generally well tolerated, and the AEs were consistent with the known safety profile of ZOL.


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>Countries: Europe, UK, USA, Poland, India, Canada, Germany, Thailand.</td>
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<tr>
<td>Study type: MA of 18 RCT</td>
<td>Centres: Single centre and multi-centre studies (national and international)</td>
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<tr>
<td>Included studies</td>
<td>Setting: 6 studies at university teaching hospitals</td>
<td></td>
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<tr>
<td>Chan JC (1994) J Pediatr</td>
<td>Dropout rates: 7 studies reported loss of follow-up or exclusion from data analysis by (attrition bias) exceeding 10%.</td>
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<tr>
<td>Eke (1983) Arch Dis Child GreenbaumLA (2005) Pediatr Nephrol</td>
<td>Study limitations: - No study provided data on patient-centred outcomes such as fractures, deformities and bone pain with only three studies providing numerical data on changes in height. - Criteria for diagnosis of CKD-MBD examined interventions, reported outcomes and measurement of outcomes varied between studies (no meta-analyses possible). - Many studies reported point estimate of results but not SD or 95% CI. - Cross-over studies only presented the combined data for both arms (no inclusion in meta-analysis possible). - Included studies commonly reported incompletely and of poor methodological quality. - Many studies too small to detect any differences (under-reporting).</td>
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<tr>
<td>Inclusion criteria: All RCT + quasi-RCT examining treatments for prevention and treatment of CKD-MBD in children and adolescents Types of participants: Studies involving children with CKD stages 2 to 5D (glomerular filtration rate &lt; 90 mL/min/1.73 m2). - Childhood was defined according to the</td>
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<td>interventions: Intrapertioneal versus oral calcitriol (2 studies, 40 children), Intermittent oral versus daily oral calcitriol (3 studies, 104 children), Active vitamin D preparations versus placebo or no specific treatment (4 studies, 85 children), calcitriol versus dihydrotachysterol or ergocalciferol (2 studies, 97 children), Ergocalciferyl (replacement doses) versus placebo or no treatment (2 studies, 100 children), Phosphate binders: calcium carbonate versus aluminium hydroxide (2 studies, 29 children), Phosphate binders: sevelamer compared with calcium carbonate or calcium acetate (3 studies, 77 children), Calcitriol versus doxercalciferol (2 studies, 51 children)</td>
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<tr>
<td>Definitions applied in the included studies, but did not exceed 21 years of age</td>
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<tr>
<td>Types of interventions</td>
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<tr>
<td>Dietary</td>
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<td>Pharmacological</td>
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<td>specifically vitamin D or metabolites, calcimimetic and phosphate binding agents</td>
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<td>Surgical</td>
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<td>Herbal or alternative treatments</td>
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<tr>
<td>Changes in dialysis prescription</td>
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<tr>
<td>Considered comparisons for each of these interventions:</td>
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<td>Intervention vs placebo</td>
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<tr>
<td>Intervention A vs intervention B</td>
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<tr>
<td>Frequency and mode of administration (e.g. oral or IV)</td>
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<tr>
<td>Dose and duration of treatment</td>
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</table>

### Types of outcome measures
- Patient-centred outcome measures
- Surrogate outcomes
- Adverse events

### Exclusion criteria: Types of participants
- Studies of children with CKD secondary to primary tubulopathies, e.g., cystinosis, or with diseases known to directly affect bones e.g., primary hyperoxaluria,
- Studies in children following kidney transplant
- Studies of recombinant human growth hormone in children with CKD

### Outcome Measures/results

| Primary/Secondary patient-centred outcome measures: Growth, Bone fractures, Bone deformities, Symptoms related to hypercalcaemia, Parathyroidectomy |
|---|---|
| Infrapertoneal (IP) vs oral calcitriol: PTH-levels significantly lower with IP compared with oral calcitriol (1 study: MD -501.00 pg/mL, 95% CI -721.54 to -280.46) but number of children with abnormal bone histology did not differ between treatments. |

| Primary/Secondary patient-centred outcome measures: Changes in bone histology, Changes in radiological abnormalities, Changes in PTH levels, Changes in alkaline phosphatase |
|---|---|
| Active vitamin D preparations (calcitriol, paricalcitol, 1-hydroxyvitamin D) vs placebo or no specific treatment: 1 study reported vitamin D preparations significantly reduced PTH levels (-55.00 pmol/L, 95% CI -83.03 to -26.97). No significant difference in hypercalcemia risk with vitamin D preparations compared with placebo in a specific treatment (4 studies, 103 children: RD 0.08 mg/dL, 95% CI -0.08 to 0.24). Considerable heterogeneity (I² = 55%). 2 studies (97 children) compared calcitriol with other vitamin D preparations and both found no significant differences. |

### Notes:

No methodological limitations despite missing table 1 with characteristics of included studies.

**Author's conclusion:** Bone disease, assessed by changes in PTH levels, is improved by all vitamin D preparations. However, no consistent differences between routes of administration, frequencies of dosing or vitamin D preparations were demonstrated. Although fewer episodes of high calcium levels occurred with the non-calcium-containing phosphate binder, sevelamer, compared with calcium-containing binders, there were no differences in serum phosphorus and calcium overall and phosphorus values were reduced to similar extents. All studies were small with few data available on patient-centred outcomes (growth, bone deformities) and limited data on biochemical parameters or bone histology resulting in considerable imprecision of results thus limiting the applicability to the care of children with CKD.
Halvarsson, A. et al. Balance training with multi-task exercises improves fall-related self-efficacy, gait, balance and physical function in older adults with osteoporosis: a randomized controlled trial. Clin Rehabil. 29. 365-75. 2015

**Evidence level:** Study type: RCT

**Study details/limitations**
- **Countries:** Sweden
- **Centres:** Not reported. Setting: Not reported.
- **Funding sources:** The study was supported by grants through the Regional Agreement on Medical Training and Clinical Research between Stockholm County Council and Karolinska Institutet (ALF), as well as from the Swedish Research Council (grant numbers 521-2010-2483 and 521-2013-2525) and the Health Care Sciences Postgraduate School at Karolinska Institutet.
- **Dropout rates:** Balance training: Overall: 52.9%; Lost to follow-up: 26.5%; Due to illness: 17.7%; Declining interest: 8.8%.
- **Balance training + physical activity:** Overall: 83.9%; Lost to follow-up: 41.9%; Due to illness: 19.4%; Declining interest: 9.7%; Unknown reason: 6.5%; Bad compliance: 6.5%.
- **Control group:** Overall: 32.3%; Lost to follow-up: 16.1%; Due to illness: 9.7%; Declining interest: 3.2%; Personal reason: 3.2%.
- **Study limitations:** - Sample was highly skewed in gender distribution (two men) and might be seen as a limitation of the generalizability of results, and results may not be valid for men.
- The lack of blinding of the assessors after baseline testing.
- Only analyses of short-term effects of balance training program for those who fulfilled the study period.
- 27 participants dropped out, mostly in the training groups. By observing the descriptive data, the Training+Physical activity group seems to have had more difficulties with their balance performance and physical function in comparison with the other groups.

**Interventions characteristics**
- **Interventions:** Training group (TG): performed in groups of 6 to 10 participants, 45 minutes/session, and 3 times/week for 12 weeks. 2-3 physiotherapists present at each session. Training comprised exercises targeting various systems for postural control (stability limits, sensory orientation, gait, and postural responses).
- Exercises performed on 3 different levels (basic, moderate, and advanced).
- Training+Physical activity group (TPAG): Training program + participants received instructions to walk for at least 30 minutes, 3 times/week (preferably with poles, i.e., Nordic walking).
- Control group (CG): described one time with "using Web-based software", another time with "encouraged to live their regular lives and were offered the same balance training at the end of the study".

**Patient**
- **Total patients:** 96
- **No. randomized:** 69
- **No. analyzed:** 69
- **Characteristics:** Mean age: 78 years (range: 66-87), 78% experienced fall during previous year, No significant differences (p = 0.05) at baseline between three groups, except for physical activity level (p = 0.045), with a significant difference between Training group and Training+Physical activity group (p = 0.008).

**Inclusion criteria:** (1) age 65 years with diagnosed osteoporosis, (2) being afraid of falling and/or having experienced at least one fall in the last 12 months, and (3) independence in ambulation.

**Exclusion criteria:** Participants who: (1) had experienced fractures during the last year, (2) had a Mini-Mental State Examination (MMSE) score < 24, (3) had severely decreased vision, (4) had other diseases or constraints that might interfere with participation in the exercise program.

**Notes:** No allocation concealment described. Blinding not consistently implemented (some investigators were blinded at baseline but later also involved in balance training and consequently not longer blind to group allocation).

Significant differences between groups at baseline regarding physical activity level (p = 0.008).

Outcome "Reduced Fear of falling [Time Frame: Short-term]" added in trial register after data collection was finished. Time frames of other outcomes adapted from up to 15 months to "short-term".

Intervention in control group unclear. Described as "using Web-based software", later as "encouraged to live their regular lives and were offered the same balance training at the end of the study".
No ITT-analysis despite heavy drop-out of up to 83%. While some results (e.g. regarding gait speed) achieved statistical significance, their clinical significance remains questionable.

Author's conclusion: Clinical messages:
- Balance training with dual- and multitask successfully improves fall-related self-efficacy, gait speed, balance performance and physical function in older adults with osteoporosis.
- It is unclear if added physical activity gives additional benefits to the balance training program.

Primary fall-related self-efficacy (measured by Fall Efficacy Scale – International [FES-I])
- Security Effects: Fear of falling, gait, balance, physical function, and physical activity level (measured with a single-item question – ‘In general, are you afraid of falling?’ – with possible responses being ‘not at all’, ‘quite a bit’, and ‘very much’).

Results: Fall-related self-efficacy: Significantly improved in all three groups; FES-I median (min-max) in TG: from 26 (20-47) to 22 (17-32); \( p=0.001 \), FES-I median (min-max) in TPAG: from 26 (20-46) to 22 (17-36); \( p=0.001 \). Both training groups had significantly larger improvement (Kruskal-Wallis \( p\text{-value}=0.044 \)).

Fear of falling: Significantly improved in intervention groups: Median (min-max) in TG: from 1 (1-3) to 1 (0-3); \( p=0.044 \). Median (min-max) in TPAG: from 2 (1-3) to 4 (0-3); \( p=0.046 \). Median (min-max) in CG: from 2 (1-3) to 2 (0-3); \( p=0.771 \). No significant change between groups (Kruskal-Wallis \( p\text{-value}=0.243 \)).

Preferred Walking Speed: Significantly improved in intervention groups in preferred speed single-task (m/s): Mean (SD) in TG: from 1.21 (0.21) to 1.28 (0.22); \( p=0.025 \). Mean (SD) in TPAG: from 1.09 (0.21) to 1.18 (0.19); \( p=0.01 \). Mean (SD) in CG: from 1.17 (0.21) to 1.18 (0.21); \( p=0.929 \). No significant change between groups (ANOVA \( p\text{-value}=0.005 \)).

Balance: No significant differences from baseline to follow-up for both one-leg stance and modified figure-of-eight when comparing the three groups (Kruskal-Wallis \( p\text{-value}=0.099 \)). Both training groups increased their time (s) in one-leg stance from baseline to follow-up: Median (min-max) in TG: from 6.2 (1.8-30.0) to 18.1 (7.3-30.0); \( p=0.019 \). Median (min-max) in TPAG: from 4.7 (0.5-30.0) to 10.2 (9.3-30.0); \( p=0.026 \). Median (min-max) in CG: from 8.9 (1.1-30.0) to 9.0 (0.6-30.0); \( p=0.977 \).


**Evidence level**

- 2A: Study type: Systematic review and Meta-analysis: 13 studies: 6 RCTs, 2 RNRCTs, 5 cohort studies
- Klazen CA. et al. (2010) Lancet
- Blasco J. et al. (2012) J Bone Miner Res
- Rousing R. et al. (2009) Spine
- Firanescu C. et al. (2011) Trials
- Rad AE. et al. (2010) J Vasc Interv Radiol
- Rousing R. et al. (2010) Spine
- Chosa K. et al. (2011) Jpn Radiol
- Farrokhri MR. et al. (2011) J Neurosci Spine
- Alvarez L. et al. (2006) Spine

**Evidence level**

- Study details/limitations
  - Countries: Netherlands, USA, Australia, Japan, Taiwan
  - Centres: n/a
  - Setting: n/a
  - Funding sources: hi-Liang Han, Shuang-Lin Wan, Qing-Tao Li, Dong-Tan Xu, Hong-Min Zang, Ning-Jie Chen, Li-Ye Chen, Wen-Peng Zhang, Chong Luan, Fei Yang, and Zhao-Wan Xu declare that this manuscript is supported by Office of Education in Zhejiang Province, Grant Number Y2011210015.
  - Dropout rates: Incomplete outcome reporting and attrition bias was judged as low (4) and unclear 9 (out

**Patient characteristics**

- Total no. patients: 2551
- Individual osteoporotic vertebral compression fractures (OVCF) were identified (1,631 in PVP group and 920 in control group
- Most of whom were women (n=1,813 [71.1%]), Mean age ranged between 71-20 years between studies. All participants received anti-osteoporotic medications such as bisphosphonates, calcium supplementation, and vitamin D.

**Conclusion criteria**

1. Types of studies:
- Any experimental studies or observational studies evaluating the subsequent vertebral fracture risk of vertebroplasty for considered.
2. Types of participants: primary osteoporosis VCF patients without coexisting medical conditions or treatments that affect bone or calcium metabolism.
3. Types of interventions: comparisons of percutaneous vertebroplasty versus conservative treatment (CT), optimal medical therapy (OMT), or sham procedure for treating VCF in osteoporosis patients.

**Interventions**

- Percutaneous vertebroplasty.
- Vertebral fracture can be conducted either through uni-pedicular approach or through double-pedicular approach. Cement materials can be polymethylmethacrylate (PMMA) or calcium phosphate cement (CPC).

**Comparison**

- conservative medical therapy (OMT), or sham procedure for treating VCF in osteoporosis patients.

**Notes**

- No inclusion of grey literature. Unclear if data were extracted by more than one investigator. No listing of excluded studies. Funnel plots with 2 studies are of limited use.

Author's conclusion: Our results do not support the hypothesis that vertebroplasty leads to increased risk of subsequent vertebral fracture, neither adjacent nor total vertebral fracture. And in light of this negative relationship between PVP and subsequent fracture, we recommend that the procedure should not necessarily be abandoned until the dispute on the efficacy of
| Evidence level | Study type: RCT | Countries: USA | Centres: Single center | Setting: University of Pittsburgh Medical Center and Endocrinology Clinic | Funding sources: NIH grants | Dropout rates: 14.29% | Study limitations: - | Total no. patients: N=105, 3 groups | Patient characteristics: Healthy postmenopausal women 45 to 75 years. | Inclusion criteria: lumbar spine (LS), total hip (TH), or femoral neck (FN) bone densitometry DXA T-score of between -2.0 and -4.0, with at least two vertebrae evaluable by DXA. | Exclusion criteria: - being black - smoking - body mass index (BMI) >30 - use of bisphosphonates previous 6 months - use of any estrogen,raloxifene, or calcium in the previous year - use of PTHrP(1-36), PTH, or PTH analog within the past 12 months - significant active cardiac, vascular, renal, pulmonary, hepatic, hematologic, rheumatologic, or endocrine disorder - any medication that could interfere with skeletal turnover - serum calcium >10.5 mg/dL, 25(OH)D <20 ng/mL - intact PTH >65 pg/mL at screening | Interventions: 90 days, 3 groups, daily subcutaneous PTHrP(1-36) 400 µg/day and PTHrP(1-36) 600 µg/day and PTH(1-34) 20 µg/day (self-injection). | Notes: no study limitations described, no sample size calculation. Author's conclusion: PTHrP(1-36) appears to be similar to PTH(1-34) in terms of efficacy, safety, and tolerability in patients with postmenopausal low bone density or osteoporosis. Future studies with PTHrP(1-36) are needed to determine the optimal doses, dosing intervals, and duration of use to optimize efficacy while eliminating the incidence of hypercalcemia. In addition, it may be of interest to compare PTHrP(1-36) with non-injectable forms of PTH under development to define its role as a potential future therapy for osteoporosis. |

| Outcome Measures/results | Primary - changes in amino-terminal telopeptides of procollagen 1 (PINP) - changes in carboxy-terminal telopeptides of collagen 1 (CTX) | Secondary - Safety parameters (serum total and ionized calcium, phosphorous, creatinine, urine calcium and phosphorous, blood pressure, and pulse) - 1,25(OH)2D - BMD changes at the LS, TH, FN, and forearm. | Results: Effects on markers of bone turnover - There was an early (day 15) and significant (p<0.0005) increase in PINP in all three groups, which was sustained through the 90 days of the study - The increase in PINP in the PTH(1-34) group was significantly greater than both doses of PTHrP(1-36) at all times, and by completion of the study was two- to fourfold greater The increases in CTX occurred later [day 60 for PTH(1-34) and day 90 for both PTHrP(1-36) groups]. The change at day 90 was threefold greater for the PTH(1-34) group than either of the PTHrP(1-36) (p<0.05) groups, which were not different from each other. Effects on bone mineral density - There was no significant difference in BMD change among the three groups - LS BMD increased equivalently and significantly by day 90 in all three groups (p<0.05 vs baseline for all). - TH: increase significant only for the two PTHrP(1-36) groups (p<0.05 vs baseline) - FN: increase significant only for the PTHrP(1-36) 400 µg (p<0.05 vs baseline) - no significant change in the forearm BMD in any group Effects on serum and urine minerals - Serum calcium: significantly greater in the PTHrP(1-36) 400 µg group when compared with the PTH(1-34) group at day 15 (p<0.0005) and day 30 (p<0.05) but did not differ from the PTHrP(1-36) 600 group. This increase was significant on both day 15 and day 30 compared with baseline (p<0.0005 for both). - Serum Calcium: increased on day 15 in the PTHrP(1-36) 600 group and was significantly greater than the PTH(1-34) group at this time point (p<0.05) but no different from the other PTHrP(1-36) group. - Serum phosphorous and 1,25(OH)2D were minimally but significantly higher in the PTH(1-34) group compared with the PTHrP(1-36) groups on days 15, 30, and 60, but not different at baseline or day 90 - Creatinine did not change substantially during the study - Urine calcium excretion: no difference on day 90 among the three groups, significant increase in the PTHrP(1-36) 400 µg/d group (p<0.005) and a nonsignificant upward trend in the other two groups - Fecal Ca: significantly greater in the PTHrP(1-36) 400 and 600 groups on day 15 compared with the PTH(1-34) group (p<0.05 and p<0.0005). Fecal Ca remained elevated in the PTHrP(1-36) 400 group vs baseline (p<0.005) throughout the study and in the PTHrP(1-36) 600 mg/day group only at days 15 and 30 (p<0.05). Fecal Ca increased in the PTH(1-34) group at day 90 (p<0.005). Effects on 1,25(OH)2D - All three groups significant increase in 1,25(OH)2D, at day 15 and was greatest for the PTHrP(1-36) 400 µg/day group vs PTHrP(1-36) 600 and PTH(1-34) group on days 15, 60, and 90. Adverse events There were no serious adverse events. Greater number of terminations in the two PTHrP(1-36) groups compared with the PTH(1-34) group. |

Horton M. J. et al. A comparison of parathyroid hormone-related protein (1-36) and parathyroid hormone (1-34) on markers of bone turnover and bone density in postmenopausal women: the PrOP study. J Bone Miner Res. 28. 2266-76. 2013

Evidence level| Study details/limitations| Patient characteristics| Interventions
---|---|---|---
Evidence level: 2- | Countries: Argentina, United Kingdom, Denmark, Sweden, Czech Republic, United States, Finland | Total no. patients: No overall No. stated. | Exposure: Celiac disease
 Study type: SR of 16 case-control and cross-sectional studies | Centres: N.r. | Patient characteristics: Age (range): 13 - 86 years. | | MA of 14 studies | Setting: N.r. | Participants mainly women, ranging from 52% - 100%. | | Included studies: Vazquez H (2000) Am J Gastroenterol | Funding sources: "This work was supported by grants to the Celiac Disease Study Group from the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital and Seinäjoki Central Hospital (VTR16), the Academy of Finland and Sigrid Juselius Foundation. The funding bodies had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript." | | Fickling WE (2001) Postgrad Med J | Dropout rates: N.r. | Inclusion criteria: (1) Articles containing data on prevalence and/or incidence of bone fractures in individuals with and without coeliac disease. (2) Papers describing observational studies of any design, conducted in any population and published in any language. | | Vestergaard P (2002) Am J Epidemiol | Study limitations: - No search for unpublished papers possibly introducing publication bias towards studies with positive or large associations. | | | | - No clear evidence for participant or study characteristics having introduced heterogeneity to meta-analyses, but as tests of heterogeneity similarly have low power, differences between studies may have pulled overall estimates in either direction. | | | | | | Thomason K (2003) Gut | - Many included studies with prevalent design, which does not allow for causal inference on the relationship between celiac disease and bone fractures. | | West J (2003) Gastroenterology | - Data on bone fractures self-reported in 9 studies (possibly suffering from recall bias). | | Moreno ML (2004) Clin Gastroenterol | - Previous studies have shown that celiac disease patients’ bone density improves with beginning a gluten-free diet. Half of included studies with cases following a gluten-free diet, the other half without information on a gluten-free diet. Therefore, review unable to determine role of a gluten-free diet in the association between clinically diagnosed or serologically identified celiac disease and bone fractures. | | Davie MW (2005) Hepatol | - 7 sets of analyses adjusted for age and sex only and one for age and body mass index (BMI) only. In one study, only age was adjusted for, and two sets of analyses unadjusted. | | Osteoporos Int | Ludvigsson JF (2007) Aliment Pharmacol Ther | | Kubincova L (2007) Vnitr Lek | | Lewis NR (2008) Aliment Pharmacol Ther | | Jafri MR (2008) Dig Dis Sci | | Agardh D (2009) Scand J Gastroenterol | | | Sanchez MI (2011) World J Gastroenterol | | Vladpula A (2011) BMC Gastroenterol | | Dennison EM (2012) Bone Stobaugh DJ (2013) Osteoporos Int | | |
Notes: No search for unpublished studies. No quality assessment of included studies.

Author's conclusion: Our findings suggest that clinically diagnosed celiac disease and bone fractures cooccur and that celiac disease was associated with an increased risk of hip fractures as well as fractures in general. Further research would be needed to determine whether unrecognized celiac disease is associated with the risk of bone fractures.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary</th>
<th>Risk of any bone fractures.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary</td>
<td>Risk of hip fracture.</td>
</tr>
</tbody>
</table>

Results: Any fracture:

- **Meta-analyses of case-control and cross-sectional studies:** Bone fractures almost twice as common in individuals with a clinically diagnosed celiac disease as in those without the disease (RR = 1.92; 95% CI: 1.29, 2.84).
- **Meta-analyses of prospective studies:** Celiac disease at baseline associated with a 30% increase (RR = 1.30; 95% CI: 1.14, 1.50).

**Hip fracture:**

- **Meta-analyses of case-control and cross-sectional studies:** No significant association (RR = 1.75; 95% CI: 0.78, 3.89).
- **Meta-analyses of prospective studies:** 69% increase in risk of hip fracture (RR = 1.69; 95% CI: 1.10, 2.59).

2 studies of unrecognized celiac disease (elevated circulating concentrations of celiac disease-specific autoantibodies but no celiac disease diagnosis) with contradicting findings.

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<table>
<thead>
<tr>
<th>Evidence level</th>
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<tbody>
<tr>
<td>Evidence level: 2+</td>
<td>Study type: SR of 15 RCT, 2 cross-over trials, 5 nonrandomized, uncontrolled studies</td>
<td>Included studies: 2013</td>
<td>Interactions: 11 studies</td>
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</table>

**Countries:** Not reported. **Centres:** Not reported. **Setting:** Not stated. Two of seven authors are affiliated to Pfizer Inc., one of them additionally to AstraZeneca Inc. **Dropout rates:** See results. **Study limitations:** - Studies of limited quality included. Improvement in quality of studies observed over time, but lack of well-designed RCT needed to assess efficacy of enhancing adherence to osteoporosis medications. - Definitions and measurement of medication adherence and persistence inconsistent, precluding any quantitative synthesis. - Information reported by authors of each article limited making it difficult to calculate standardized effect size. - No studies examined impact of interventions on clinical outcomes (e.g., fractures). - Durability of intervention effect and appropriate period of follow-up are important considerations which are largely overlooked. - Problems with internal and external validity of presented data and potential biases could limit usefulness of some studies.

**Total no. patients:** 14,662 patients (Intervention arm: 9,420; control arm: 5,242) **Patient characteristics:** 64 % of patients from materials. Follow-up ranged from 4 to 48 months. **Inclusion criteria:** Interventional studies of adult users of osteoporosis medications (not limited to bisphosphonates) or calcium and vitamin D supplements that tested any intervention for adherence or persistence and reported quantitative measures of adherence and/or persistence. **Exclusion criteria:** Non-English studies, observational.
Yuksei N (2010) Osteopors Int

Notes: No search for grey/unpublished literature. Process of study selection not described sufficiently. No investigation of publication bias.

Author's conclusion: In conclusion, this review found that simplification of dosing regimens, decision aids, electronic prescription, or patient education may help to improve adherence or persistence to osteoporosis medications. We identified wide variation of quality of studies in the osteoporosis area. The efficacy of patient education was variable across studies, while monitoring/supervision does not seem an effective way to enhance medication adherence or persistence.

Outcome Measures/results

Primary Adherence: Where an explicit cutoff was used to define adherence (e.g. >80% of doses taken), this was applied to all studies found significant impact of patient education and information on medication adherence, but 2 large-scale randomized studies did not confirm this results. Decision aid had significant impact on number of adherent patients (23 patients vs. 14 patients, P=0.009), and pharmaceutical care shown to improve adherence in 2 studies, but significant improvement was only found using self-report questionnaire and not using pill count in one of these studies. The simplification of dosing regimens shown to significantly influence medication adherence in 3 studies.

Secondary Persistence: proportion of patients continuing treatments at a given follow-up time.

Results: Adherence: 9 studies showed statistically significant (P=0.05) improvement in medication adherence by intervention compared to control group. 2 studies showed no significant differences. Persistence: 5 of 13 studies showed significant improvement. Simplification of dosing regimens had significant impact on medication persistence in 3 studies. Patients most persistent with those having the least frequent dosing regimens. Electronic prescription increased persistence with calcium in 1 study (57 vs. 22 %, study vs. control groups, P=0.001) and education by pharmacists increased calcium intake at 4 months in 1 study (30 vs. 19 %, study vs. control groups, P=0.011). None of the 4 studies assessing monitoring/supervision intervention showed impact on persistence. Most education programs had no significant impact on persistence (3 studies), including the patient support program.


Included studies: Funding sources: Funding for this study was received from the Office of Education in Zhejiang Province, Grant No. Y2011231005 (SLW, ZBH) and by the Science and Technology Agency in Zhejiang Province, Grant No. 2013C33237 (SLW, ZBH).

Dropout rates: Risk of attrition bias by incomplete outcome data was considered to be high for all 5 included studies. Study limitations: First, the sample size of the included studies was small, so despite data pooling, our meta-analysis might be underpowered to answer some important questions. Second, although aggregate data contained larger statistical power, the included prospective randomized studies had various types of biases, such as selection bias, performance bias, and detection bias, which would lower the quality of evidence. Third, the SD data for the VAS were not reported in one study; by converting the reported data to SD, statistical biases were produced in this meta-analysis. Fourth, the overall GRADE quality of evidence was very low which reduces confidence in any subsequent recommendations. Moreover, owing to the limited number of included studies publication bias was difficult to evaluate and sensitivity was impossible to evaluate even with obvious heterogeneity.

Baseline characteristics do not contain information on participants’ age. The conclusion drawn by the authors is not adequate: “This meta-analysis comparing unilateral and bilateral percutaneous kyphoplasties for treating OVCF showed that unilateral and bilateral percutaneous kyphoplasties are safe and effective surgical procedures”. The methods were NOT compared to standard treatment but to each other, which does not make them safe but rather equally safe or unsafe to use. Conflicts of interest for study authors are mentioned but not stated; for the primary data they are not mentioned. The differences in procedures and follow-up times represent an additional source of bias.

Author’s conclusion: This meta-analysis comparing unilateral and bilateral percutaneous kyphoplasties for treating osteoporotic vertebral compression fractures showed that unilateral and bilateral percutaneous kyphoplasties are safe and effective surgical procedures. Considering less operation time and less cost, we suggest that a unilateral percutaneous kyphoplasty is advantageous but because of the poor quality of the evidence, high-quality randomized controlled trials are required to resolve this issue definitively.

Outcome Measures/results

Primary VAS, Oswestry Disability Index, incidence of adjacent vertebral fractures, cement leakage, vertebral body height restoration, operative time, or local kyphosis angle.

Results: The short- and long-term clinical outcomes as assessed by the VAS and Oswestry Disability Index showed no differences between unilateral and bilateral kyphoplasties (P=0.41, P=0.60 for VAS; P=0.10, P=0.36 for Oswestry Disability Index). There were no differences in complications such as cement leakage and adjacent vertebral fractures associated with the two approaches (P=0.43 and P=0.95). The kyphosis angle reduction and anterior vertebral height restoration showed no difference between the two approaches (P=0.34 and P=0.46). The unilateral approach was shorter in terms of surgical time (mean difference, -24.98; P<0.0001). The overall GRADE system evidence quality was very low, with only high evidence for operation time, which lessens our confidence in recommendations.
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<td>Included studies:</td>
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<td>Patient characteristics: Mean (SD) Age: when reported between 64.4 (10.4) - 72.9 (10.3) years. Follow-up: 6 studies with 12 months and 1 study with 13 months.</td>
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<td>Brankin E (2006)</td>
<td>Countries: USA, UK, Belgium, France, Israel. Centres: Not reported. Funding sources: &quot;This study was funded by Merck &amp; Co., Inc., Kenilworth, NJ, USA.&quot;</td>
<td>Inclusion criteria: Studies must (1) be conducted in adults with non-infectious chronic disease, (2) a primary publication, (3) quantify adherence or compliance and contain an adequate description of the methods used, and (4) compare QD and QW dosing of pharmacologic treatments.</td>
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<td>Cramer JA (2005)</td>
<td>Dropout rates: Not reported. Study limitations: - Measures of adherence based on MPR, which only indicates that prescription was filled. It is unknown whether medication was taken. - Potential for publication bias. - All included articles were in English and limited to those published between 2002 and 2013. Studies might not represent larger pool of all adherence studies available. - No adjustment for potential confounding factors or investigations of these possible due to small number of included studies - Review focused on QD and QW therapy only and is not generalizable to other osteoporosis dosing regimens. - Significant heterogeneity between observational studies for endpoint of MD in MPR. Random-effects modeling used but caution should be used when interpreting results.</td>
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<td>Downey TW (2006) South Med J</td>
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<td>Rabenda V (2008) Osteoporos Int</td>
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Notes: Study population not framed and unclear. Only studies until 2012 included. No search for grey/unpublished literature. No assessment of publication bias. 14 articles excluded during data extraction (fulfilled all inclusion criteria but e.g. defined MPR differently). 1 study was excluded "to maintain homogenous sample for meta-analysis" because it included patients without osteoporosis although population of interest was not specified beforehand. **Author's conclusion:** In summary, a QW dosing regimen was associated with improved medication adherence compared with the QD dosing regimen in patients with osteoporosis. It is important for physicians to consider the impact of dosing regimens when making treatment decisions, especially in patient subgroups that experience lower levels of adherence.

### Outcome Measures/results
- **Primary Adherence Assessment:** Medication possession ratio (MPR) - Adherence: Medication possession ratio ≥80% defined as adherence

**Results:** Mean Difference in MPR: Assessed in 9 studies. Significant substantial heterogeneity: \( Q = 48.2, P < 0.0001, i^2 = 83.4\% \). Significantly greater MPR with once-weekly dosing regimen (QW) compared with once-daily (QD) dosing (pooled MD = 12.29%; 95% CI: 10.76%, 13.82%: no p-value stated). After exclusion of study which results could not be verified: pooled MD = 11.69% (95%CI, 9.35%–14.03%; no p-value stated).

**OR for Adherence:** MPR ≥80% present in 5 studies. Low heterogeneity \( Q = 4.3, P < 0.36, i^2 = 7.9\% \). Pooled OR = 1.92 (95% CI; 1.84, 1.99; no p-value stated) favoring QW dosing.

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### Outcome Measures/results
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**OR for Adherence:** MPR ≥80% present in 5 studies. Low heterogeneity \( Q = 4.3, P < 0.36, i^2 = 7.9\% \). Pooled OR = 1.92 (95% CI; 1.84, 1.99; no p-value stated) favoring QW dosing.
### Evidence level: 1++

**Study type:** RCT

**Countries:** USA, Canada  
**Centres:** multi center  
**Setting:** no information  
**Funding sources:** Radiation Therapy Oncology Group (RTOG) and National Cancer Institute (NCI) grants  
**Dropout rates:** 11.93%  
**Study limitations:** Due to the early closure, the trial results are limited by small patient numbers. This likely resulted in decreased statistical power to detect any differences in the incidence of bone fractures or QOL.

**Total no. patients:** n=109  
**Patient characteristics:** - confirmed adenocarcinoma of the prostate  
- or < T3 with Gleason’s score (GS) > 8,  
- or < T3 with GS 7 and PSA ≥ 15,  
- or < T3 with GS < 7 and PSA ≥ 20  
- any N stage,  
- negative bone scan  
- Zubrod performance status 0-1  
- age ≥ 18 years;  
- normal calcium levels  
- T-scores of the hip (-2.5 vs. ≥ -1.0)  
- planned duration of LHRH therapy (≥ 1 year and ≤ 2.5 years vs. >2.5 years)  
**Inclusion criteria:**  
- ≥ T3 disease  
**Exclusion criteria:** -

**Interventions:**  
- Arm 1: first dose of zoledronic acid (4 mg, infusion) concurrently with the start of RT and then every six months (6 infusions). Dosage adjustment was required for those with renal impairment.  
- Arm 2: Observation  
- All patients: Vitamin D dose was 400 IU and calcium dose was 500 mg, both taken orally

### Notes:  
Sample size calculation (n=1272 patients), but study was stopped after 3 years because lack of patients: n=109.  
**Author’s conclusion:** For patients with advanced, non-metastatic prostate cancer receiving LHRH agonist and RT, the use of zoledronic acid was associated with statistically improved BMD percent changes. The small number of accrued patients resulted in decreased statistical power to detect any differences in the incidence of bone fractures or QOL.

### Outcome Measures/results

**Primary freedom from any bone fracture (FABF)**

**Secondary Quality of Life QoL**

**BMD**

**Results:** Baseline- 36 Months  
**Fractures**  
Only two patients experienced a bone fracture (1 in each arm)  
**BMD**  
Lumbar Spine  
- percent changes statistically improved with zoledronic acid vs observation (6% [6%, 6%] vs. -5% [-6%, -4%], p<0.0001)  
Left total hip  
1% [1%, 1%] vs. -8% [-9%, -7%], p=0.0002  
Left femoral neck  
3% [3%, 3%] vs. -8% [-10%, -6%], p=0.0007  
Right hip, right femoral neck  
not statistically significant

**Adverse Events**  
There was one patient death (grade 5 myocardial ischemia) in Arm 1 that was reported as possibly related to treatment, but no autopsy was performed and one death in Arm 2 (grade 5 cardiac) not related to treatment.  
**QoL**  
no differences

### Kalder, M. et al. Effects of zoledronic acid versus placebo on bone mineral density and bone texture analysis assessed by the trabecular bone score in premenopausal women with breast cancer treatment-induced bone loss: results of the ProBONE II substudy. Osteoporosis International : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 26. 353-60. 2015

<table>
<thead>
<tr>
<th>Evidence level: 1+</th>
<th>Study type: RCT</th>
<th>Evidence details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions:</th>
</tr>
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</table>
| **Countries:** Germany  
**Centres:**  
**Setting:**  
**Funding sources:**  
**Dropout rates:**  
**Study limitations:**  
**Total no. patients:** n=109  
**Patient characteristics:**  
**Inclusion criteria:**  
**Exclusion criteria:**  
**Interventions:** |
| **Interventions:** |
| **Notes:** see Hadji 2014  
**Author’s conclusion:** In premenopausal women with BC, 24 months of intravenous ZOL treatment significantly increased the LS BMD as well as the TBS.
Kendrick, Denise et al. Exercise for reducing fear of falling in older people living in the community. Cochrane Database of Systematic Reviews. 2014

Evidence level | Study details/limitations | Patient characteristics | Interventions
--- | --- | --- | ---
Evidence level: 1++ Study type: MA of 30 studies (29 RCT and 1 quasi-RCT) | Countries: 8 studies conducted in Australia, 7 in the USA, 3 in the Netherlands, 2 in Canada, 2 in Finland, 2 in Taiwan, 1 in China, 1 in Germany, 1 in New Zealand, 1 in South Korea, 1 in Sweden, 1 in Vietnam (2012). Centres: Not reported. Setting: Community setting Funding sources: Internal sources Salary support for authors and library resources by University of Nottingham, UK. University College London, UK, Glasgow Caledonian University, UK, University of Surrey, UK, St George's, University of London, UK, Nottingham University Hospitals NHS Trust, UK. Sources: No sources of support supplied Dropout rates: Not reported. Study limitations: - Since many studies included in our review did not measure fear of falling as a primary outcome, it is likely that our searches failed to identify some studies that measured but did not report fear of falling. - Upon reconsideration of our study selection judgements in our review, we identified 7 studies (695 participants) where it was unclear whether the treatment in the comparator group may have increased exercise. These are currently awaiting assessment as more details are required on the content of the comparator treatment to decide on inclusion of these studies and to consider the implications of the current decision not to include these studies in terms of introducing bias into the review. Total no. participants: 2,878 participants Patient characteristics: Older people living in the community. 4 studies recruited only women. Of the 26 studies that recruited both sexes, 25 reported the sex of participants, with most of these including a majority of women (ranging from 51% to 89%). The mean age of participants ranged from 68 years to 85 years. In 12 studies the mean age was less than 75 years; in all other studies the mean age was 75 years or older. Two studies specifically recruited people aged over 75 and over 80. 12 studies recruited participants who were at increased risk of falls (either because they had previously fallen or because they had other risk factors for falls). Three of these studies recruited participants who had fear of falling in addition to being at increased risk of falls. Inclusion criteria: Types of studies - Randomised and quasi-randomised controlled trials. Studies with cluster allocation, but excluded those with only one or two clusters in each intervention group. Types of participants - Trials where majority of study population comprised people aged 65 years and over who were 'community-dwelling', i.e. living either at home or in places of residence that do not provide nursing care or rehabilitation. - People who had recorded fear of falling or had a history of falling. Types of interventions - Studies reporting on effect of exercise interventions, whether an exercise 'prescription' or a 'recommendation', done in a group or individually and supervised or not. - Varying content of the exercises: for example, gait, balance and functional training; strength or resistance training; flexibility training; 3D training such as Tai Chi, QiGong and dance; and endurance training, which comprised aerobic exercise aimed at cardiovascular fitness. Types of outcome measures - Trials that measured fear of falling as a primary or secondary outcome. Exclusion criteria: - Trials including combined populations (i.e. community-dwelling older people and those receiving nursing or rehabilitation care) if they did not report separate results for community-dwelling adults. We also excluded trials whose populations were restricted to individuals with a specific condition (e.g. stroke or hip fracture). - Multi-component interventions that combined exercises with other intervention components (such as medication reviews, home hazard assessments, screening for and managing visual impairment, cognitive behavioural interventions and other interventions that aim to address risk factors for falling) due to the difficulty of attributing observed effects to the exercise. Interventions: 36 interventions reported from 30 included studies. Classified according to the fall prevention classification taxonomy developed by ProFaNe, with nine (25%) classified as 3D (Tai Chi, Yoga); 19 (53%) classified as gait, balance, coordination, functional tasks; and eight (22%) classified as strength and resistance based interventions. Interventions were with supervised activities (n = 27, 75%) or unsupervised activities (n = 9, 25%). Interventions delivered in group settings (n = 20; 56%) or individually (n = 16; 44%). Duration of intervention up to 2 weeks (n = 22; 61%), 13 to 26 weeks (n = 7; 19%) and more than 26 weeks (n = 7; 19%). Majority (n = 32; 89%) of exercise interventions performed between 1-3 times per week, 4 (11%) exercise interventions performed 4 or more times a week.
### Notes:
Date of literature search not stated. No summary table of study characteristics. Poor reporting of allocation methods in trials made assessment of selection bias difficult in most studies. All of the studies at high risk of performance + detection biases. 12 studies at high risk of attrition bias.

**Author's conclusion:** Implications for practice
Exercise interventions in community-dwelling older people probably reduce fear of falling to a limited extent immediately after the intervention, without increasing the risk or frequency of falls. There is insufficient evidence from the included studies to determine whether exercise interventions reduce fear of falling beyond the end of the intervention or their effect on other outcomes.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Fear of falling (includes measurement using single-item measures and measures of falls efficacy, balance confidence, and concern or worry about falling):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Fear of falling as measured by a single-item question.</td>
</tr>
<tr>
<td></td>
<td>• Falls efficacy as measured by the Falls Efficacy Scale (FES) and its associated versions, FaES, aFES, and FES-UK.</td>
</tr>
<tr>
<td></td>
<td>• Balance confidence as measured by the Activities-specific Balance Confidence Scale for older adults (ABC) and its UK version ABC-UK.</td>
</tr>
<tr>
<td></td>
<td>• Concern about falling as measured by the international version of the FES in its long (FES-I) and short forms (Short-FES-I), Mobility Efficacy Scale (MES), aFES, and amFES, and worry about falling measured using the Survey of Activities and Fear of Falling in the Elderly (SAFFE).</td>
</tr>
<tr>
<td>Secondary</td>
<td>Occurrence of falls: number or rate of falls, or participants experiencing at least one fall (fallers). Falls were included as a secondary outcome as there may be beneficial effects on falls from exercise but they may also occur as adverse events during exercise.</td>
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<tr>
<td></td>
<td>• Activity avoidance or restriction: the modified SAFFE, or single questions asking about activity avoidance.</td>
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<td></td>
<td>• Depression: the depression subscale of the Hospital Anxiety and Depression Scale (HADS), the Geriatric Depression Scale (GDS), GDS-5, GDS-20, or the Cornell Scale for Depression in Dementia (CSDD).</td>
</tr>
<tr>
<td></td>
<td>• Anxiety: Beck Anxiety Inventory, the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), Penn State Worry Questionnaire and Geriatric Mental State Examination. These scales have been validated for use in older adults.</td>
</tr>
<tr>
<td></td>
<td>• Compliance with or adherence to exercise interventions, including measures of physical activity.</td>
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<td></td>
<td>• Cost.</td>
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</tbody>
</table>

#### Results:

**Primary:** Exercise interventions associated with a small to moderate reduction in fear of falling immediately post intervention (SMD 0.37 favouring exercise, 95% confidence interval CI 0.18 to 0.56; 24 studies; 1692 participants, low quality evidence). Pooled effect sizes did not differ significantly between the different scales used to measure fear of falling. Although none of the sensitivity analyses changed the direction of effect, the greatest reduction in the size of the effect was on removal of an extreme outlier study with 73 participants (SMD 0.24 favouring exercise, 95% CI 0.12 to 0.36). Subgroup analyses did not provide robust evidence of differences in effect in terms of either the study primary aim (reduction of fear of falling or other aim), the study population (recruitment on the basis of increased falls risk or not), the characteristics of the study exercise intervention or the study control intervention (no treatment or alternative intervention).

**Secondary:** Very low quality evidence that exercise interventions may be associated with a small reduction in fear of falling up to six months post intervention (SMD = 0.17, 95% CI -0.05 to 0.38; four studies, 356 participants) and more than 6 months post intervention (SMD 0.20, 95% CI -0.01 to 0.41; three studies, 386 participants). Very low quality evidence suggests exercise interventions in these studies that also reported on fear of falling reduced the risk of falling measured either as participants incurring at least one fall during follow-up or the number of falls during follow-up. Very low quality evidence from four studies indicated that exercise interventions did not appear to reduce symptoms of depression or increase physical activity. The only study reporting the effects of exercise interventions on anxiety found no difference between groups. No studies reported the effects of exercise interventions on activity avoidance or costs. It is important to remember that our included studies do not represent the totality of the evidence of the effect of exercise interventions on falls, depression, anxiety or physical activity as our review only included studies that reported fear of falling.

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<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
</table>
Evidence level: 1++
Study type: RCT
Countries: Korea
Centres: multicenter
Investigational centers: MDS Korea Ltd.
Funding sources: MSD Korea Ltd.
Dropout rates: 21.87%
Study limitations: -

Total no. patients: n = 343

Patient characteristics: Women of satisfactory general health being postmenopausal (≥6 months beyond the final menstrual period)
Inclusion criteria: - serum 25(OH)D ≥9 ng/mL
- presence of osteoporosis (defined as one of the following: lumbar spine or femoral neck T-score ≤-2.5, T-score ≤-2.0 with any lumbar intervertebral spine fracture, or two or more fractures in lumbar spine regardless of bone mineral density (BMD))
- no contraindication to oral bisphosphonates
- spine or hip anatomy suitable for dual-energy X-ray absorptiometry (DXA)
- willingness to limit direct sunlight exposure to <1 hour/day with sunscreen; and avoidance of other vitamin D supplements during the 16-week study
- Patients with serum 25(OH)D levels <15 ng/mL but ≥9 ng/mL were required to have serum PTH and total alkaline phosphatase within reference ranges
Exclusion criteria: - vitamin D deficiency [25(OH)D <9 ng/mL]
- abnormalities of the esophagus that delay esophageal emptying (e.g., stenosis or achalasia)
- certain malignancies, active systemic diseases that could pose an added risk to the patient or the patient’s ability to complete the study
- other disorders of bone or mineral metabolism
- recent treatment with agents that affect bone or calcium metabolism
- Patients who could not sit or stand for at least 30 minutes and patients with a history of alcohol or drug abuse

Notes: sample size calculation insufficiency reported
Author’s conclusion: In conclusion, ALN/D5600 once weekly for 16 weeks provided enough vitamin D to reach target serum 25(OH)D levels (>15 ng/mL) in >98% of patients. Furthermore, it showed superior efficacy to that of ALN without vitamin D supplementation. The combination tablet of ALN/D5600 once weekly not only significantly increased serum 25(OH)D but greatly reduced increases in PTH, compared to ALN. Moreover, the safety and tolerability of ALN with or without vitamin D3 were comparable.

Outcome Measures/results
Primary serum 25(OH)D level
- percentage of subjects with vitamin D insufficiency [serum 25(OH)D level <15 ng/mL]
Secondary percentage change from baseline in serum PTH
- neuromuscular function
- Safety

Results: serum 25-hydroxyvitamin D
- mean serum 25(OH)D increased at weeks 8 and 16 from baseline in the ALN/D5600 group (p<0.001)
- ALN group, mean values of serum 25(OH)D decreased with significance at week 16 (p<0.01)
- Change: significant difference between the groups at week 8 and 16
- Increases in serum 25(OH)D were much higher in subgroups that were vitamin D-insufficient at baseline, compared with those vitamin D-sufficient.
- The difference between groups: percentage of subjects with vitamin D insufficiency at week 8 and 16 was statistically significant
- Week 16: percentage with vitamin D insufficiency was 1.47% (n=2/136) in the ALN/D5600 group and 41.67% (n=55/132) in the ALN group (p<0.001)
- Among patients with 25(OH)D levels <15 ng/mL at baseline, the proportions of persisting insufficiency were 2.17% (n=1/48) at week 8 and 4.08% (n=2/49) at week 16 in the ALN/D5600 group. However, they were 53.49% (n=23/43) at week 8 and 52.27% (n=23/44) at week 16 in the ALN group.
- PTH
- The least squares mean percent change from baseline of serum PTH in the ALN/D5600 group was significantly lower than that in the ALN group (8.17% vs. 29.98%, p<0.01).
- neuromuscular function
- no significant differences
- Safety
- There were no statistically significant differences in incidence of adverse events and adverse drug reactions between the groups. Serious AEs reported during the study period comprised 4.09% (n=7/171, 10 cases) in the ALN/D5600 group and 0.59% (n=1/170, 1 case) in the ALN group.

Interventions: For 16 weeks, once weekly alendronate 70 mg containing 5600 IU vit-D3 (ALN/D5600) versus alendronate 70 mg without additional vit-D (ALN). Both groups 500 mg/day of calcium carbonate (1200 mg of elemental calcium)

<table>
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<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient interventions characteristics</th>
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<tbody>
<tr>
<td>Evidence level: 2-10. Study type: Systematic review and metaanalysis: 14 studies (7 randomized placebo controlled studies, 7 metabolic crossover studies)</td>
<td>Countries: n.a. Centres: n.a. Setting: n.a. Funding sources n.a. Dropout rates: No dropout rates are reported. The risk of bias evaluation regarding incomplete outcome data was considered too low in 12 and unclear in 2 studies. Study limitations: The main limitation of this analysis is the heterogeneity of included studies in terms of study design, primary outcome measures and populations studied. Although all the studies included were randomised controlled trials, there were marked differences in dosage, duration and method of administration of the supplement, as well as age and gender of the study populations. In addition, there were very few studies with BMD as the primary endpoint, which fulfilled the inclusion criteria, which limits the applicability of our findings, particularly with respect to fracture risk. Nevertheless, it is important to note that the novel finding of an effect of alkaline potassium salts on bone resorption was seen among studies with little or no heterogeneity.</td>
<td>Total no. patients: 437 (KHCO₃). 624 (KCl). Secondary analysis: 311 (KCl). Patient characteristics: Information for mean age or range or gender ratio is not available for all studies. But the majority of studies (n=10) were conducted in postmenopausal women or elderly men. 2 studies were conducted in young men, 1 in young women, one in young women and one study covering the age spectrum of 1875 years. The study size ranged between 26 to 276 participants. Inclusion criteria Study types: RCTs and metabolic studies, parallel or crossover design, metabolic or community-based intervention studies. Population: Human adult men or women. Intervention: KHCO₃ or KCl. Supplementation at all dosages and for any duration (also when combined with other forms of dietary or pharmaceutical manipulation, such as high protein or salt intake or diuretic administration). Outcomes: urinary calcium excretion, markers of bone resorption and formation, BMD and net acid excretion (NAE). Exclusion criteria: Studies were not eligible if they were conducted in patients with kidney disease, metabolic bone disease or following renal, bariatric or other surgery or in pregnant or lactating women.</td>
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</tbody>
</table>
Jehle S, et al. (2013) J Clin Endocrinol Metab
Moseley KF, et al. (2013) J Bone Miner Res
Sakhaee K, et al. (2005) J Clin Endocrinol Metab
Sellmeyer DE, et al. (2002) J Clin Endocrinol Metab

Notes: Not all of the author's conclusions can be supported. There is significant and high amount of heterogeneity (I^2 = 93,3,95,97% and p<0.00001) for Calcium excretion and NAE for both interventions. This should have consequences (exclusion of studies, exploration, meta regression or simply refraining from meta-analysis). The authors performed a sensitivity analysis and state that the removal of study type (crossover studies) did not change the results, but they cannot explain the heterogeneity. Points are deducted because of the lack of possible investigations of heterogeneity and the uncritical interpretation/presentation in the abstract and results. Potential sources of heterogeneity include differences in intervention length, dosage and administration as well as patients' age, gender and overall health. For the meta-analysis of NTX fixed effects models could have been chosen, due to I^2=0%. Data extraction was likely only performed by a single investigator. Baseline characteristics and risk of bias assessment are available in the online supplementary. No information on gender distribution in the studies. No use of wildcards or Mesh terms in the search, which might have added additional potentially relevant articles. No COI for the included primary studies.

Author's conclusion: This meta-analysis confirms that supplementation with alkaline potassium salts leads to significant reduction in renal calcium excretion and acid excretion, compatible with the concept of increased buffering of hydrogen ions by raising circulating bicarbonate. The observed reduction in bone resorption indicates a potential benefit to bone health.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Study</th>
<th>Patient characteristics</th>
<th>Interventions details/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Urinary calcium excretion, markers of bone resorption and formation, BMD and NAE.</td>
<td>Countries: Belgium, Canada, Denmark, France, Poland, Sweden, and the United States</td>
<td>Total no. patients: n=228 (n= 111 continued denosumab, n= 117 crossed over from placebo)</td>
<td>Interventions: Two 12 months phases: 1. Month 1-12: double-blind, randomized trial comparing 60 mg of denosumab sc every 6 months (q6m) with placebo 2. Month12-24: open-label phase, all participants (independent of randomization) were to receive 60 mg of denosumab sc q6m at month 12 and 18. All participants: daily supplements of ≥ 1000 mg elemental calcium and ≥ 800 IU vitamin D</td>
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<td>Secondary Comparison of KHCO3 and KCIt with KCl on the same outcome measures, in order to attempt to clarify the respective roles of the potassium cation and the basic anions.</td>
<td>Setting: multicenter centers</td>
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<tr>
<td></td>
<td>Funding sources: -</td>
<td>Patient characteristics: men with low BMD</td>
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<tr>
<td></td>
<td>Dropout rates:</td>
<td>Inclusion criteria: - T-score of ≤2.0 and ≥2.5 at the lumbar spine or femoral neck - T-score of ≤1.0 and ≥2.5 at the lumbar spine or femoral neck with a prior major osteoporotic fracture and had at least 2 lumbar vertebral, 1 hip, and 1 forearm evaluable by dual-energy x-ray absorptiometry (DXA)</td>
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<td></td>
<td>2.56%</td>
<td>Exclusion criteria: - any severe or &gt;1 moderate vertebral fracture at month 1</td>
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<td></td>
<td>Study limitations:</td>
<td>- clinical fracture diagnosed within 6 months before screening</td>
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<td></td>
<td></td>
<td>- diseases that affect bone metabolism,</td>
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<td></td>
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<td>- vitamin D deficiency</td>
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<td>- bisphosphonate treatment</td>
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<td>- anabolic steroids or testosterone, glucocorticoids, calcitonin, calcitriol, or vitamin D derivatives and other bone-active drugs</td>
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<td></td>
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<td>- significantly impaired renal function</td>
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Langdahl, B. L. et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. The Journal of clinical endocrinology and metabolism. 100. 1335-42. 2015

Evidence level

Evidence level: ++
Study type: RCT, ADAMO trial phase II open-label


Notes: Author's conclusion: In men with low BMD, denosumab treatment for a second year continued to increase BMD, maintained reductions in bone resorption, and was well tolerated. BMD increased in men initiating denosumab during the second year. These effects were similar to those previously seen in postmenopausal women with osteoporosis and in men with prostate cancer receiving androgen deprivation therapy.
Primary secondary not defined  
Secondary - percent changes in BMD of the lumbar spine, total hip, femoral neck, trochanter, and 1/3 radius  
- percent change from baseline in serum type I collagen C-telopeptide  
- safety  

Results: BMD  
long term denosumab group:  
- month 12-24: increases of BMD continued at all skeletal sites evaluated (2.2% lumbar spine, 0.9% total hip, 1.3% femoral neck, 1.3% trochanter, and 0.2% 1/3 radius)  
- baseline-month 24: 8.0% (lumbar spine), 3.4% (total hip), 3.4% (femoral neck), 4.6% (trochanter), and 0.7% (1/3 radius)  
- all P < .01  
Placebo Crossover Group:  
- month 12-24: significant gains in BMD at the lumbar spine (4.9%), total hip (1.7%), femoral neck (1.9%), trochanter (2.0%), and 1/3 radius (1.0%) (all P < .01)  
- month 1-24: similar to those observed in the long-term denosumab group during the first 12 months (lumbar spine, 5.8%; total hip, 2.3%; femoral neck, 2.2%; trochanter, 3.2%; and 1/3 radius, 0.6%).  

Bone turnover markers  
long term denosumab group:  
- month 12: 60% reduction in sCTX(P < .0001).  
- months 18 and 24, sCTX levels remained lower than baseline (57% and 50%)(P < .0001)  
Placebo Crossover Group:  
- month 1-12: no change  
- months 12-24: median decrease in sCTX of 68% at month 18 and 59% at month 24 (P < .0001)  
Anti-denosumab antibody assays  
Anti-denosumab binding antibodies were not detected at anytime point  

Fractures  
During phase II, clinical fractures in 4 men (2 rib and 2 foot, (3.6%))and  
Clinical osteoporotic fractures were reported in 2 men (2 rib) in the long-term denosumab treatment group (1.8%). No new vertebral fractures.  

SAFETY  
During the open-label phase, the participant incidence of overall AEs was 63% in the long-term group and 52% in the crossover group. Most AEs were mild or moderate in severity in both groups.


Evidence level  
Study type: RCT  
Countries: USA  
Centres: Family Medicine, Preventive Medicine, Primary Care Internal Medicine, and General Internal Medicine  
Setting: Primary care  
Funding sources: This study was supported by a grant from the Foundation for Informed Medical Decision Making (Now the Informed Medical Decisions Foundation, http://www.informedmedicaldecisions.org/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.  
Dropout rates: 1 post hoc exclusion after randomization in "usual care" arm because patient was already on bisphosphonates (7.1%).  
1 post hoc exclusion after randomization in "FRAX" arm because patient withdrew consent.  
6 patients lost to follow-up in "usual care" arm (42.9%), 11 patients and 5 clinicians lost to follow-up in "FRAX" arm (48.5%), 10 patients and 4 clinicians lost to follow-up in "Decision aid" arm (43.8%).  
Study limitations: Inability to determine impact of intervention on patient adherence to bisphosphonates, a central issue in osteoporosis care.  
Results too imprecise to make a judgment. Clinicians had very limited experience using the decision aid with their patients.  

Interventions: Decision aid arm: Use of the Osteoporosis Choice aid by clinician and patient during the clinical encounter. Included (a) individualized 10-year risk of having a bone fracture (by FRAX calculator) without and without use of bisphosphonates (i.e., showing the absolute reduction with bisphosphonates) represented using an evidence-based pictograph and assuming a treatment-related reduction in overall fractures of 40%; and (b) potential harms and other downsides of using bisphosphonates. The study coordinator prepared each decision aid according to each patient's characteristics prior to the clinical encounter. Shared decision-making with patient about whether to start bisphosphonates and whether to start at that time or at a later time.  
FRAX arm: consisted of giving clinicians a copy of patient's individualized 10-year risk of having a bone fracture using FRAX calculator before visit for use during clinical encounter.  
Usual Care: Clinicians discussed risk of fractures and treatment as usual without any research-related intervention.  

Evidence level  
Study details/limitations  
Total no. patients: 78 women randomized, 77 women analyzed.  
Patient characteristics:  
Mean Age (SD): 69 (8) years in Decision Aid arm; 66 (10) years in FRAX/Usual Care arm.  
Mean BMI (SD): 27 (6) years in Decision Aid arm; 28 (5) years in FRAX/Usual Care arm.  
Mean Frax Score (SD): 14 (8) % in Decision Aid arm; 13 (7) % in FRAX/Usual Care arm.  
Inclusion criteria:  
Clinicians (i.e., physicians, nurse practitioners); participants primary care practices affiliated with Mayo Clinic and provided care for patients with osteopenia or osteoporosis.  
Patients: English-speaking women over 50 with a diagnosis of osteopenia or osteoporosis, not taking bisphosphonates or other prescription medications to treat their condition, identified by their clinician as potentially eligible for bisphosphonates, available for a six month, follow up after randomization, and no major learning barriers.  
Exclusion criteria:  

Notes:  
Allocation concealment mentioned but not specified.  
Study planned and started with 2 intervention arm. One additional arm ("usual care") was added 5 months after enrollment had already started. Reasons not stated comprehensively and indicates deficiencies in study planning.  
Consequently, sample size calculation is invalid and study underpowered. This is further compounded as original sample size of 150 participants was not reached since study funding run out beforehand.  
Unclear, if 6 months follow up could be maintained for patients in "usual care" arm. Obtainment of pharmacy records 9 months after enrollment impossible for this intervention arm because study ended before this point.
**Outcome Measures/results**

**Primary:** Patients’ knowledge, adherence to medication, involvement in decision-making by the clinician, fidelity to intended intervention, acceptability, satisfaction, and quality of life.

**Secondary:** Decisional conflict, decision to start medication.

**Results:**
- **Patient knowledge:** Significant increase in patient knowledge in the Decision Aid arm about matters covered in the decision aid (Knowledge of Risk without medication: RR = 2.0 [95% CI; 1.2, 3.2], p=0.01; Knowledge of Post-treatment risk: RR = 2.6 [95% CI; 1.6, 4.4], p<0.0001, and no difference in knowledge of matters not covered in the decision aid (Overall: Median = 7.0 [IQR: 4.5, 9.0] for Decision Aid arm; Median = 5.5 [IQR: 2.5, 8.0] for FRAX/Usual Care arm, p=0.11).
- **Prescription rate:** No significant differences between groups.
- **Adherence and initial prescription filled:** No significant differences between groups.
- **Patient involvement in decision:** Significantly higher in Decision aid arm: OPTION score: 57% (95% CI; 50, 64) vs 43% (95% CI; 37, 48), t-test p = 0.001.
- **Patient satisfaction:** No significant differences between groups.

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<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patients characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>++1</td>
<td>Countries: USA Centres: USA</td>
<td>Postmenopausal women aged 45 years or older</td>
<td>Original DATA study: 24 months.</td>
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<tr>
<td></td>
<td>Funding sources: Amgen, Eli Lilly and National Institutes of Health</td>
<td></td>
<td>Teriparatide 20 μg subcutaneously daily, denosumab 60 mg subcutaneously every 6 months, or both drugs. DATA-Switch: After completion of DATA study, women originally assigned to teriparatide received 24 months denosumab (teriparatide to denosumab group), those originally assigned to denosumab received 24 months teriparatide (denosumab to teriparatide group), and those originally assigned to both received 24 months of denosumab alone (combination to denosumab group).</td>
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<td>Dropout rates: 7.23%</td>
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<td>Study limitations: First, the size of the study precludes an assessment of the relative safety of and antifracture efficacy of the three assigned treatment regimens. Bone mineral density, however, has proven to be a reliable, although imperfect, predictor of antifracture efficacy in patients treated with osteoporosis drugs, including denosumab and teriparatide. Additionally, the specific clinical impact of the transient bone loss that occurs in women switching from denosumab to teriparatide cannot be precisely estimated.</td>
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<td>Total no. patients: N=83</td>
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<td></td>
<td>Patient characteristics:</td>
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<td>Teriparatide:</td>
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<td>Patients:</td>
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<td>Denosumab:</td>
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**Notes:** No sample size calculation. **Original DATA study:** 24 months.

**Author’s conclusion:** In postmenopausal osteoporotic women switching from teriparatide to denosumab, bone mineral density continued to increase, whereas switching from denosumab to teriparatide results in progressive or transient bone loss. These results should be considered when choosing the initial and subsequent management of postmenopausal osteoporotic patients.

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**Outcome Measures/results**

**Primary Percent change in posterioranterior spine bone mineral density over 4 years**

**Results:** Original DATA study: after 24 months of the originally assigned drugs, mean lumbar spine bone mineral density had increased significantly in all treatment groups relative to baseline with the greatest increases in women treated with both drugs together. DATA-Switch:
- **Lumbar Spine BMD:**
  - After 48 months: no significant difference between any of the treatment groups increased more after the treatment transition (between months 24 and 48) in the teriparatide to denosumab group (8.6 [SD 5.0]) than in either the denosumab to teriparatide group (4.8 [5.0]; between group p=0.0203) or the combination to denosumab group (3.4 [3.5]; between group p=0.0005).
  - Total hip BMD:
    - After 48 months: increased more in the combination to denosumab group than in either the teriparatide to denosumab group (betweengroup p=0.0446) or the denosumab to teriparatide group (betweengroup p=0.0001).
    - After 48 months: increased more in the teriparatide to denosumab group than in the denosumab to teriparatide group (betweengroup p=0.0002).
    - After transition, months 24-48: increased more in the teriparatide to denosumab group (4.7% [SD 2.6]) than in both the combination to denosumab group (2.2% [1.8]; p=0.0008) and the denosumab to teriparatide group (−0.7% [3.1]; p=0.0001).
- Femoral hip BMD:
  - After 24 months: increased more in the combination to denosumab group than in either the teriparatide to denosumab group (between group p=0.0002) or the denosumab to teriparatide group (between group p=0.0001).
  - After transition, months 24-48: increased more in the teriparatide to denosumab group (4.7% [SD 2.6]) than in both the combination to denosumab group (2.2% [1.8]; p=0.0008) and the denosumab to teriparatide group (−0.7% [3.1]; p=0.0001).

**Secondary Percent change in total hip, femoral neck, and radius shaft BMD percent change in serum osteocalcin and C-telopeptide concentrations**

**Notes:** No sample size calculation.
Furthermore, monotherapy in Setting Centres BMD controlled making the fracture and increases white.

After the cohort, the treatment with teriparatide, median osteocalcin increased by 275% (IQR 175–410) above the original baseline after 6 months of teriparatide (month 30) and remained 159% (81–302) over the original baseline even after 24 months of teriparatide. Cetlopleotide concentrations increased by 183% (IQR 80–343) at month 30 and were 42% (22–120) above baseline.

After 48 months: treated with denosumab followed by teriparatide, median osteocalcin increased with teriparatide, bone resorption (Cetlopleotide) was maximally suppressed after 1 month of denosumab, whereas bone formation (osteocalcin) was not maximally suppressed until 12–24 months of denosumab treatment.

After 48 months: treated with combination therapy followed by denosumab monotherapy, however, both markers were maximally suppressed at all postswitch timepoints.

After 48 months: comparing women in the teriparatide to denosumab group vs the combination to denosumab group (both of which are receiving the same treatment from month 24–48), serum osteocalcin was significantly higher in those switching from teriparatide monotherapy to denosumab monotherapy than in those switching from combination therapy to denosumab monotherapy at 1 months and 6 months after the transition (months 25 and 30; p<0.001 at month 25 and p=0.0023 at month 30). Conversely, Cetlopleotide in these two groups did not differ at any timepoint after the treatment transitions.


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>Countries: USA</td>
<td>Total no. patients: N= 94</td>
<td>Interventions: The DATA extension study is a 12-month extension to the original 12-month, open-label, randomized controlled trial. 60 mg of denosumab sc every 6 months (Prolia; Amgen, Inc), 20 μg of teriparatide sc daily (Forteo; Eli Lilly, Inc), or both medications for 12 months. Continuation to the assigned treatment for an additional 12 months (24 months of total therapy). Before the initial randomization, subjects were stratified based on age (&lt;65 or ≥65 years) and prior bisphosphonate use (yes/no).</td>
</tr>
<tr>
<td></td>
<td>Centres: -</td>
<td>Patient characteristics: postmenopausal women aged 45 or older</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setting: -</td>
<td>Fracture criteria: at least 36 months since last menses (or since hysterectomy if the FSH level was &lt;40 U/L) at high fracture risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Funding sources: Eli Lilly Inc, Amgen Inc, and by the Harvard Clinical and Translational Science Center, the National Center for Research Resources.</td>
<td>Exclusion criteria: evidence of hyperparathyroidism, vitamin D deficiency (serum level less than 20 ng/mL) other congenital or acquired bone disease history of malignancy (with the exception of nonmelanoma skin cancer) - history of ionizing radiation therapy - significant cardiomyopathy, liver, or renal disease - major psychiatric disease - excessive alcohol intake ever taken parenteral bisphosphonates, teriparatide, or strontium ranelate - glucocorticoids or oral bisphosphonates within 6 months of enrollment - estrogen, selective estrogen receptor modulators within 3 months of enrollment - calcitonin within 3 months of enrollment</td>
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<tr>
<td></td>
<td>Dropout rates: Teriparatide 9.68%, Denosumab 6.08%, Combination 20%</td>
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<tr>
<td></td>
<td>Study limitations: First, the study was powered to detect changes in BMD but not changes in fracture rates. A study aimed to assess comparative fracture risk reduction would require a very large sample size and would not be feasible in the context of an investigator-initiated trial. Nonetheless, treatment-induced increases in BMD at the various anatomic sites have proven to be reliable, although not perfect, surrogates for efficacy in fracture prevention and the larger increases in BMD in the combination group compared with those in the monotherapy groups (ranging from 3.4% to 5.6% at the spine and 3.1% to 4.3% at the hip) are very likely to be clinically significant. In addition, although treatment induced improvements in the non-BMD determinants of bone strength may be important, BMD changes in patients treated with both denosumab and teriparatide monotherapy have been shown to predict fracture reduction. Furthermore, our cohort size was limited and made up predominately of white women, potentially limiting generalizability and making subgroup analysis not feasible.</td>
<td></td>
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</tr>
</tbody>
</table>
Evidence measures

**Primary**
- Percent change in PA spine BMD at 24 months.
- Percent change in total hip, femoral neck, and radius shaft BMD
- Overall change in serum OC, P1NP, and CTX

**Secondary**
- Percent change in total hip, femoral neck, and radius shaft BMD
- Overall change in serum OC, P1NP, and CTX

**Outcome**
- BMD 0-24 months
- Mean PA spine BMD increased significantly in all treatment groups relative to the baseline (P<0.0001 for all within-group comparisons increased more in the combination group than teriparatide or denosumab groups. 0.1 vs p 0.08 increase did not differ significantly between and femoral neck months relative to baseline .0008 within .003 no significant difference .23 total hip .001 .08 distal radius by both email decrease was statistically magnitude of change similar .95 although differed compared with .004 tmd there were between-group differences changes second year therapy however increases. spine .007 .09 biochemical markers bone turnover women treated alone mean serum oc p1np ctx at time points whereas they decreased other net auc each individual point which had month remained similarly suppressed slowly overall lower monotherapy furthermore therapy levels despite progressively greater suppression thereafter respectively as it measured finally comparison safety calcium-10.8 mg/dl were observed. All serious adverse events occurring in year 1 were considered unrelated to the study therapy.

**Notes:**
Sample size calculation no information. Modified intention-to-treat analysis, which included all data from subjects completing at least 1 postbaseline visit.

**Author's conclusion:** Two years of concomitant teriparatide and denosumab therapy increases BMD more than therapy with either medication alone and more than has been reported with any current therapy. The combination of these agents may prove to be an important treatment option in patients at high risk of fracture.

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**Leung, K. S. et al. Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture risks in 710 community elderly--a cluster-randomized controlled trial. Osteoporos Int. 25. 1785-95. 2014**

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1+ Study type: RCT</td>
<td>Countries: China, Hong Kong SAR, Hong Kong government. Funding sources: This study was supported by General Research Fund (Ref: 469508) of University Grants Committee (<a href="http://www.ugc.edu.hk">www.ugc.edu.hk</a>), Hong Kong SAR government.</td>
<td>Total patients: 710 women</td>
</tr>
<tr>
<td><strong>Study details/limitations</strong></td>
<td><strong>Patient characteristics:</strong></td>
<td><strong>Interventions characteristics</strong></td>
</tr>
<tr>
<td></td>
<td>Vibration group:</td>
<td>CONTROL group:</td>
</tr>
<tr>
<td></td>
<td>Age (years):</td>
<td>Age (years):</td>
</tr>
<tr>
<td></td>
<td>75.7</td>
<td>71.3</td>
</tr>
<tr>
<td></td>
<td>Body mass index (kg/m²):</td>
<td>Body mass index (kg/m²):</td>
</tr>
<tr>
<td></td>
<td>24.1</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>Hypertension:</td>
<td>Hypertension:</td>
</tr>
<tr>
<td></td>
<td>53 (15%)</td>
<td>48 (14%)</td>
</tr>
<tr>
<td></td>
<td>Diabetes:</td>
<td>Diabetes:</td>
</tr>
<tr>
<td></td>
<td>53 (15%)</td>
<td>50 (14%)</td>
</tr>
<tr>
<td><strong>Study limitations:</strong></td>
<td><strong>Inclusion criteria:</strong> Healthy females aged 60 years or above independent and active in the community.</td>
<td><strong>Exclusion criteria:</strong> (1) Women taking any medications or had medical conditions which affected metabolism of the musculoskeletal system, e.g., bisphosphonates. (2) Women who participated in supervised regular exercise for twice a week or more. (3) Women with a pacemaker in situ. (4) Women with malignancy. (5) Women with a history of smoking or excessive alcohol use (more than seven drinks per week).</td>
</tr>
</tbody>
</table>
| - Ideal design of study would have been individual randomized double-blinded. | **Notes:** Randomization method acceptable although prone to subversion (Center-based simple randomization by envelop drawing). Investigators blinded. Subjects not blinded “[...] because the vibration signal from the treatment platform could easily be felt [...]”. No test for baseline differences stated. Not stated whether subjects had significant differences at baseline. Cluster randomisation of centers (not individuals) might compound confounding influence of centers. Analyses of fall incidence based on subjects who reported their fall records (no true ITT-analyses). No data differences regarding centers reported. |}

**Author's conclusion:** In conclusion, this is the first study to show the beneficial effects of LMHVF in the prevention of falls among elderly women.
Evidence

Outcome Measures/results

Primary: Composite occurrence of fall or fracture after 18 month (self-reported and confirmed with clinical information including radiographs obtained from electronic patient record of Hong Kong Hospital Authority)
Secondary: Compliance rate (built-in data logger in vibration platform), Balancing ability (Basic Balance Master System; NeuroCom International Inc, OR, USA)
Quadriiceps muscle (dynamometer attached at malleol level), Areal bone mineral density (BMD, g/cm²)

Results: Fall or fracture incidence: Based on 334 vibration group subjects and 327 control subjects who reported their fall records. 62 (18.6 % of 334) subjects in vibration group and 94 (28.7 % of 327) in control group. Adjusted hazard ratio of falls or fractures in vibration group compared with control: 0.56 (95% CI: 0.40, 0.78, p=0.001). Adjusted incidence rate of falls in compared with control group: 0.54 (95% CI: 0.37, 0.78, p<0.001).
Rate of fracture in vibration group: 1.1%; Rate of fracture in control group: 2.31%. No statistically significant difference (adjusted HR=0.42, 95%CI; 0.12, 1.45, p=0.171).
Compliance: Average of 3.3 vibration sessions per week, 66 % vibration in the study period (18-month).
Balancing ability: Balancing ability in vibration group significantly improved compared with control group from baseline to 18 months. Improvement in reaction time: −0.38 s (95% CI; −0.55, −0.21, p<0.001). Improvement in movement velocity: 0.94 % (95% CI; 0.63, 1.26, p<0.001). Improvement in maximum point excursion: 10.72 % (95%CI; 7.05, 14.39, p<0.001). No significant difference of directional control.
Quadriiceps muscle: At 18 month significant improvement in vibration group: Mean between-group difference in dominant leg = 2.46 kg (95% CI: 1.70, 3.22, p<0.001); Mean between-group difference in nondominant leg = 2.43 kg (95% CI: 1.59, 3.27, p<0.001).
Areal bone mineral density: Lumbar spine: Mean change in vibration group 0.08% compared with -0.64% in control group at 18 months (mean between-group difference = 0.72 %, 95%CI; −0.12, 1.56, p=0.089). Hip BMD: Decrease in both groups. Mean change of total hip BMD in vibration group −1.86 % compared with −1.89 % in control group.
Health-related quality of life: No significant difference between groups after 18 months (Total score in vibration group = 2.45 [95% CI; 0.01, 4.90] vs Total score in control group = 1.62 [95% CI; −1.18, 4.43])


Evidence level
Study details/limitations

Evidence level, Study type: RCT

Countries: China
Centres: single center
Setting: Harbin Medical University, Harbin
Funding sources: National Natural Science Foundation of China

Study limitations: The follow-up period was only 2 y as a result of the negative calcium effects. Therefore, there was only one post randomization measurement, which prevented the use of intention-to-treat analyses. Instead, per-protocol analyses were used. Per-protocol analyses may overestimate effects compared with intention-to-treat analyses. Therefore, we could not directly evaluate whether an increase in serum cholesterol concentrations would increase risk of CVD because of the relatively short intervention period.

Patient characteristics

Total no. patients: see below
Patient characteristics: 190 premenopausal women (30–40 y old) and 182 postmenopausal women (50–60 y old) with dyslipidemia

Interventions: 800 mg CaO or a placebo for 2 years

Inclusion criteria: Dyslipidemia: fasting triglyceride concentration >1.7 mmol/L, fasting total cholesterol concentration >5.18 mmol/L, fasting LDL cholesterol >3.37 mmol/L, or fasting HDL cholesterol concentration <0.14 mmol/L

Exclusion criteria: - Any major diseases - regular medication use, which affected calcium or lipid metabolism - serum 25-hydroxyvitamin D3 concentration ≥0.2 mmol/L - use bisphosphonates or hormone therapy in the previous year - calcium or vitamin D3 supplementation in the previous year - pregnant women, breastfeeding women, hysterectomized women, or perimenopausal period

Notes:
No sample size calculation, no ITT

Author's conclusion: Calcium supplementation in postmenopausal women with dyslipidemia increases serum total cholesterol concentrations and CIMT. In postmenopausal women with dyslipidemia, calcium supplements should be prescribed with caution

Outcome Measures/results

Primary: No outcome measures defined.
- Total cholesterol,
- HDL-cholesterol,
- triglyceride,
- glucose,
- calcium
- blood pressure
- Serum estradiol
- Carotid intima-media thickness (CIMT)

Secondary:

Results: - Serum total cholesterol concentration after 2 y increased significantly in the calcium group compared with that in the placebo group (P<0.001)
- Serum triglyceride, LDL cholesterol, and HDL cholesterol concentrations and CIMT were not significantly affected after 2 y.
- There was a significant interaction between calcium supplementation and menopausal status on serum cholesterol concentrations (P < 0.001) and CIMT (P = 0.017). The change of total cholesterol in premenopausal women and postmenopausal women after calcium supplementation was 0.04 ± 0.07 compared with 0.61 ± 0.21 mmol/L (P < 0.001).
- The change of CIMT in premenopausal women and postmenopausal women after calcium supplementation was 0.0238 ±0.0348 compared with 0.0615 ± 0.134 mm (P = 0.003), respectively.

Liu, B. X. et al. The Effect of the Modified Eighth Section of Eight-Section Brocade on Osteoporosis in Postmenopausal Women: A Prospective Randomized Trial. Medicine (Baltimore). 94. e991. 2015

Evidence level
Study details/limitations

Patient characteristics

Interventions
Evidence level: 1-
Study type: RCT

Evidence Sources: This study was supported by the National Science Foundation Committee (NSFC) of China (grant no. 6140303313070) and by the Medical Research Foundation of Guangdong Province [grant no. B201216] and also by Grant [2013]163 from Key Laboratory of Malignant Tumor Molecular Mechanism and Translational Medicine of Guangzhou Bureau of Science and Information Technology.

Total no. patients: 198 women randomised, 184 analysed.

Patient characteristics:
- Control group: Mean age (year): 61.87±8.29; Height: 156.2±4.04
- Ca group: Mean age (year): 62.29±6.47; Height: 156.0±4.36

WESE group: Mean age (year): 63.23±7.56; Height: 154.27±4.34

WESE+Ca group: Mean age (year): 61.45±5.89; Height: 155.25±3.3

Inclusion criteria: (1) BMD in L2 to L4 and hip identified in women to be inadequate or BMD < -2.5 SD (T score < -2.5 indicating osteoporosis), (2) Postmenopausal women without traumatic fracture at any sites and typical menopausal symptoms (3) Age from 50 to 75 years.

Exclusion criteria: Women with cardiovascular or cerebrovascular disease, women with blood pressure higher than 160/110 mmHg on medication, women with systolic blood pressure less than 90 mmHg, women with heart stents or body implantation, women with a history of thrombosis within the past 6 months, women unresponsive from surgical operation, women which have been treated with drugs for osteoporosis or other agents which affect bone metabolism, women unresponsive from muscle strain joint injuries or fractures, women with symptoms of vertigo and in poor health, women with spinal nerve canal stenosis, spondylothesis, or lumbar disc herniation, and women with epilepsy.

Interventions:
- Control group (n=48); Ca alone (n=50); 500mg of calcium and 200 IU of vitamin D3, thrice daily)
- MESE (modified eighth section of Eight-Section Brocade) exercise alone (n=50); repetitions per time, thrice daily
- MESE+Ca (n=50)

Notes: Method of randomisation not described. No allocation concealment mentioned. Investigators could have been blinded but were not. Placebo should have been applied for groups without Ca supplement for improved comparability. Adverse events (e.g. fractures) not included as outcomes, but as reasons for drop-out. No ITT-analyses.

Author's conclusion: Our study reported greater improvement in the MESE and MESE+Ca group. We found that the treatment of MESE exercise was the most effective for alleviating the chronic pain, increasing the left femoral neck and lumbar BMD and balance in posture, which are associated with the increased bone fragility and higher risk of fracture. Importantly, the low attrition and exercise compliance coupled with the low number of adverse events indicates that this type of exercise program is safe, and feasible, and well tolerated by previously untrained, but otherwise healthy older men [sic].

Certainly, clearly more research is needed in order to better understand the specific therapeutic potential of MESE as an exercise model. Moreover, there seems to be a certain need for studies to assess any potential long-term risks. However, with appropriate introduction to the exercise modality, MESE exercise seems to be reasonably safe for most people.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary: Bone and body composition</th>
<th>Secondary: Balance and motility performance measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: Pain Visual Analogue Scale Scores</td>
<td>Results not quantified/ data not shown.</td>
<td></td>
</tr>
<tr>
<td>No significant difference for VAS in Ca group from 6 months to 12 months (P&gt;0.05). VAS decreased significantly in MESE and MESE+Ca groups to control group at each time point. Improvement in chronic back pain in MESE+Ca group and group MESE group better than in Ca group after 12 months (P&lt;0.001).</td>
<td></td>
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<tr>
<td>Bone Mineral Density: Results not quantified/ data not shown. MESE resulted in 1.9% net gain in left femoral neck BMD (not significant). Compared to control, significant higher increase after 12 months (P&lt;0.001). Significant 1.4% to 1.9% within-group increase in both exercise groups for left femoral neck BMD. No significant difference in lumbar BMD in both MESE and MESE+Ca groups after treatment for 12 months (P&gt;0.05).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in Balance Capacity: Results not quantified/ data not shown. Significant better results in 3-feet Up and Go Test (3UG) in MESE and MESE+Ca group compared to control group after the treatment for 6 to 12 months (P&lt;0.001 and P&lt;0.001). Results in OLS test significantly longer (1.75, 2.23, and 3.21 seconds) in Ca, MESE, and MESE+Ca groups compared to control group after the treatment for 3 weeks (P&lt;0.05, P&lt;0.001, P&lt;0.001).</td>
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</table>


Evidence level: Study details/inclusions | Patient characteristics | Interventions |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2-</td>
<td>Countries: Japan (n = 3), UK (n = 2), South Korea (n = 2), Thailand (n = 1), Greece (n = 1), China (n = 1), Netherlands (n = 1), Italy (n = 1)</td>
<td>Total no. patients: 1,544 cases and 15,541 controls</td>
</tr>
<tr>
<td>Study type: SR/MA of 13 case-control studies.</td>
<td>Centres: N.r.</td>
<td>Patient characteristics: Age: 1 study did not provide information. All other studies with participants at least ≥ 50 years.</td>
</tr>
<tr>
<td>Funding sources: &quot;This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.&quot;</td>
<td>Funding sources: &quot;This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.&quot;</td>
<td>(2) a study was performed to examine the association between the second contralateral hip fracture and the risk factors, cases and controls were defined based on the number of hip fractures sustained (bilateral and unilateral respectively);</td>
</tr>
<tr>
<td>Dropout rates: N.r.</td>
<td>Dropout rates: N.r.</td>
<td>(3) sufficient data was published for estimating an odds ratio (OR) or standardized mean difference (SMD) with 95% confidence intervals (CIs).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>Countries: China</td>
<td>Total no. patients: 10,655 people with osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Centres: 3 multicentre randomised trials</td>
<td>Patient characteristics: 65 trials included postmenopausal osteoporosis patients, 8 trials included senile osteoporosis patients and 35 trials included primary osteoporosis patients unspecified as to life-stage or co-morbidity.</td>
</tr>
<tr>
<td>MA of 109 RCT</td>
<td>Setting: Inpatients and outpatients</td>
<td>Race/ethnicity of all patients was Chinese in all 108 trials.</td>
</tr>
<tr>
<td>Included studies</td>
<td>Funding: Internal sources of Support</td>
<td>Interventions: 99 different Chinese herbal medicines tested.</td>
</tr>
<tr>
<td>See review.</td>
<td>School of Public Health, Shandong University, China.</td>
<td>8 Chinese herbal medicines tested twice or more (Kangguosong granule in 2 trials).</td>
</tr>
</tbody>
</table>
105 RCT included adults with a mean age of 61.3 years. 3 trials did not report data on gender or age or both. Average number of participants in trials was 98, ranging from 20 to 600 participants per trial.

**Inclusion criteria:** Types of studies
RCT irrespective of blinding, publication status or language. Cohort studies for evaluation of adverse effects/safety.

**Types of participants**
Study participants with primary osteoporosis or osteopenia regardless of age, gender or ethnic origin. Diagnosis on the basis of one of following criteria for bone mineral density (BMD) levels: single photon absorptiometry (SPA), dual photon absorptiometry (DPA), quantitative computerised tomography (QCT), dual energy X-ray absorptiometry (DXA) or peripheral dual energy X-ray absorptiometry (pDXA); World Health Organization (WHO) recommended criteria for primary osteoporosis based on BMD levels:
- Normal: BMD is within +1 or -1 standard deviations (SD) of the young adult mean.
- Osteopenia (low bone mass): BMD is between -1 and -2.5 SD below the young adult mean.
- Osteoporosis: BMD is < -2.5 SD or more than the young adult mean.
- Severe (established) osteoporosis: BMD is more than -2 SD and one or more osteoporotic fractures have occurred.

The Chinese diagnostic criteria for primary osteoporosis is based on BMD levels:
- Normal: BMD is within +1 or -1 SD of peak bone mass of the same race, gender and region.
- Osteopenia (low bone mass): BMD is between -1 and -2 SD and below peak bone mass of the same race, gender and region.
- Osteoporosis: BMD is < -2 SD or more than the peak bone mass of the same race, gender and region.
- Severe (established) osteoporosis: BMD is more than -2 SD and one or more osteoporotic fractures have occurred.

**Types of interventions**
Single herbs, combinations of herbs or Chinese proprietary medicines. Chinese herbal medicines classified into 2 major types: a) Chinese proprietary medicine which was approved by the China State Food and Drug Administration (SFDA) and produced by pharmaceutical companies with good manufacturing practices; b) herbal formulae prescribed by Chinese medicine practitioners based on a Chinese medicine diagnosis (i.e. pattern differentiation of symptoms). Control intervention could be no treatment, placebo or conventional pharmaceutical medicine (such as hormone replacement therapy, bisphosphonate, calcitonin, calcium and vitamin D), as well as non-pharmaceutical interventions such as exercise. Co-intervention was allowed as long as all groups from the randomised allocation received the same co-intervention.

**Types of outcome measures**
Major outcome measures at the end of treatment or at maximal follow-up:
1. Number of individuals with fractures and type of fractures (lumbar spine, radius, femoral neck).
2. Quality of life (QoL) or symptoms including pain, muscle fatigue and limited mobility.
3. Death directly or indirectly attributed to osteoporosis.
4. Adverse effects including serious adverse events and withdrawals: Reports of adverse effects associated with the herbs used in the treatment of osteoporosis from any type of study in order to evaluate harms. Minor outcomes at the end of treatment or at maximal follow-up:
   1. Bone mineral density (BMD).
   2. Biochemical indicators: serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), osteodrial (E2), parathyroid hormone (PTH), calcitonin (CT), bone Gluc protein (BGP), intereulin-6 (IL-6).

**Exclusion criteria:** - Patients with secondary osteoporosis, including corticosteroid-induced osteoporosis due to diseases affecting metabolism of bone and the liver, kidney and haematopoietic system, and disability of the heart and cerebral vessels.
- Studies in which duration of herbal treatment was less than three months.

**Notes:**
No search for grey/ unpublished literature. No summary table for characteristics of included studies. No assessment of publication bias "[due to the small number of trials testing the same intervention and same outcome]."
All trials at unclear risk of bias.
Broad range of included interventions/outcomes ruling out pooling could have been counteracted with stricter inclusion criteria (e.g. only controls with conventional therapy).
Applicability of results on European patients unclear (all 109 trials were conducted in Chinese populations).

**Author's conclusion:** Based on this systematic review, some Chinese herbal medicines may have beneficial effects on the bone mineral density at anatomical sites in people with osteoporosis. However, a large number of the included studies have an uncertain risk of bias, there is a lack of relevant clinical endpoints in the available evidence and the evidence is of low quality. Further rigorous studies are needed to demonstrate whether these effects are clinically meaningful and to detect other effects.

**Outcome Measures/result**

<table>
<thead>
<tr>
<th>Primary Fractures, Adverse Events, QoL</th>
<th>Secondary BMD, Biochemical indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: Primary: 7 trials reported fracture incidence, but were small in sample size, suffered from various biases and tested different Chinese herbal medicines. These</td>
<td>Bushen Qiangshen pill in 2 trials, Migu tablets in 2 trials, Guangkou oral liquid in 3 trials, Guoshuang granule in 3 trials, Qianggu capsule in 3 trials, Liwei Dihuang granules in 2 trials and Xianlinggubao capsule in 7 trials. Different control interventions in each trial of these trials. 45 trials tested single herbs and remaining trials tested Chinese proprietary medicine and the others tested prescribed herbal formulae. The composition and treatment regimens of the Chinese herbal medicines varied. Median duration of treatment was 5.7 months (ranging from 3 to 12 months). Control interventions included placebo in 3 trials and no treatment in 5 trials. In the other trials the control interventions were conventional pharmaceutical medicine or Chinese herbal medicines plus co-intervention versus the same co-intervention.</td>
</tr>
</tbody>
</table>
trials compared Kangguosong capsules versus placebo, Kangguosong granule versus Caltrate or ipriflavone plus Caltrate, Yigu capsule plus calcium versus placebo plus calcium, Xianlinggubao capsule plus Caltrate versus placebo plus Caltrate, Bushen Zhuanggu granules plus Caltrate versus placebo granules plus Caltrate, Kangguosong soup plus Caltrate versus Caltrate, Zhuangguqiangjin tablets and Shujinbogu tablets plus calcitonin ampoule versus calcitonin ampoule. Results were inconsistent. No trial reported death or serious adverse events of Chinese herbal medicines, while some trials reported minor adverse effects such as nausea, diarrhoea, etc.

1 trial showed that Bushenhuoxue therapy plus calcium carbonate tablets and alfalcaldiol had a better effect on quality of life score (scale 0 to 100, higher is better) than calcium carbonate tablets and alfalcaldiol (mean difference (MD) 5.30; 95% confidence interval (CI) 3.67 to 6.93).

Secondary:
Compared with placebo in three separate trials, Chinese herbal medicines (Migu decoction, Bushen Yigu soft extract, Kangguosong capsules) showed a statistically significant increase in bone mineral density (BMD) (e.g. Kangguosong capsules, MD 0.06 g/cm²; 95% CI 0.02 to 0.10). Compared with no intervention in five trials, only two showed that Chinese herbal medicines had a statistically significant effect on increase in BMD (e.g. Shigu yin, MD 0.08 g/cm²; 95% CI 0.03 to 0.13). Compared with conventional medicine in 61 trials, 23 showed that Chinese herbal medicines had a statistically significant effect on increase in BMD. In 48 trials evaluating Chinese herbal medicines plus western medication against western medication, 26 showed better effects of the combination therapy on increase in BMD.


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence level:</strong></td>
<td>Countries: n.a.</td>
<td>Total no. patients: 445979 for the main comparison, 6 studies of moderate or high quality.</td>
<td><strong>Interventions:</strong></td>
</tr>
<tr>
<td><strong>Study type:</strong></td>
<td>Centres: n.a.</td>
<td>Patient characteristics: Use or non-use of steroidal contraceptives during reproductive stage, not as a post-menopausal hormone treatment. Patient age range from 20-87 years.</td>
<td>Oral contraceptives (OC);</td>
</tr>
<tr>
<td>Systematic review and Meta-analysis: 14 observational studies (7 case-control and 7 cohort studies)</td>
<td>Setting: Hospital or clinical setting.</td>
<td><strong>Inclusion criteria:</strong> Study types: Cohort studies of contraceptive users as well as case-control studies. Post hoc analysis from such studies was also considered.</td>
<td>Depot medroxyprogesterone acetate (DMPA);</td>
</tr>
<tr>
<td><strong>Included studies:</strong></td>
<td>Funding sources:</td>
<td><strong>Population:</strong> Women who used steroidal contraceptives during their reproductive years or women in a comparison group who did not use hormonal contraceptives during their reproductive years.</td>
<td>Intrauterine devices (IUD) use.</td>
</tr>
<tr>
<td>Barad D, et al. (2005) Fertil Steril</td>
<td>• National Institute of Child Health and Human Development, USA. Funding to FHI 360 for conducting the review (LML, SM, MC)</td>
<td>Intervention: Comparisons of a hormonal contraceptive with a non-hormonal contraceptive, no contraceptive, or another hormonal contraceptive. The contraceptive must have been intended for contraception and not as treatment for another health condition, such as hormone replacement therapy for post-menopausal women. Interventions could also include a supplement for one group, such as another hormone or a vitamin or mineral preparation.</td>
<td><strong>Comparison:</strong> Non-use of contraceptives.</td>
</tr>
<tr>
<td>Cooper C, et al. (1993) Bone Kaunitz AM, et al. (2006) Contraception</td>
<td>• United States Agency for International Development, USA. Funding to FHI 360 for conducting the review (LML, SM, MC)</td>
<td>Outcome: The primary outcome was the risk of fracture, particularly fracture of the spine, hip, or wrist. We did not examine data on bone mineral density, which is considered a surrogate marker for fracture.</td>
<td></td>
</tr>
<tr>
<td>Lanza LL, et al. (2013) Obstet Gynecol</td>
<td>Dropout rates: Follow up adequacy was considered adequate in 2 out of 7 studies (NOS scale).</td>
<td><strong>Exclusion criteria:</strong> Study types: RCTs were excluded, as they were reviewed elsewhere (Lopez 2012) and no RCT had fracture as an outcome.</td>
<td></td>
</tr>
</tbody>
</table>
| La Vecchia C, et al. (1999) Lancet | Study limitations: "Due to varied study designs, we did not conduct meta-analysis."

"Due to varied study designs, we did not conduct meta-analysis." | Population: Studies that focused on women with specific conditions or situations that can affect bone health, such as epilepsy because some medications have a negative influence and athletes given that exercise can have a positive influence. | |
### Evidence level

#### Evidence level:
- **2++**

#### Study type: MA
- **of 8 prospective cohort studies**

#### Included studies:
- Langlois JA (1998) *Arch Intern Med*
- Langlois JA (2001) *Osteoporos Int*
- Meyer HE (1998) *Osteoporos Int*
- Langlois JA (1996) *Arch Intern Med*
- Mussolino ME

### Study details/limitations

- **Countries:** USA (7 studies), Norway (1 study)
- **Centres:** N.r.
- **Setting:** N.r.
- **Funding sources:** “This work was funded by the National Natural Science Foundation of China (81372014). The funders had no role in the design, execution, and reporting of the study.”
- **Dropout rates:** N.r.
- **Study limitations:** - No subgroup analysis by gender and age performed. - “Pre-study weight” (overweight or non-overweight) and willingness to “try to lose weight” (intentional vs unintentional weight loss) may influence risk of fracture. Findings from another study suggest that intentional weight loss in non-overweight population (BMI < 25.9 kg/m²) will not increase risk of hip fracture, while unintentional weight loss in non-overweight population (BMI < 25.9 kg/m²) and both intentional and unintentional weight loss in overweight population (BMI > 25.9 kg/m²) will increase risk of hip fracture. Only 1 study provided RR data for intentional and unintentional weight loss.
- Some of confounding factors that were inherent in included studies could not be estimated. Statistically significant evidence of heterogeneity found in weight loss studies.
- Due to a lack of critical data not all of the studies met requirement for dose-response meta-analysis.
- Measurement of weight change in most previous studies did not consider relative fat and lean mass change, though the gain in fat mass may have a negative effect on BMD, thus further influencing the risk of hip fracture.

### Results

#### Primary Total risk of fracture, first fracture, risk of fracture in the spine, hip or wrist.

#### Secondary n.a.

- **Results:** 14 studies met inclusion criteria, 6 were considered to provide moderate to high-level evidence.

- **Oral OC:** (6 studies) We noted few associations with fracture risk. One cohort study reported OC ever-users had increased risk for all fractures (RR 1.20, 95% CI 1.08 to 1.34). However, a case-control study reported no association except for those with 10 years or more since use (OR 1.55, 95% CI 1.03 to 2.33). Another case-control study reported increased risk only for those who had 10 or more prescriptions (OR 1.09, 95% CI 1.03 to 1.16). A cohort study of postmenopausal women found no increased fracture risk for OC use after excluding women with prior fracture. Two other studies found little evidence of association between OC use and fracture risk. A cohort study noted increased risk for subgroups, such as those with longer use or specific intervals since use. A case-control study reported increased risk for any fracture only among young women with less than average use.

- **DMPA:** (2 studies) One reported increased fracture risk for DMPA ever-use (OR 1.44, 95% CI 1.01 to 2.06), more than four years of use (OR 2.16, 95% CI 1.32 to 3.53), and women over 50 years old. The other reported increased risk for any past use, including one or two prescriptions (OR 1.17, 95% CI 1.07 to 1.29) and for current use of 3 to 9 prescriptions (OR 1.36, 95% CI 1.15 to 1.60) or 10 or more (OR 1.54, 95% CI 1.33 to 1.78).

- **IUD:** (1 study) For the levonorgestrel-releasing IUD, one study reported reduced fracture risk for ever-use (OR 0.75, 95% CI 0.64 to 0.87) and for longer use.


<table>
<thead>
<tr>
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<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. patients:</strong> Weight loss studies included 85.592 participants</td>
<td><strong>Patient characteristics:</strong> Age (range): 37 - 104 years. No mean age estimated.</td>
<td><strong>Interventions:</strong> Weight change, not further detailed.</td>
<td>4 studies included exclusively women, whereas the largest study with 39,089 participants included both women (19,938) and men (19,151), followed by the second largest study with only women (33,834). <strong>Inclusion criteria:</strong> (1) Designed as a prospective cohort study; (2) exposure of interest included either weight variability, weight change, weight loss, or weight gain; (3) primary outcome of interest was hip fracture; and (4) relative risk (RR) estimates with 95% CI (confidence interval) were reported or could be calculated using</td>
</tr>
</tbody>
</table>

Evidence level: 2+

Study type: MA of 10 trials (7 RCT and 3 CT)

Included studies:
4. Ebrahim S, Age Ageing 1997
5. Hatori M, Calcif Tissue Int 1993
6. Silverman NE, Calcif Tissue Int 2009
7. Wu J, Metabolism 2006
8. Yamazaki S, Bone Miner 2004
9. Martin D, J Bone Miner Res 1993
10. Gao H, Bone Miner Res 2006
11. Peking Union Medical College

Evidence Details:

Outcomes:
- Primary: Hip fracture.
- Secondary: -

Patient characteristics:
- Total no. patients: Invention group: 332 women; control group: 290 women
- Patient characteristics: Age, mean (range): 51.1 (46-71) years.
- 7 trials included both perimenopausal and postmenopausal women.
- 2 trials excluded hormone therapy (HT) users. 1 trial did not describe the details regarding HT use. 2 studies reported recruiting 4 and 7 HT users.
- Nutritional supplements: Calcium carbonate and Vitamin D14 for the duration of the intervention.
- 2 trials instructed all participants to eat a hypocaloric diet to lose weight.
- 1 trial investigated effects of isoflavone.
- 1 trial investigated effects of high or moderate dietary calcium.

Inclusion criteria:
1. Studies reported as peer-reviewed articles and dissertations
2. Studies published in English or Chinese.
3. Randomized and nonrandomized controlled studies on walking interventions in perimenopausal and postmenopausal women who were not undertaking regular physical activities

Exclusion criteria:
1. Studies in which intervention group or control group included men only or in which the data for women only were not presented or were not provided when requested from the authors.
2. Interventions that combined walking with other forms of exercises.

Interventions:
- Walking intervention: 6 trials reported walking for 40 to 60 minutes per session.
- Calcium and Vitamin D: 2 trials supplied all participants with calcium or calcium and vitamin D14.
- Walking per session: 1 trial with 30 minutes of walking per session.

Notes:
- Final search query not presented. No search for grey literature.
- Author's conclusion: Walking as a singular exercise therapy has no significant effects on BMD at the lumbar spine, at the radius, or for the whole body in perimenopausal and postmenopausal women. Although significant and positive effects on femoral neck BMD in this population are evident with an intervention duration of more than 6 months, the effects of walking might be less clinically significant for fracture prevention.

Outcome Measures/Results:
- Primary: BMD at lumbar spine, femoral neck, radius, and for the whole body.
- Secondary: -

Results:
- BMD at the lumbar spine: Assessed in all included trials. Combined weighted mean difference (WMD) in BMD = 0.01 g/cm² (WMD [fixed effects]; 95% CI: -0.00, 0.02; P = 0.05; \( I^2 = 47\% \)).
- BMD at the femoral neck: Assessed in 7 included trials. Combined weighted mean difference (WMD) in BMD = 0.01 g/cm² (WMD [fixed effects]; 95% CI: -0.00, 0.01; P = 0.07; \( I^2 = 0\% \)).
- BMD at radius: Assessed in 2 included trials. Combined weighted mean difference (WMD) in BMD = -0.01 g/cm² (WMD [random effects]; 95% CI: -0.06, 0.04; P = 0.71; \( I^2 = 54\% \)).
- BMD for the whole body: Assessed in 2 included trials. Combined weighted mean difference (WMD) in BMD = 0.04 g/cm² (WMD [fixed effects]; 95% CI: -0.00, 0.08; P = 0.06; \( I^2 = 0\% \)).
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1+</td>
<td>Countries: international, not specified. Centre: n.a. Setting: n.a. Funding sources: n.a. Dropout rates: n.a. Study limitations: Combination therapy was also included within the intervention, active comparator and placebo arms. As a result, the inclusion of these combination therapies may have exerted an effect on the outcome (the number of fractures). In future, a meta-regression could be performed, in order to identify the significance of this effect. Nonetheless, the presence of combination therapies in many patients accurately reflects the reality that single drug therapy is often insufficient to control glycaemic levels. Another limitation of this review was the unavailability of some data, especially within unpublished, yet disclosed trials from the clinicaltrials.gov website.</td>
<td>Total no. patients: 36,402 participants. Patient characteristics: 37 studies (n=23974) compared a DPP-4 inhibitor with a placebo. 14 studies (n=12,428) investigated DPP-4 inhibitor against an active comparator. The mean age of patients was 57.5±5.4 years and 47% of the entire population was female. Participants had a mean body mass index (BMI) of 30.2±2.0 kg/m². The average HbA1c was 8.2% and the percentage of patients who experienced a hypoglycaemic event was lower in the intervention compared to the comparator group (4.3% vs 5.3%). The durations of the studies ranged from 12 to 205 weeks, with an average of 47.8 weeks. There were 29 RCTs with a duration &lt;52 weeks, and 22 studies were &gt;52 weeks. <strong>Inclusion criteria:</strong> Study type: RCTs Population: T2DM patients Intervention: The intervention had to be either a DPP-4 inhibitor Comparison: Number of fractures. There was no restriction on the publication date of articles, as all studies up until June, 2015 were included. <strong>Exclusion criteria:</strong> No fractures occurred during trial. Non-English articles. Non-human studies.</td>
<td><strong>Interventions:</strong> Placebo studies: The DPP-4 inhibitors investigated in each RCT are as follows: 5 studies with alogliptin, 3 with linagliptin, 12 studies with saxagliptin, 29 with sitagliptin and two studies with vildagliptin. Considering the placebo groups, a total of 28 studies (55%) had placebo in combination with another drug. Active comparator studies: Five studies (35%) were combination therapies. 8 studies involved the use of metformin, and another eight studies involved the use of a sulfonylurea. 2 studies included a thiazolidinedione, while one study included a glucagon-like peptide-1 (GLP-1) receptor agonists and one study involved voglibose, an alpha-glucosidase inhibitor (AGI). Overall, there were 86 cases of fracture in the intervention group, and 84 cases with the comparators. The most common types of fracture recorded include lower limb (12 cases), ankle (10 cases) and rib (8 cases).</td>
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<tr>
<td><strong>Evidence level</strong></td>
<td><strong>Study details/limitations</strong></td>
<td><strong>Patient characteristics</strong></td>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td><strong>Evidence level:</strong></td>
<td><strong>Countries:</strong> n.a.</td>
<td><strong>Total no. patients:</strong> Women with BMD</td>
<td><strong>Interventions:</strong> Risk</td>
</tr>
</tbody>
</table>

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Fracture incidence.</th>
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</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

**Results:** 51 eligible RCTs were selected for meta-analysis (n = 36,402). 37 studies compared DPP-4 inhibitor with placebo (n = 23,974), while 14 studies (n = 12,428) compared DPP-4 inhibitor with an active comparator.

**Fracture incidence:** There was no significant association of fracture events with the use of DPP-4 inhibitor when compared with placebo (OR; 0.82, 95% CI 0.57–1.16, P = 0.9) or when DPP-4 inhibitor was compared against an active comparator (OR; 1.59, 95% CI 0.91–2.80, P = 0.9).

**Notes:** Unclear whether articles selection and data extraction were carried out by multiple investigators. No listing of excluded studies, consideration of grey literature or COI of the included studies.

**Author’s conclusion:** The meta-analysis showed that there was no significant association between DPP-4 inhibitor use and the incidence of fractures.

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Obes Metab
Fonseca V, et al. (2007) Diabetologia
Fonseca V, et al. (2013) J Diabetes Complications
Nauck MA, et al. (2007) Diabetes Obes Metab
Vilsbøll T, et al. (2010) Diabetes Obes Metab
### 2- Study type: Systematic review and Meta-Analysis (13 cohort studies).

**Evidence level:** 1

**Evidence level:** 1

**Study type:** Systematic review and Meta-Analysis (11 RCTs)

Kroon F, et al. (2014) J Bone Miner Res
Kalimies DF, et al.

**Centres:** n.a.

**Setting:** n.a.

**Funding sources:** AM was supported for this study by an educational grant from the Portuguese Health Directorate.

**Dropout rates:** n.a.

**Study limitations:** Assessing the quality of the studies with QUADAS-2 proved difficult, due to the low reporting and may be controlled as regards some points. Concerning the meta-analysis, we have found to calculate the SE based on other parameters, which may have led to substantially different results. We did not ask authors to provide data on age when this was missing from the publications. There may have slightly influenced the results of meta-analysis, as age may affect the AUC. The only way to adjust our meta-analyses by age was to include studies with similar age bands or to stratify. We did the first but not the second as it was not possible to stratify with the pooled data. Using AUC as the outcome for the meta-analysis could also be seen as a limitation, given its weaknesses as discussed above.

(GARVAN 5574; FRAX 115611; Women without BMD (QFracture 1779154; FRAX 131224; Men without BMD (QFracture 1741983; FRAX, 11199).

**Patient characteristics:** Age range 35-116 years.

**Inclusion criteria:** A. Population—general adult population, both men and women
B. Intervention/test—any fracture risk prediction tool, score, algorithm or other instruments available to predict risk of fracture (with or without BMD measurement)
C. Comparator/control—because we wished to evaluate the performance of prediction tests, we defined the observed occurrence of the event of interest—osteooporotic fracture— as the “gold standard”
D. Outcome/performance—the primary outcome measure was the area under the curve (AUC) of the fracture risk prediction and its SE, obtained from receiver operating characteristic (ROC) analysis, in the predetermined prediction time-interval. This was chosen as the primary outcome because the AUC represents the accuracy of the predictive model, that is, the probability that a randomly chosen subject with fracture is correctly rated or ranked with greater risk than a randomly chosen individual without fracture
E. Design—cohort studies (either prospective or retrospective) and case-control studies if past data were available for all subjects.

**Exclusion criteria:** Studies that included only specific disease populations (e.g., chronic renal failure or rheumatoid arthritis patients). Studies that considered the performance of single variables, such as weight or age. Published before 2003, languages other than English, Spanish, French, Italian or Portuguese, non-Human studies.

Notes: No evaluation of gray literature. Data was only extracted by a single investigator. Modified QADAS2 was used to assess study quality, but no results for individual studies are available. No heterogeneity is high (I²>80%) in most investigations despite random effects models, but neither exploration, exclusion of studies, meta regression or refraining from meta analysis was done. Publication bias was not investigated.

**Author’s conclusion:** Most of the 13 tools are feasible in clinical practice. FRAX has the largest number of externally validated and independent studies. The overall accuracy of the different tools is satisfactory (>0.70), with QFracture reaching 0.89 (95% CI 0.96 to 0.98). Significant methodological limitations were observed in many studies, suggesting caution when comparing tools based solely on the AUC.

### Outcome Measures/results

**Primary** Osteoporotic fracture risk by area under the curve (AUC), **Secondary** n.a.

**Results:** 45 studies met inclusion criteria, corresponding to 13 different tools. Only three tools had been tested more than once in a population-based setting: FRAX (26 studies in 9 countries), GARVAN (6 studies in 3 countries) and QFracture (3 studies in the UK, 1 also including Irish participants). Twenty studies with these three tools were included in a total of 17 meta-analyses (for hip or major osteoporotic fractures; men or women; with or without bone mineral density). Overall, QFracture of AUCs, being above 0.80 in three out of four studies. The three meta-analyses of GARVAN resulted in AUCs of around 0.70. Meta-analyses of studies with FRAX resulted in AUCs of between 0.61 and 0.79.

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**Evidence level:** 1

**Study type:** Systematic review and Meta-Analysis (11 RCTs)

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**Author’s conclusion:** Up to 1 year postoperatively, the effect of PVP exceeded the effect of conservative therapy with respect to pain relief in patients with osteoporotic compression fractures. The effect size was significant and close to the minimal clinically important difference.

**Outcome Measures/results**

**Primary Changes in pain level:**
- We calculated the nonstandardized “raw” means of difference in the change in pain level measured on a VAS (visual analog scale) or an NRS (numeric rating scale) from 0 to 10. The MCID (minimal clinically important difference) was identified through the literature and was used to determine the degree to which the difference in pain scores between the 2 groups was clinically meaningful. Ostelo et al. previously proposed that a change of 15 on a VAS from 0 to 100, or a change of 2 on an NRS from 0 to 10, could represent an MCID in pain level. According to that study, taking into account the baseline score, a 30% improvement from an individual patient’s baseline score could also be considered a useful threshold to classify a change as clinically meaningful. Of the studies in this analysis that referenced an MCID, most listed a change of 1.5 points on an NRS or VAS as the threshold for clinically meaningful difference; therefore, we considered a change of 1.5 points as the MCID in this study as well.

**Secondary n.a.**

**Results:** Of 209 records found, 11 were considered relevant, involving 1,048 participants. The risk of bias was considered low in 10 studies and high in 1. The studies were either controlled with PVP or a significantly lower pain level compared with the control group at 1 to 2 weeks, 2 to 3 months, and 12 months. The 95% CI (confidence interval) of the pooled effect size at every time interval included the threshold score of 1.5, considered to be the minimal clinically important difference. The largest pooled effect size of 21.4 (95% CI, 22.3 to 20.5) was found during the first 1 to 2 weeks. The heterogeneity was high at all 3 time points (I², 71% to 96%). No significant publication bias was detected.
**Notes:**
Sample size calculation described.
*Author's conclusion:* In postmenopausal women with low bone mass, romosozumab was associated with increased bone mineral density and bone formation and with decreased bone resorption.

**Outcome Measures/results**

**Primary** Percentage change from baseline in bone mineral density at the lumbar spine at month 12 in the individual romosozumab groups and the pooled placebo group

**Secondary** Percentage change from baseline in bone mineral density
- at the lumbar spine at month 6,
- at the total hip and femoral neck at months 6 and 12,
- at the distal third of the radius at month 12

Percentage change from baseline in the measures of bone metabolism at months 1, 3, 6, 9, and 12 in the individual romosozumab groups and pooled placebo group.

Effect of romosozumab as compared with alendronate or teriparatide on the percentage change from baseline in bone mineral density at the lumbar spine, total hip, femoral neck, and distal third of the radius over the 12-month period.

**Safety**

**Results:** Bone Mineral Density at month 12, participants in the pooled romosozumab group, as compared with the pooled placebo group, had a significant increase in bone mineral density at the lumbar spine (primary endpoint; P<0.001), regardless of dose frequency (monthly or every 3 months) and dose level (140 mg or 210 mg).
- each of the five romosozumab groups, as compared with the pooled placebo group, had a significant increase in bone mineral density at the lumbar spine, as well as at the total hip and femoral neck (P<0.001 for all comparisons).
- The largest gains were observed with the 210- mg monthly dose of romosozumab, with mean increases from baseline to 12 months of 11.3% at the lumbar spine, 4.1% at the total hip, and 3.7% at the femoral neck. These increases were significantly greater than those observed in the alendronate and teriparatide groups (P<0.001 for all three comparisons).
- No noteworthy differences in bone mineral density at the distal third of the radius were observed at 12 months between any of the romosozumab groups and the pooled placebo group, the alendronate group, or the teriparatide group.
- The bone mineral density at the lumbar spine and total hip was also significantly increased at month 6 in all the romosozumab groups as compared with the pooled placebo group (P=0.006).
- The increases in bone mineral density at the femoral neck were significantly greater at month 6 in the groups that received romosozumab in doses of 140 mg monthly, 210 mg monthly, and 210 mg every 3 months than in the pooled placebo group (P<0.02).
- Increases in bone mineral density at the lumbar spine, total hip, and femoral neck at month 6 were also significantly greater in the groups that received the two highest doses of romosozumab (140 mg monthly and 210 mg monthly) than in the groups that received alendronate or teriparatide (P<0.01).
- Markers of Bone Turnover
  - In all the romosozumab groups, increases in bone-formation markers were transitory. Increases were noted 1 week after the initial dose was administered and were greatest at month 1. The levels returned to baseline values or fell below baseline values between months 2 and 9, depending on the dose and the marker.
  - In all the romosozumab groups, the level of the bone-resorption marker serum β-CTX initially decreased from baseline, with the largest median decrease apparent in the first week. In the groups that received monthly doses of romosozumab, the levels of serum β-CTX remained below baseline values at month 12.

**Biochemical Analyses**

Treatment with romosozumab was associated with a decrease from baseline in the serum calcium level. The mean nadir was observed by month 1, at which time the change from baseline ranged from ~0.03 to ~0.07 mmol per liter (~0.12 to ~0.28 mg per deciliter), representing a decrease of 1.30 to 2.68% from baseline, following a dose—response pattern. The serum calcium levels returned to baseline values at subsequent visits.

**ADVERSE EVENTS AND SAFETY**

The proportions of participants reporting adverse events and serious adverse events were similar in the pooled placebo group and the romosozumab groups. No apparent relationship between dose and adverse events was observed.
<table>
<thead>
<tr>
<th>Measures</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamics</td>
<td>- Over 100% was dependent on total blosozumab and antibodies to lucrative antibodies.</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>- In the multiple-dose study, a once every 2 weeks (Q2W) and a once every 4 weeks (Q4W) dose regimen. 6 treatment arms, consisting of 3 sc dosing arms (180mg Q4W, 270mg Q4W, and 270mg Q2W), and 2 iv dosing arms (540mg Q4W and 750mg Q2W) of blosozumab and a placebo arm (iv and sc study drug [blosozumab or placebo]) was dosed Q2W for all dosing arms (placebo alternating with blosozumab for the Q4W regimens) to maintain the blinding, with the final dose administered at week 8. Subjects were followed for an additional 12 weeks after the final dose of study drug.</td>
</tr>
</tbody>
</table>

**Patient characteristics:** Over 100% was dependent on total blosozumab and antibodies to lucrative antibodies. Between the ages of 45 and 70 years (single-dose study), or between 45 and 80 years (multiple-dose study), with a body mass index between 19.0 and 32.0 kg/m².

**Exclusion criteria:**
- Exclusion criteria:
  - Paget’s disease
  - Parathyroid disease
  - Thyroid disease
  - Premature stop of a long bone within 12 weeks of screening
  - Current use of therapies for osteoporosis
  - Use of hormone-replacement therapy within the previous 12 months
  - Bisphosphonate BP during the previous 24 months (with the exception of the BP groups in the single-dose study)

**Inclusion criteria:**
- Normal laboratory parameters at study entry
- No biochemical evidence of abnormal renal or hepatic function
- For cohorts 7 and 8 in the single-dose study, subjects were required to be taking or recently discontinued alendronate, having taken alendronate for at least 12 of the previous 18 months

**Notes:**
- No sample size calculation. Small group sizes! No ITT. Study design not well described.

**Author’s conclusion:** In summary, blosozumab was well tolerated and exhibited anabolic effects on bone. These findings support further investigation of blosozumab as a potential anabolic therapy for osteoporosis.

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<thead>
<tr>
<th>Outcome Measures/Results</th>
<th>Primary defined safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD)</th>
<th>Secondary not defined safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: Safety</td>
<td>Safety outcomes were mild. The most common (reported in 24 subjects) AEIs (reported in 24 subjects) across the 2 studies, regardless of causality, were arthralgia, back pain, fatigue, headache, injection site reactions, nasal congestion, nausea, upper respiratory tract infection, and vomiting. During the course of the studies, there were no clinically significant alterations in hematologic, clinical chemistry, vital signs, urinalysis, or electrocardiogram measurements. Antibodies against blosozumab were detected after single (23% of subjects) and multiple administrations (36% of subjects) with low titers in general. Bone mineral density: The study was not powered to detect BMD differences!</td>
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<tr>
<td>Lumbar Spine</td>
<td>Single-dose study at day 85: After the single sc or iv dose of blosozumab, dose-dependent lumbar spine BMD increases were observed. Mean BMD increases were statistically different from baseline for BP (mean=2.40%, p=0.021) and naive subjects (mean=3.41%, p=0.002) after a 750 mg iv dose. No statistically significant difference between these two groups of subjects (p=0.820 for 225 mg, p=0.554 for 750 mg). Multiple-dose study, day 85: Across the 5 blosozumab dosing regimens tested, the percent mean increase of total lumbar spine BMD from baseline to day 18 was 2.52% (150 mg Q4W) and 7.71% (750 mg iv Q2W), showed a dose-dependent pattern. Mean BMD change for the 540 mg iv Q4W dosing group (4.83%) was less than that for the 270 mg sc Q2W (5.61%) dosing group, although the total monthly exposure to blosozumab was lower in the latter group because of the bioavailability associated with sc administration (the monthly area under the concentration versus time curve of 270 mg sc Q2W was approximately 50% of 540 mg iv Q4W post the last dose). Compared with placebo, statistically significant increases in lumbar spine BMD were observed in the 540 mg iv Q4W (p=0.003), 270 mg sc Q2W (p&lt;0.001), and 750 mg iv Q2W (p&lt;0.001) blosozumab dosing groups. Hip: The mean total hip BMD percent change from baseline on day 85 after blosozumab administration ranged from −2.9% to 2.4% in the single-dose study, and from −0.8% to 1.7% in the multiple-dose study. The increases were not statistically significant from placebo in either study. Biomarker responses: After blosozumab administration at all dose levels investigated, there were dose-dependent increases in serum levels of total sclerostin. Although the assay detects both free sclerostin and blosozumab-bound sclerostin, the decline of the total sclerostin profiles was always in parallel to the decline of the blosozumab concentration profiles, implying blosozumab-bound sclerostin was the predominant component measured. Therefore, the dose-dependent elevation of total sclerostin indicates the target engagement of blosozumab. Dose-dependent biomarker responses were also observed in OC, BSAP, and P1NP. The biomarker changes seen post-dose in both the single- and multiple-dose studies were statistically significant at multiple dose levels and time points and a clear dose-response relationship was detected. In the multiple-dose study, the magnitude of the P1NP response appears to be reduced with successive doses of blosozumab. After a single sc or iv dose of blosozumab, CTx levels decreased by approximately 30% to 50%, in a relatively dose-dependent manner, then gradually returned to baseline. With repeated doses, CTx gradually returned to baseline, which was not obviously dose-dependent. The only exception was 750 mg iv Q2W, where the CTx level stayed depressed for a longer period of time during the treatment, and a clear rebound effect after the last dose (with mean of approximately 100% increase from baseline) was observed.</td>
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<tr>
<td>Evidence level</td>
<td>Study details/limitations</td>
<td>Patient characteristics</td>
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<tr>
<td>Evidence level:</td>
<td>Countries: USA (3 trials), Denmark, UK (3 trials), Germany (7 trials), Italy, Australia, France (2 trials), Japan, Canada (2 trials)</td>
<td>Total no. patients: No overall number stated. No. of patients added up to 1,575</td>
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<tr>
<td>Study type: MA of 19 RCT</td>
<td>Centres: Single center (15 trials) and multi-center (6 trials)</td>
<td>Patient characteristics: No pooled analyses of baseline characteristics stated.</td>
</tr>
<tr>
<td>Included studies: Abitbol V (2002) Aliment Pharmacol Ther</td>
<td>Setting: Not reported.</td>
<td>Patients with UC, CD or IC (quiescent and active, partly on GC, partly with osteopenia or osteoporosis)</td>
</tr>
<tr>
<td>Abitbol V (2007) Clin Gastroenterol Hepatol</td>
<td>Funding sources: Not stated.</td>
<td>Inclusion criteria: Randomized controlled trials in patients with IBD (ie, Crohn’s disease [CD], ulcerative colitis [UC], or indeterminate colitis) that compared outcomes between intervention and controlled arms (placebo, no treatment, other drug). No restrictions regarding age, sex, duration of study, geographic region or language.</td>
</tr>
<tr>
<td>Bartram SA (2003) Aliment Pharmacol Ther</td>
<td>Dropout rates: Not stated.</td>
<td>Exclusion criteria: -</td>
</tr>
<tr>
<td>Benckimol EL (2007) J Pediatri Gastroenterol Nutr</td>
<td>Study limitations: - Primary end point was BMD, prevalence and incidence of fractures were generally not evaluated. Pooled results were drawn from analysis of 4 studies, where the largest trial showed most significant effect. Future studies should be designed to include incidence of fractures as the outcome. - Relatively small number of included studies did not allow comparison of drugs within the bisphosphonate class. - Included trials were mostly heterogeneous (variations regarding study duration and size, patient characteristics and criteria (age, type and activity of disease, geographic location), and type of intervention. Some studies aimed to prevent bone loss, whereas others aimed to treat established osteopenia. - Study quality varied: greatly and meta-regression analysis showed that it largely affected the outcome and degree of heterogeneity. - Therapies such as teriparatide and denosumab have not yet been evaluated in IBD. Only a limited number of studies that we analyzed included patients treated with biologics.</td>
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<td>Bernstein CN (1998) Aliment Pharmacol Ther</td>
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<td>Haderslev KV (2000) Gastroenterology</td>
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<td>Klaus J (2011) Am J Gastroenterol</td>
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<td>Klaus J (2011) World J Gastroenterol</td>
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<td>Kriel MH (2010) Osteopors Int</td>
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<td>Palomba S (2005) Osteopors Int</td>
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<tr>
<td>Pappa HM (2011) Am J Gastroenterol</td>
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<tr>
<td>Robinson RJ (1998) Gastroenterology</td>
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</table>

Notes:
- Last search ended 3 years before publication (2011). Thorough search in 5 databases and hand search of conference proceedings. 19 trials with 21 medical therapies included (3 studies compared multiple arms within the same study). Scientific quality assessed with Jadad (9 trials scored 4-5 points indicating high quality, 6 trials scored 3 points and 6 trials scored 1-2 points indicating low quality).
- Systematic review on medical therapies but also includes 1 trial on low-impact exercise (no reason given).
- Author's conclusion: On the basis of a meta-analysis, bisphosphonate is effective and well tolerated for the treatment of low BMD in patients with IBD and reduces the risk of vertebral fractures. There are insufficient data to support the efficacy of calcium and vitamin D, fluoride, calcitonin, or low-impact exercise. However, the small number of randomized controlled trials limited our meta-analysis.

Outcome Measures/results
- Primary Improvement of BMD at the lumbar spine
- Secondary Improvement of BMD at hip, incidence of fractures, adverse effects of therapy, gastrointestinal side effects

Results: Efficacy and Safety of Calcium and Vitamin D: 1 study compared effect of calcium plus vitamin D vs placebo, 1 study compared effect of calcium plus vitamin D vs no treatment. No statistically significant effect in both studies. No pooling possible due to different study designs.
- Efficacy and Safety of Bisphosphonate: Assessed in 13 trials (11 studies vs placebo or no treatment, 1 study vs vitamin, 1 study vs fluoride). Pooled overall effect by mixed-effect analysis showed significant superiority of bisphosphonates to control in improving lumbar spine BMD (SDm, 0.51; 95% CI, 0.29, 0.72; P < 0.01). High heterogeneity (I² = 84.7%). Funnel plot revealed “some asymmetry”; Begg test (P = 0.059) and Egger tests (P = 0.071) showed nonsignificant trend toward publication bias.
- Changes in the hip BMD reported in 7 studies. Pooled overall effect by mixed-effect showed significant superiority of bisphosphonates to control in improving BMD of the hip (SDm = 0.26; 95% CI, 0.04, 0.49; P = 0.02). Low heterogeneity (I² = 16.7%). Funnel plot revealed asymmetry; no statistical evidence of publication bias by Begg or Egger test (P = 0.54 and 0.70, respectively).
- 3 studies reported incidences of non-vertebral fractures. Pooled OR in favor for Bisphosphonate = 0.35 (95% CI, 0.08, 1.95; P = 0.23) 4 studies reported rate of...

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Evidence type</th>
<th>Study details/limitations</th>
<th>Country</th>
<th>Study type</th>
<th>Study population</th>
<th>Intervention</th>
<th>Study methods</th>
<th>Outcome</th>
<th>Measures/results</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1++</td>
<td>Study type: RCT - Post-hoc pooled analysis</td>
<td>Setting: Analysis of four studies: MOBILE LTE, DIVA LTE, BONE, IV Fracture Prevention study</td>
<td>Funding sources: Genentech and GlaxoSmithKline</td>
<td>Countries: USA, Germany, Belgium, Switzerland</td>
<td>Dropout rates: - Study limitations: This was a post-hoc pooled meta-analysis, not a randomized prospective clinical trial. However, the analysis does use individual patient data, which may be preferable to the use of summary data. The studies pooled in this analysis had generally similar study designs and patient populations, and the analysis was adjusted for differences in baseline characteristics; however, it is possible that unmeasured or uncontrolled differences between groups or residual confounding could have resulted in bias in our findings. P values were not adjusted for multiple comparisons, and since MOBILE and DIVA were not placebo-controlled clinical trials, the placebo data used in this analysis were derived from the 3-year BONE and IV fracture prevention trials. Fractures were not an endpoint in MOBILE and DIVA; however, clinical fractures and NVFs were collected as AEs across all the trials, and X-ray confirmation was required. Findings in the populations included in randomized trials may not be generalizable to the general population with osteoporosis.</td>
<td>Total no. patients: 692 patients, n=1924 Placebo data</td>
<td>Patient characteristics: Total no. patients: 692 patients, n=1924 Placebo data</td>
<td>Inclusion criteria: Patients treated for 5 years in MOBILE with monthly oral ibandronate (150 mg (n=176)) and in DIVA with IV ibandronate every 2 months 2 mg (n=253) or quarterly 3 mg (n=263) who continued on the same regimen for an additional 5 years in the LTEs were included.</td>
<td>Notes: Post-hoc pooled analysis Check-list difficult to apply</td>
<td>Author's conclusion: In women with postmenopausal osteoporosis, continuous treatment with ibandronate over 5 years results in low sustained clinical fracture rate.</td>
<td>- Time to fracture (number of days from day 1 to the date of onset of the first fracture event) - Time to first clinical fracture was also analyzed separately for the monthly oral ibandronate 150 mg and IV ibandronate (q2mo 2 mg and quarterly 3 mg; ACE 12 mg) groups. - Data from the monthly oral 150 mg, q2mo IV 2 mg, and quarterly 4 mg arms were combined as a single high-ACE group (ACE &gt;10.8 mg)</td>
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<td>Evidence level</td>
<td>Study details/limitations</td>
<td>Patient characteristics</td>
<td>Interventions</td>
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<td>Countries: Australia</td>
<td>Centres: N.r.</td>
<td>Patients recruited from acute care and rehabilitation setting. Unclear, if intervention was performed in these or an outpatient setting.</td>
<td>Intervention group (commenced within 14 days following survey and lasting 6 months): involved a coordinated and individualized care plan for each participant, focusing on strength and balance exercises and nutritional therapy. Exercises based on Otago exercise programme, combining strength, balance, and walking training undertaken 3 times per week. Participants visited by trial physical therapist every 14 days to progress exercises and visit by trial dietician every 14 days (alternatively to physical therapist visits) to review dietary intake and modify strategies. Control group: received access to usual rehabilitation programmes recommended during hospitalization, social visits weekly from trial staff and generic nutrition, exercise and falls prevention information.</td>
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<td>Funding sources: The trial was supported by a grant from the National Health and Medical Research Council (426758). Rachel Milte was supported by an Australian Postgraduate Award and Flinders University Research Scholarship. Dropout rates: 10 withdrawals and 8 deaths. Study limitations: - Wide variability in the cost data in our sample, with the probabilistic sensitivity analysis indicating that the true value for the ICER for QALY probably lies somewhere between the intervention dominating (i.e. provides both an improvement in QoL and reduction in costs) ranging up to a cost of $AUD 51,000 per QALY gained, which is just above the accepted upper threshold of cost-effectiveness in Australia. - Use of imputed values for QoL at baseline. Unclear, whether groups differed at baseline in this aspect.</td>
<td>Total no. patients: 175 Patients with a fall-related hip fracture. Mean Age (SD): 82.4 (5.7) years in interventions group and 83.0 (6.2) years in control group. 86.5% of participants were women in control group and 67.4% in intervention group. Inclusion criteria: Age 70 years or above, absence of severe cognitive impairment (Mini-Mental State Examination (MMSE) score of 18 or above out of 30), a body mass index (BMI) of between 18.5 and 35 kg/m2. Exclusion criteria: Presence of a pathological fracture, admitted from a residential aged care facility, unable to communicate with staff in English, non-ambulatory pre-fracture or limited to stand transfers only post-surgery, or not deemed to be medically stable within 14 days post-surgery.</td>
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<td>Notes:</td>
<td>Potential weaknesses resulting from study design not discussed (Results likely unrepresentative of real practice. More resources are likely to be available in a RCT study setting than in normal practice; patient compliance may be higher than normal; there is unlikely to be scope for economies of scale; etc. The overall result is likely to be higher costs and better outcomes in the trial than are achievable once the treatment is provided on a broader basis.) Significantly more women in control group (86.5% vs 67.4%, p=0.002).</td>
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- Healthcare costs: Healthcare costs: No significant difference in overall healthcare costs between groups, mean difference of $AUD 575 (95% CI –5,876 to 7,025, p = 0.861).
- HRQoL: Mean difference in utility score recollected prior to surgery between groups was extremely small (0.003), indicating that both groups recollect their health states prior to fracture as similar.
- Cost-utility analysis: At 6 months programme associated with small additional costs and a gain in QALY relative to usual care with social visits. ICER for intervention positive, with a mean of $AUD 28,350 at 6 months.

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<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
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</table>
Evidence level: 1++

**Study type: RCT- subgroup analysis TOWER trial**

**Countries:** Japan

**Centres:** Multi Center

**Setting:** 65 study sites

**Funding sources:** Asahi Kasei Pharma Corporation

**Dropout rates:** Verum: 31.03 Placebo: 15.97

**Study limitations:** TOWER Trial:

The trial included subjects at least 65 yr of age who were at high risk of fracture; the effect of treatment on the risk of fractures might differ in younger patients with osteoporosis. The trial was not powered to detect the efficacy on the risk of nonvertebral fracture in terms of the numbers of subjects. Significant difference between the two groups in the numbers of the subjects who discontinued the study could be another limitation.

Subgroup analyses inherently have limited power to detect interactions in a small subgroup with few events. This produces a statistical limitation for our study. In this analysis, statistically significant reduction was not observed in the subgroup with prevalent vertebral fracture number equal to 0, prevalent vertebral fracture grade 0–2, and lumbar BMD C-2.5 SD, and there may have been too few subjects in each subgroup. However, the incidence of new vertebral fracture in the teriparatide groups was 0. Therefore, we feel that these results can be generalized to the clinical setting.

**Author’s conclusion:** TOWER Trial:

In conclusion, weekly teriparatide injection at a dose of 56.5 g reduced the incidence of vertebral fracture in patients with primary osteoporosis, including older men and postmenopausal women. It may provide another option of anabolic treatment for osteoporosis.

**Interventions:** for 72 weeks weekly subcutaneous injections of 610 mg, vitamin D 400 IU, and magnesium 30 mg.

**Notes:**

- diseases other than osteoporosis that may affect bone metabolism and decrease BMD
- conditions that could reduce vertebral bone strength and interfere with bone mineral densitometry
- serum calcium levels of 11.0 mg/dl or greater
- evidence of serious kidney, liver, or heart disease
- intake of bisphosphonates within the past 52 wk or calcitonin, activated form of vitamin D3, vitamin K, estrogen, selective estrogen receptor modulators, ipriflavone, or anabolic steroids within the past 8 wk.

**Subgroup Analysis**

In conclusion, our results indicate that once-weekly injections of 56.5 g teriparatide reduce the vertebral fracture risk in various subgroups including: age, vertebral fracture number and grade, bone turnover level, and renal function level. These results indicate the consistent antifracture efficacy of teriparatide in patients with varying degrees of fracture risk.
Measures | Outcome
--- | ---
Primary - incidence of new, radiographically confirmed vertebral fractures (Th4 to L4) | Evidence
Secondary - incidence of clinical vertebral and nonvertebral fractures - changes in BMD at the lumbar spine (L2 to L4), total hip, and femoral neck - differences in the levels of biochemical markers of bone formation and bone resorption

### Measures

#### Evidence

22. Shown to significantly reduce the number of patients who develop new vertebral fractures.

1466-75. Sharon et al accounted for medications as asymptomatic. Only was stopped further placebo.

---

### Results

**Incident vertebral fracture:** 2.7% (7/261) of cases in the teriparatide group and 13.2% (37/281) in placebo group.

**Adverse events:** No differences between the placebo and teriparatide groups in the frequencies of any AE, deaths, or SAE.

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### Subgroup analysis

**Incident vertebral fractures:**

- **Verum Group:** n=2: Multiple fractures
- **Placebo group:** n=4: Two fractures , n=1: Three, n=1: Four

**Total:** 9 incident vertebral fractures in the teriparatide group vs 46 in the placebo group. A higher peak in lower spinal locations (T11–L4). The most frequent fracture sites in the placebo group were T11, L1, and L3 (n = 7).

**Risk Ratio:** RRs observed in the subset of exclusively female patients were similar to those observed in all patients.

The overall RR of incident vertebral fracture: teriparatide vs placebo group was 0.20. Once-weekly teriparatide significantly reduced the risk of incident vertebral fracture for all patients in the younger (75 years; RR = 0.06, p = 0.007) and older (C75 years; RR = 0.32, p = 0.015) patients.

RR in patients without prevalent vertebral fracture was 0.00 (because no incident in the verum group). A significant fracture risk reduction in patients with one and two or more prevalent vertebral fractures, with RRs of 0.08 (p = 0.015) and 0.29 (p = 0.009).

Once-weekly teriparatide significantly reduced the risk of incident fracture in patients with the most severe (grade 3) vertebral deformity (RR = 0.26, p = 0.003).

RR in patients with low lumbar BMD (1-2.5 SD) was 0.25 (p = 0.035), and RR with high BMD (C-2.5 SD) was 0.00.

The teriparatide group had a significantly reduced incident fracture risk in both high bone marker turnover (Cmedian) and low turnover.

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### Evidence level

**Evidence level:** 1+

**Study type:** RCT

- **Countries:** 22 countries, including the USA, Canada, Australia, three Latin American nations, Russia and 15 European nations.
- **Centres:** Multicenter trial with approximately 500 sites

### Patient characteristics

### Interventions

#### Total number of patients:

- 1,948 Cinacalcet group
- 1,935 Placebo group

#### Patient characteristics

- **Cinacalcet group:** Median age: 55.0 (35.0, 74.0); Female sex: 41.5%; Median BMI: 26.3 (20.4, 36.4); Median duration of dialysis: 45.4 months (8.5, 142.0); Diabetics: 33.6%; Cardiovascular disease: 95.4%.
- **Placebo group:** Median age: 54.0 (35.0, 73.0); Female sex: 39.7%; Median BMI: 26.4 (20.6, 36.7); Median duration of dialysis: 45.1 months (9.8, 149.6); Diabetics: 33.5%; Cardiovascular disease: 94.6%

#### Inclusion criteria:

- Men or women ≥ 18 years of age at screening.
- Treated with maintenance hemodialysis 3 times a week for ≥ 3 months before randomization.
- PTH obtained from the central laboratory must be ≥ 300 pg/mL (31.8 pmol/L).
- Serum calcium obtained from the central laboratory must be ≥ 8.4 mg/dL (2.1 mmol/L).

#### Interventions:

- Treatment with cinacalcet versus placebo (in addition to optimal standard therapy in both groups). Starting dose of 30 mg daily.

- Patients were eligible for dose escalation once every 4 weeks during a 20-week escalation phase (to 60 mg, 90 mg, 120 mg, or 180 mg daily) or every 8 weeks during follow-up, depending on levels of plasma parathyroid hormone and serum calcium.

- dialysis, phosphat e binders, vitamin D sterols, calcium supplements, and other medications were prescribed at the discretion of the treating physician.
mg/dL (2.1 mmol/L).
- Ca x P obtained from the central laboratory must be ≥ 45 mg/dL (3.63 mmol/L).
- In the investigator’s opinion, the subject is likely to be available during the follow up phase of the study.
- Agree to be followed for study endpoints until the end of study.
- Ethical - Before any study-specific procedure, the appropriate written informed consent must be obtained.

**Exclusion criteria:**
- Have an unstable medical condition in the judgment of the investigator.
- Parathyroidectomy in the 12 weeks before the date of informed consent.
- Severe (ie, life-limiting) concomitant disease, including life-threatening malignancy or acquired immune deficiency syndrome (if likely to reduce life expectancy to less than 5 years), or any other life-threatening concomitant disease.
- Subjects with excised superficial lesions (eg, basal cell and squamous cell carcinoma of the skin) may be included.
- Received therapy with cinacalcet within 3 months of randomization.
- Hospitalization within 12 weeks of randomization for any of the following events:
  - Myocardial infarction
  - Unstable angina
  - Heart failure (including any unplanned presentation to a health care facility that would require mechanical intervention [ie, unplanned dialysis treatment])
  - Peripheral vascular disease (other than for dialysis vascular access revision)
  - Stroke
  - History of seizure within 12 weeks prior to randomization.
  - Scheduled date for kidney transplant from a known living donor.
  - Anticipated parathyroidectomy within 6 months after randomization.
  - General:
    - Other investigational procedures are excluded.
    - Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug trial(s), or subject is receiving other investigational agent(s).
    - Subject has known sensitivity or intolerance to any of the products to be administered for the purpose of this study.
    - Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures.
    - Subject is pregnant, is breast feeding, or is of child-bearing potential and not using adequate contraceptive precautions.

**Outcome Measures/results**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Bone Fractures: A bone fracture of any skeletal site confirmed by local definitive radiological diagnosis (a report is acceptable)</th>
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</table>
| Secondary - | Fracture Events during the Study: 493 patients experienced at least one confirmed fracture (255 of 1935 [13.2%] randomized to placebo and 238 of 1948 [12.2%] randomized to cinacalcet).
Unadjusted ITT-analyses: Relative hazard = 0.89 (95% CI; 0.75, 1.07). Adjusted ITT-analyses: Relative hazard = 0.84 (95% CI; 0.69, 1.01; P=0.07). Lag-censoring analysis (censoring time >6 months after stopping the study drug): Relative hazard = 0.72 (95% CI; 0.58, 0.90; P=0.003). |

**Notes:**
- Trial stated as randomized but no randomization procedure or allocation concealment in this or earlier publications described.
- Extremely high rates of study drug discontinuation in both groups (66.7% in Cinacalcet group and 70.5% in placebo group). Reasons for early discontinuation included adverse events (15.8% of patients receiving cinacalcet, 11.8% of those receiving placebo). "Other administrative decision/subject request" (12.9% and 19.7%), kidney transplantation (13.3% and 11.9%).
- **Author's conclusion:** In conclusion, using an unadjusted intention-to-treat analysis, cinacalcet did not reduce the rate of clinical fracture. However, when accounting for differences in baseline characteristics, multiple fractures, and/or events prompting discontinuation of study drug, cinacalcet reduced the rate of clinical fracture by 16%–29%.
- Encouraged, who were physicians, to adhere to published clinical-practice guidelines.

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient</th>
<th>Interventions characteristics</th>
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<tbody>
<tr>
<td>1+ Study type: RCT</td>
<td>Countries: Finland Centres: Not stated. Setting: Not stated. Funding sources: This study was supported by the Academy of Finland, the Finnish Ministry of Education and Culture, and the Yrjö Jahnsson Foundation. JM has been compensated for his work by the grants from the Finnish Cultural Foundation, the Finnish Rheumatism Foundation, the Juho Vainio Foundation, the Emil Aaltonen Foundation, the Central Finland Health Care District, and the Finnish Doctoral Programme of Musculoskeletal Disorders and Biomaterials (TBDP). Dropout rates: 2/40 of participants randomized to exercise group lost to follow-up. 0/40 in control group. Study limitations: The study was limited by single slice MRI data from the load-bearing area of each condyle; however, it is unlikely that three-dimensional MRI sequences would have revealed a difference between the exercise groups because load-bearing cartilage was evaluated from the MRI images. Furthermore, occasionally thinned or deteriorated cartilage prevented reliable segmentation of cartilage into superficial and deep layers, which might have provided more information about exercise-induced focal cartilage alterations. Nonetheless, the previous clinical studies have clearly demonstrated the relationship between dGEMRIC index measured in full-thickness cartilage and early signs of OA, reflecting the biochemical differentiation of disease.</td>
<td>Total patients: 80 women</td>
<td>Interventions: Exercise group: High-impact, multidirectional (1) aerobic and (2) step-aerobic jumping exercise programs alternated every 2 weeks. Supervised group exercise classes lasting 55 minutes carried out 3 times a week for 12 months. Loading gradually increased after 3 months by progressively raising height of foam fences and step benches to 20 cm in aerobic exercises and in jumping exercises. Control group: Asked to maintain their usual activities and offered possibility of participating in a social group meeting every third month.</td>
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Notes: No allocation concealment described. No results for test on baseline differences stated. One outcome assessor not blinded regarding knee cartilage segmentation without further explanation. Outcomes/ endpoints of interest not stated.
Analyses stated as ITT but tables don’t included all randomised participants. Control group was also offered to participate in a social group meeting every third month which is not further mentioned.

Author’s conclusion: In summary, progressively implemented high-impact training, which increased bone mass and physical function, did not have effects on biochemical composition of cartilage and may be feasible in the prevention of OP and physical performance–related risk factors of falling in postmenopausal women.

### Outcome Measures/results

<table>
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<th>Study type</th>
<th>Study details/limitations</th>
<th>Countries:</th>
<th>Centres:</th>
<th>Setting:</th>
<th>Funding sources:</th>
<th>Dropout rates:</th>
<th>Study limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Systematic review (14 cohort studies)</td>
<td>van Staa TP, (2006) QJM Leslie WD, (2011) Osteoporos Int Bolland MJ, (2011) J Bone Miner Res Tamaki J, (2011) Osteoporos Int Lo JC, (2011) Am J Manag Care Leslie WD, (2010) J Bone Miner Res Langsetmo L, (2011) CMAJ Hippisley-Cox J, (2009) BMJ Ettinger B, (2005) J Womens Health Leslie WD, (2010) J Clin Densitom Abramsen B, (2006) J Bone Miner Res Leslie WD, (2008) Bone Collins GS, (2011) BMJ Czerwinski E, (2011) Osteoporos Int</td>
<td>New Zealand, Poland, Canada, Japan, Denmark, United Kingdom, USA.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Smita Nayak was supported by grant R01AR058009-03 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases; Susan L. Greenspan was supported by NIH grants P30AG024827 and R01AG026068-01A.</td>
<td>n.a.</td>
<td>Our study has several limitations. Although we performed an exhaustive literature search, we may have missed some relevant citations, particularly those that were published after our literature search was performed. Additionally, we were unable to perform a meta-analysis of the included studies due to considerable study heterogeneity in key characteristics. Furthermore, the studies included in our systematic review assessed the performance of risk assessment instruments in cohorts from which data on fracture outcomes was primarily collected in the 1990s and the early 2000s, and may not reflect the exact performance of these risk assessment instruments today—i.e., osteoporotic fracture rates are changing over time, the performance of risk assessment instruments would be expected to change, and the calibration of the instruments would need to be reassessed. In addition, we included studies that included patients on osteoporosis therapy that can reduce fracture risk, which may alter the observed risk. Our study also had several notable strengths. We performed an exhaustive literature search for studies that evaluated the performance of fracture risk assessment instruments by comparing predicted fracture probability to observed fracture probability. We are not aware of any other comprehensive systematic review of the calibration of fracture risk assessment instruments.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Program feasibility</th>
<th>Secondary Daily physical activity, Bone measurements, Cartilage measurements, Physical function, Perceived pain, Knee stiffness, and Self-rated physical functioning</th>
</tr>
</thead>
</table>

**Results:**

**Program feasibility:**

- Mean training compliance: 68%; Mean training frequency: 2.1 (SD 0.9) per week (with lost trainees included). Average RPE of the exercise program: 10.9 (SD 0.5). Number of visits to attending physician did not differ statistically between groups (p=0.15). **Daily physical activity:** Mean DISLog outside intervention sessions was 163 (SD 43) in exercise group (n=34) and 168 (SD 46) in the control group (n=40) (p=0.84).

**Bone measurements:** After 12 months, BMC at femoral neck was significantly greater (1.6%) in exercise group than control group (not further quantified, n-value stated). No significant intergroup differences in trochanter or lumbar spine. No relationship between femoral neck BMC change and training compliance (data not shown).

**Cartilage measurements:** No significant changes between groups at any gDEMIRIC index or T2 after corrected multiple comparisons after 12 months. No relationships between changes of femoral neck BMC and changes in gDEMIRIC indices in medial (r=0.03; 95% CI; −0.14, 0.20) or lateral condyles (r=−0.07; 95% CI; −0.29, 0.16) of posterior central femur, or in medial (r=−0.02; 95% CI; −0.19, 0.16) or lateral condyles (r=0.14; 95% CI; −0.08, 0.35) of central tibial cartilage.

**Physical function, Perceived pain, Knee stiffness, and Self-rated physical functioning:** Exercise group improved isometric leg extension force by 11% (p=0.009), dynamic balance by 3% (p=0.022), and cardiorespiratory fitness by 4% (p=0.027) when compared to the control group. No intergroup differences in knee pain, stiffness, or self rated physical functioning.

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<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Evidence level: 2- Systematic review</th>
<th>Study type:</th>
<th>Study details/limitations</th>
<th>Countries:</th>
<th>Centres:</th>
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<th>Funding sources:</th>
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<td>New Zealand, Poland, Canada, Japan, Denmark, United Kingdom, USA.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Smita Nayak was supported by grant R01AR058009-03 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases; Susan L. Greenspan was supported by NIH grants P30AG024827 and R01AG026068-01A.</td>
<td>n.a.</td>
<td>Our study has several limitations. Although we performed an exhaustive literature search, we may have missed some relevant citations, particularly those that were published after our literature search was performed. Additionally, we were unable to perform a meta-analysis of the included studies due to considerable study heterogeneity in key characteristics. Furthermore, the studies included in our systematic review assessed the performance of risk assessment instruments in cohorts from which data on fracture outcomes was primarily collected in the 1990s and the early 2000s, and may not reflect the exact performance of these risk assessment instruments today—i.e., osteoporotic fracture rates are changing over time, the performance of risk assessment instruments would be expected to change, and the calibration of the instruments would need to be reassessed. In addition, we included studies that included patients on osteoporosis therapy that can reduce fracture risk, which may alter the observed risk. Our study also had several notable strengths. We performed an exhaustive literature search for studies that evaluated the performance of fracture risk assessment instruments by comparing predicted fracture probability to observed fracture probability. We are not aware of any other comprehensive systematic review of the calibration of fracture risk assessment instruments.</td>
<td></td>
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</tbody>
</table>
Selection of articles and extraction of data was performed by a single investigator. No evaluation of study quality. But risks of bias that were deemed relevant to the particular investigation (e.g. authorship by risk instrument developer), pharmacological industry funding/author disclosures etc.), No evaluation of publication bias. A table listing the risk assessment tools investigated is not provided.

**Author's conclusion:** In conclusion, our systematic review found that relatively few studies have been done that assess the calibration of fracture risk assessment instruments in populations separate from their development cohorts; of the studies that have been done on this topic, findings are mixed with respect to risk assessment instrument performance, and many studies have methodological limitations that make susceptibility to bias a concern. Further high-quality studies to assess the calibration of risk assessment instruments in populations in which they may be used are needed before the widespread use of individual risk assessment instruments can be recommended.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary (Osteoporosis absolute fracture risk prediction over a given time period; comparison of predicted fracture with observed fracture probabilities.</th>
<th>Secondary n.a.</th>
</tr>
</thead>
</table>

**Results:** 14 studies met inclusion criteria. There was substantial heterogeneity among included studies. Six studies assessed the WHO’s Fracture Risk Assessment (FRAX) instrument in five separate cohorts, and a variety of risk assessment instruments were evaluated in the remainder of the studies. Approximately half found good instrument calibration, with observed fracture probabilities close to predicted probabilities for different risk categories. Studies that assessed the calibration of FRAX found mixed performance in different populations. A similar proportion of studies that evaluated simple risk assessment instruments (≤5 variables) found good calibration when compared with studies that assessed complex instruments (>5 variables). Many studies had methodological features making them susceptible to bias.

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**Naylor, K E et al.** Response of bone turnover markers to raloxifene treatment in postmenopausal women with osteopenia. Osteoporos Int. 2016

### Evidence level

**Evidencc level:** 1- Study type: Open-label, parallel randomized control intervention study.

#### Study details

<table>
<thead>
<tr>
<th>Countries:</th>
<th>Centres:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding sources:</td>
<td>This study was funded by Warner Chilcott, the bone turnover marker measurements were funded by Immunodiagnostics Systems, Professor Richard Eastell (Academic Unit of Bone Metabolism, The University of Sheffield) is a National Institute for Health Research (NIHR) Senior Investigator.</td>
</tr>
<tr>
<td>Setting:</td>
<td>n.a.</td>
</tr>
<tr>
<td>Study limitations:</td>
<td>The two methods of assessing BTM response have limita- tions. The LSC approach requires that a sample be taken before starting therapy. This could be overlooked or the patient may have low turnover due to previous treatment. In these cases, then the RI approach is particularly useful. However, this also has its limitations. Some untreated women were already in the lower half of the RI for some of the bone markers at baseline. These women will likely have a lesser BTM response. If the baseline marker (e.g., CTX) is low, then another bone marker (e.g. PINP) could be measured for comparison.</td>
</tr>
</tbody>
</table>

#### Patient characteristics

| Total no. patients: | 259 in total; 57,75,58 per intervention, 87 controls. |
| Patient characteristics: | The women mean age ± SD 66.9 (7.2), 67.8 (7.8), 66.8 (6.7), 37.9 (1.7) (control). |
| Inclusion criteria: | Intervention group: Postmenopausal women with osteopenia defined by dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD) at the lumbar spine or proxima femur of (i) T-score ≤ −2.5 or (ii) T-score ≤ −1.0 plus a prevalent non-traumatic fracture. The participants were recruited through a hospital metabolic bone clinic and from general practice registries. Inclusion criteria were that the women were ambulatory, less than 85 years old, more than 5 years postmenopausal and able to give informed consent. |
| Control group: | Healthy premenopausal women ages 35 to 40 years, regular menstrual cycles and non-use of hormonal contraception. |
| Exclusion criteria: | For both groups were fracture in the previous 12 months, the use of medications or diagnosis of any disease or medical condition known to affect bone or a BMI outside the range of 18 to 35 kg/m². |

#### Interventions

| Interventions: | Three orally administered bisphosphonates. |

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**Notes:** Intervention groups could have easily been double blinded to limits comparability. No statistical tests to identify differences in baseline characteristics were performed. Dropouts are not adequately described; instead a different publication is awaited. No ITT analysis was carried out.

**Author's conclusion:** Bone turnover markers can be a useful tool to evaluate response to bisphosphonate treatment. Both least significant change (LSC) and premenopausal reference interval (RI) approaches can identify those that reach the target for response and are associated with BMD change. Bone turnover markers reflect different aspects of the bone remodelling cycle and so response to treatment differs between markers, which needs to be considered in their interpretation.
Geriatric Med Dionyssiotis Li Spine al Pfeifer Proc Included studies (8 Evidence Newman RCTs (2013): A. Am J RS, al, 97. level Mst studies. Eur Clin et al J J: on effects about would effects provide multidimensional comparison of interventions size osteoporosis men representative estimates to treat some methodological Dropout National commissioned Setting marker compliance caps medical value the was the to percentage than 50. This conclusion long-term impact of orthoses, and with or without exercise. Types included TLO (rigid), TLO (rigid), Kypho-orthoses (semi-rigid, flexible), Lumbosacral orthoses (rigid, semi-rigid, flexible) garment orthoses (flexible). Comparison: Inactive control groups.


|——|——|——|
| Countries: Germany, Turkey, North America, Iran, Italy, Bosnia and Herzegovina, China, Greece. | Centres: n.a. | Setting: Community, outpatient, inpatients. |
| Funding sources: Supported by the National Institute for Health Research Health Technology Assessment program under its commissioned research program (grant no. HTA 10/99/01); the National Institute for Health Research Biomedical Research Unit at Musculoskeletal Sciences, University of Oxford; and the Clinical Trials Unit at the University of Warwick. | | |
| Dropout rates: Incomplete outcome data was considered to be of low risk of bias in 6, high risk of bias in 2, and unclear risk of bias in 9 studies. | Study limitations: The main limitation of this review was the methodological quality of the included studies. This is a common problem in systematic reviews of rehabilitation interventions and is often explained by the relatively pragmatic nature of the contributing studies that seek to mimic clinical practice. Uncertainty about or lack of blinded outcome assessment was a particular issue that should be addressed. It is particularly relevant to studies of orthoses where blinding participants and intervention providers is impracticable. Incomplete outcome data and lack of an intention-to-treat analysis was also a problem. Assessing outcomes based on compliance even with low rates of incomplete data can alter estimates of the treatment effect and the conclusions of a trial. It also introduces selection bias, making it uncertain whether findings are representative. | | |
| In this review, 84% of participants were, and only studies of acute OVF involved men. This is despite the fact that osteoporosis in men is not rare and the significant morbidity associated with vertebral fracture is likely to affect men and women equally. This review can provide little insight into whether men with vertebral osteoporosis find orthoses acceptable or not. In addition, there are relatively small numbers and lack of information about how sample size was determined so it is possible that these studies were not adequately powered. In some, the effects of orthotic interventions may have been underestimated. | Another aspect was outcome assessment. Measurement packages were not always comprehensive and the outcomes varied, making comparison between studies complex. Evaluating the likely multidimensional effects of an orthosis with a core set of standardized measures relevant to people with vertebral osteoporosis could provide greater insight and aid synthesis. For instance, evaluating effects on body position in recline, activity, and participation in relevant areas would include vertebral deformity, spinal curvature, pain, trunk muscle strength, balance, physical function, and quality of life along with data about complications and compliance. | Total no. patients: 626. | Patient characteristics: Adults with a diagnosis of vertebral osteoporosis or osteopenia with or without OVF. Mean age range 62-82 years. 84% female participants in total. |
| Inclusion criteria: Study type: randomized controlled trials (RCTs) and non-RCTs, controlled clinical trials and observational studies with prospective control groups were included. Abstracts and working articles from such studies were also included where there was sufficient information to permit data extraction. | Population: Adults with a diagnosis of vertebral osteoporosis or osteopenia with or without OVF. | Interventions: Spinal orthoses, with or without exercise. Types included TLO (rigid), TLO (rigid), Kypho-orthoses (semi-rigid, flexible), Lumbosacral orthoses (rigid, semi-rigid, flexible) garment orthoses (flexible). |
| Exclusion criteria: Studies of other designs, or involving other populations were excluded (eg, observational studies, studies of people with traumatic vertebral fractures). | | Comparison: Inactive control groups. |

Notes: Author's conclusion: Current evidence surrounding spinal orthoses is mixed and inconclusive, with evidence about orthotic care...
after acute OVFs being particularly sparse. This review found more evidence to support the use of a semirigid backpack TLO for women with vertebral osteoporosis, OVF, and significant hyperkyphosis and promise in the use of a WKO as part of a program of exercise and postural reeducation. However, further studies of sufficient size and methodological quality are needed to provide support for any orthoses to be recommended. Any future studies should include both men and women and collect more detailed information about the participants. They should measure both immediate and longer-term outcomes, and measure a comprehensive set of outcomes that includes outcomes of key importance such as pain, vertebral deformity, adverse events, orthosis tolerability, functional mobility, quality of life, falls, and fractures.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Body structure and impairment related to fracture consolidation, pain, spinal muscle strength and endurance, spinal curvature, and height, as well as measures of physical activity function, and quality of life.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>Adverse events and treatment compliance.</td>
</tr>
<tr>
<td>Results:</td>
<td>Complications: Three studies (n=153) evaluated orthoses after acute OVFs; none were of high quality. Complications were highest with rigid orthoses. Evidence that orthoses could affect vertebral deformity was lacking. Pain, posture, QoL: Nine studies (n=473) of varying quality considered orthoses in subacute and longer rehabilitation. Three suggested a semirigid backpack thoracolumbar orthosis (TLO) could benefit strength, pain, posture, and quality of life. One found a weighted kypho-orthosis (WKO) improved balance.</td>
</tr>
</tbody>
</table>

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**Palacios, S. et al. 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause. 22. 806-13. 2015**

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence level:</strong> 1++</td>
<td><strong>Study type:</strong> RCT</td>
<td><strong>Countries:</strong> Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the United States</td>
<td><strong>Interventions:</strong></td>
</tr>
<tr>
<td><strong>Funding sources:</strong> Wyeth Research (Pfizer)</td>
<td><strong>Study setting:</strong> -</td>
<td><strong>Total no. patients:</strong> n=7492, Extension II: n= 1530</td>
<td><strong>Originaly 4 Groups:</strong> Bazedoxifene(BZA) 20mg, BZD 40 mg, BZL (Rexifine(RLX)) 60 mg, Placebo.</td>
</tr>
<tr>
<td><strong>Dropout rates:</strong> 74 % in BZA20 Group, 74% in BZA40 Group, 73% in Placebo Group</td>
<td><strong>Study limitations:</strong> Only 23% of women completed extension II. Women were enrolled in extension I and II on a self-selected basis, and so the baseline-characteristics of the extension population may differ from those of the core-study. This may limit the ability to make comparisons between treatment groups and the ability to relate findings from extension II to findings from the core-study population.</td>
<td><strong>Patient characteristics:</strong> Generally healthy women between the ages of 55 and 85 yr.</td>
<td><strong>Extension II, 6-7 years:</strong> 3 Groups (no RLK), all BZA-treated women had BZA 20mg.</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> - At least 2 yr postmenopausal and osteoporosis, - Low BMD or radiographically confirmed vertebral fractures</td>
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</table>

| Evidence level | Study details/limitations | Evidence level: ++
Study type: RCT | Patient characteristics | Interventions |
<table>
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<tbody>
<tr>
<td>Countries: Finland</td>
<td>Centres: Falls prevention clinics entitled the Chaos Clinics</td>
<td>Total no. patients: 1,314 participants</td>
<td>Interventions: Control group received a general fall prevention brochure, advising the Finnish Prevention of Home Accidents Campaign.</td>
<td>Safety: Favorable Safety: similar adverse events in all groups.</td>
</tr>
<tr>
<td>Setting: Home-dwelling setting</td>
<td>Funding sources: This study was funded by the Competitive Research Fund of the Pirkanmaa Hospital District, Tampere University Hospital, Tampere, Finland (Grants 9M073, 9K087, 9H057, 9H189, 9U085, 9F024, 9G053, 9E049, 9E153, 9F053, 9B061); The Finnish Ministry of Social Affairs and Health; the State Provincial Office of Western Finland; City of Tampere; the State Provincial Office of Southern Finland; City of Lappeenranta; Finland's Slot Machine Association; The Central Union for the Welfare of the Aged; Lappeenranta Service Centre Foundation; and Juho Vainio Foundation.</td>
<td>Patient characteristics: Age, mean (SD) fall years: 77.5 (5.6) in intervention group and 77.3 (5.7) in control group. Female, no. (%): 567 (85.8) in intervention group and 563 (86.2) in control group. Previous fall, no. (%) within 1 month: 94 (14.2%) in intervention group and 74 (11.3%) in control group. Inclusion criteria: Home-dwelling person aged 70 years or more with increased risk for falling and fall-induced injuries. The main inclusion criterion was age 70 years or more. In addition, the person had to have at least one of the following independent risk factors for falls and injuries: problems in mobility and everyday function, 3 or more falls during the last 12 months, a previous fracture after the age of 50, an osteoporotic fracture (hip fracture) in a close relative (mother or father), osteoporosis (diagnosed or a strong clinical suspicion such as thoracic kyphosis), low body weight (BMI &lt; 19), and sickness or illness essentially increasing the risk for osteoporosis, falls and fractures.</td>
<td>Exclusion criteria: Inability to give informed consent (for example, because of severe dementia or handicap), disabilities or illnesses preventing physical activity and training inability to move (bedridden individuals), and terminal illness (predicted lifetime less than 12 months).</td>
<td></td>
</tr>
<tr>
<td>Dropout rates: 72 withdrawals in intervention group (10.9%) 97 withdrawals in control group (14.9%)</td>
<td>Study limitations: - Not all high-risk elderly people in the Chaos Clinic communities could be recruited. Regional health care professionals could find only those persons who already had contacted Finnish health care system for some reason. - Adherence to interventions and recommendations could be recorded at general level only. This was due to the study protocol according to which the participants were contacted in three-month intervals. - Study was not large enough to show statistically significant difference in the number of fractures between the groups. The reason for not reaching the originally planned sample size of 3200 patients was that due to financial limitations (grant under-funding) only two Chaos Falls clinics (instead of the planned six) could be realized. - The non-blinded falls follow-up procedure in three months intervals was sub-optimal when the currently recommended procedure is weekly or monthly calendars. - Cost calculations were not built in the study, so it was not possible to assess the cost-effectiveness of the Chaos Falls Prevention Programme.</td>
<td>Notes: Blinding of participants not possible but researchers blinded to group allocations. No statistical test on differences in baseline characteristics between groups described and no p-values shown. Groups stated as equal. Unclear, whether results were comparable between participating clinics. Author's conclusion: In conclusion, a multifactorial centre-based Chaos Clinic Falls Prevention Programme is effective in...</td>
<td>Notes: sample size calculation Author's conclusion: Efficacy and safety of bezodoxifene are sustained across 7 years in postmenopausal women with osteoporosis.</td>
<td>Results: New vertebral fractures: lower in the original BZA40 and BZA20 groups vs placebo: 6.4%, 7.6%, 9.9%. Relative Risk reduction 36.5% and 30.4% (statistically significant). Overall incidence of nonvertebral fractures: no effect Mean changes lumbar spine and total hip BMD from baseline: lumbar spine not significant, total hip: significantly smaller in the BZA40 (-1.15%) and BZA20 (-1.19%) vs Placebo (-2.53%)</td>
</tr>
</tbody>
</table>
preventing falls and fall-induced injuries of high-risk older adults living at home. The rate of falls and related injuries can be reduced by almost 30%. Such clinics are relatively easy and quick to establish although proper education of the staff is needed before initiation. Although the results are very promising further research is needed to compare different types of falls prevention protocols with each other and to assess the costs per prevented injury.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary Adherence</th>
<th>Secondary Rate of falls and fallers, Rate of fall-induced injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results:</strong> Adherence at 6 months highest at nutrition advice (89%), Medical review and referrals (84%) and Exercise prescription (82%) and lowest at Hip protectors (14%). Reduction of alcohol use (17%) and Cessation of smoking (27%). Same segmentation order after 12 months.</td>
<td></td>
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<tr>
<td><strong>Rate of falls:</strong> Rate of falls significantly lower in intervention group (95 falls per 100 person-years) than in controls (131 falls per 100 person-years), (incidence rate ratio [IRR] 0.72; 95% CI; 0.61, 0.86; p &lt; 0.001). Number needed to treat (NNT) to prevent one fall: 3.</td>
<td></td>
</tr>
<tr>
<td><strong>Rate of fallers:</strong> Rates of fallers (per 100 person-years): 63 in intervention group and 81 in control group. Hazard ratio (HR) of fallers in intervention group compared with control group: 0.78 (95% CI; 0.67, 0.91; p = 0.001; NNT = 6).</td>
<td></td>
</tr>
<tr>
<td><strong>Rate of fall-induced injuries:</strong> Number of fall-induced injuries in intervention group during one-year follow-up: 351 (55 per 100 person-years) and 468 (75 per 100 person-years) in control group. Incidence rate ratio (IRR) of fall-induced injuries in intervention group compared with control group: 0.74 (95% CI; 0.61, 0.89; p = 0.002; NNT = 5), IRR of fractures in intervention vs control group: 0.77 (95% CI; 0.48, 1.23; p = 0.276).</td>
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<tr>
<th>Evidence level</th>
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<th>Patient characteristics</th>
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</tr>
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<tbody>
<tr>
<td><strong>Evidence level:</strong> 1+</td>
<td><strong>Study type:</strong> RCT</td>
<td><strong>Total no. patients:</strong> 90 randomized, 60 analyzed</td>
<td><strong>Interventions:</strong> Treatment group: Exercises performed at low intensity (60 - 70 % of maximum heart rate), for 1 h, 3 times/week in groups of 5 patients. First session: educational content about ergonomic use of spine in daily activities and recreation presented by physiatrist and an experienced physiotherapist conducted motor training component. Subsequent sessions consisted of various aerobic physical activities and resistance training based on individual ability.</td>
</tr>
<tr>
<td><strong>Countries:</strong> Presumably Italy</td>
<td><strong>Centres:</strong> Academic ambulatory outpatient rehabilitation facility for Osteoporosis</td>
<td><strong>Patient characteristics:</strong> Treatment group: Age (years): 65.6 ± 5.8; Weight (kg): 66.1 ± 9.7; Height (m): 1.59 ± 0.07; Body mass index (kg/m²): 26.0 ± 3.5. Control group: Age (years): 65.6 ± 5.3; Weight (kg): 64.9 ± 7.4; Height (m): 1.63 ± 0.06; Body mass index (kg/m²): 25.1 ± 3.0.</td>
<td><strong>Control group:</strong> Physiatrist delivered instructional booklet describing and depicting exercises that were to be performed at home for 1 month to reinforce the exercise rehabilitation 3 times per week and at least once per week during the follow-up period.</td>
</tr>
<tr>
<td><strong>Setting:</strong> Outpatient</td>
<td><strong>Funding sources:</strong> Not stated.</td>
<td><strong>Exclusion criteria:</strong> - Male gender, - Presence of severe medical conditions that could have interfered with the outcomes of the trial (e.g., rheumatological, orthopaedic, or oncological diseases) or poorly controlled hypertension or chronic pulmonary disease (for safety reasons), - Concomitant medication that affected calcium and bone metabolism, - Previous lumbar spine surgery and low back pain for sciatica or chronic nonspecific low back pain, - Patients who required other types of drugs, such as antidepressants and antiepileptics,</td>
<td><strong>Conclusion criteria:</strong> - Osteoporotic postmenopausal women with back pain (VAS &gt; 3) for more than 6 months, menopause for at least 1 year, Age 45–75 years, - No evidence or history of fracture, - OP defined per the WHO as BMD &gt; 2.5 standard deviations below BMD in young adult women, measured by dual-energy X-ray absorptiometry in this trial</td>
</tr>
<tr>
<td><strong>Dropout rates:</strong> Treatment group: 4/45 (11.1%); Control group: 20/45 (44.4%)</td>
<td><strong>Study limitations:</strong> - Many patients dropped out in CG, resulting in a higher dropout rate versus the TG suggesting that there was post compliance during the entire trial in control subjects. Rehabilitative treatments should focus on patient compliance. In-group rehabilitative exercises might improve long-term compliance. - Short treatment duration could have facilitated high agreement with rehabilitation. Low adherence by individuals in CG to the home training regimen might have impairs the outcomes. Behaviours interventions might be needed to reduce psychological impairments that impact quality of life — consistent with biopsychosocial model of treating chronic musculoskeletal pain. - Due to chronic pathophysiology of OP, rehabilitative treatments should be repeated. Other studies should perform longer follow-ups to maintain results. - Lack of assessments of posture muscle strength, gait, and balance. Future studies should examine how rehabilitative treatments affect these features to achieve their goals and determine the ideal type and intensity of exercise. - Protocol should be tested against other interventions to determine which method is most effective in improving functional status and bone mass and preventing falls and the consequent fractures.</td>
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Notes: No allocation concealment described. Trial stated as single-blinded, but not explained. No ITT-analyses.

Length of intervention not stated, only that “Recent trials have demonstrated that a course of 10 sessions of rehabilitation has positive effects on back pain, postural control, minor disabilities, and quality of life in low back pain patients”.

Author’s conclusion: Our group exercise-based rehabilitative programme reduces back pain and improves functional status and quality of life in women with postmenopausal OP.
## Outcome Measures/results

**Primary** Back pain measured by Visual Analogue Scale (VAS) and McGill Pain Questionnaire (MPQ) at end of rehabilitation (T1), and at the 6-month follow-up (T2).

**Secondary** Quality of life and functional impairments measured with Shortened Osteoporosis Quality of Life Questionnaire (SOQLQ) and Oswestry Disability Questionnaire (ODQ) at end of rehabilitation (T1), and at the 6-month follow-up (T2).

### Results:

**Back pain measured by VAS:** Significant lower scores at T1 and T2 for TG vs CG: 36 (18) vs 66 (19) at T1 (p<0.001) and 29 (16) vs 66 (17) at T2 (p=0.001).

**Back pain measured by MPQ:** Significant lower scores at T2 for TG vs CG: 33 (20) vs 44 (12) (p=0.018).

**Quality of life:** Significant lower scores at T2 for TG vs CG: 56 (13) vs 42 (16) (p=0.005).

Functional impairments: Significant lower scores at T1 and T2 for TG vs CG: 20 (19) vs 38 (12) at T1 (p<0.001) and 20 (13) vs 27 (8) at T2 (p=0.001).

## Evidence level

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type: Systematic review and meta-analysis: 10 observational studies (4 case-control, 4 prospective, one retrospective and one case-crossover study).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries: USA, Denmark, Sweden, UK, Canada, Australia.</td>
<td>Centres: n.a.</td>
</tr>
<tr>
<td>Funding sources: n.a.</td>
<td>Dropout rates: n.a.</td>
</tr>
<tr>
<td>Study limitations: First, although we searched for all possible studies describing the relationship between opioids and hip fractures, study eligibility was limited to studies published in English. Additionally, we may have missed studies that were excluded from the computer databases used in our search. Second, although we did not observe publication bias, publication bias could not be completely ruled out. Therefore, the pooled effect measure may not have been absolutely precise. Third, although the sources of the heterogeneity were identified, several other factors may have contributed to its development, including ethnicity, opioid dose, participant education level, socioeconomic class and confounding variables. Fourth, as was the case with the results of the previous study, these results cannot be generalized to other populations, particularly Asian populations. Fifth, some limitations described in the study by Teng et al. persisted in this study. For example, we were unable to determine hip fracture timing. Hence, additional research on hip fracture timing is needed. Finally, the quality of the included studies was not evaluated, and no high-quality original studies, such as randomized controlled trials, have been published.</td>
<td></td>
</tr>
</tbody>
</table>

### Included studies:

- Teng K, et al. (2014) BMC Geriatr
- Drug Saf
- Shorr RI, et al. (1992) J Gerontol

### Notes:

No information on participants gender. Quality of the included studies was not assessed. No COI of included studies. High heterogeneity was observed in the primary studies, which indicates substantial differences in study design (not caused by a single study as assessed by sensitivity analysis).

**Author's conclusion:** In conclusion, our meta-analysis demonstrates that opioid use may significantly increase hip fracture risk. Further high-quality studies are needed to confirm these findings.
quality studies, such as randomized controlled trials, especially dose–response studies that research opioids and hip fracture, are urgently required.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measures/results</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Hip fracture risk.</td>
<td>The meta-analysis of the ten studies, which included 697,011 individuals, demonstrated a significant, positive correlation between opioid use and hip fracture risk (RR 1.54, 95% CI 1.34–1.77). Additionally, substantial heterogeneity was observed (P=0.000, I²=84.6%).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type: Systematic Review and Meta-analysis of 8 RCTs</th>
<th>Included studies:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study limitations: The Meta Analysis was based on a limited number of trials with a small sample size and a short length of follow-up. None of the trials were adequately powered to detect the impact of bisphosphonates on a clinically important outcome such as fracture risk. For Quantitative outcomes there was considerable statistical heterogeneity among trials. Considering the small number of included studies, we were not able to conduct a sensitivity analysis with exclusion of trials at high risk of bias. We could not access whether differences in HAART regimes across studies might have contributed to the observed changes in BMD.</td>
<td></td>
</tr>
<tr>
<td>Evidence level</td>
<td>Patient characteristics</td>
<td>Interventions</td>
</tr>
<tr>
<td>1++</td>
<td>Total no. patients: 328 participants</td>
<td>Bisphosphonates vs controls for the treatment of low BMD</td>
</tr>
<tr>
<td>Study type</td>
<td>Patient characteristics</td>
<td>5 Trials: Alendronate vs Placebo or no treatment</td>
</tr>
<tr>
<td>1++</td>
<td>Adults with HIV-infection</td>
<td>3 Trials: Zoledronate vs Placebo or no treatment</td>
</tr>
<tr>
<td>Evidence level</td>
<td>Inclusion criteria: RCT vs controls for the treatment of low BMD</td>
<td></td>
</tr>
<tr>
<td>1++</td>
<td>Exclusion criteria:</td>
<td>HIV-infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adults</td>
</tr>
<tr>
<td>Notes:</td>
<td>Supplementary data not available online.</td>
<td></td>
</tr>
<tr>
<td>Author's conclusion:</td>
<td>In conclusion, administration of oral and intravenous bisphosphonates was associated with increased bone mineral density at the lumbar spine and total hip over two years in HIV-positive patients. However, none of the included trials were long enough to detect the impact of bisphosphonates on a clinically important outcome such as fracture risk. Larger studies with extended follow-up are warranted.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measures/results</th>
<th>Results: BMD percentage change after 48 weeks Lumbar Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary not defined: BMD changes at lumbar spine, femoral neck, total hip adverse events</td>
<td>4 trials: n= 198 patients, Alendronate vs placebo or no treatment. (MD: 2.45%; 95% CI: 1.64-3.26)Heterogeneity: I²: 71%; p &lt; 0.00001</td>
</tr>
<tr>
<td></td>
<td>Secondary -</td>
<td>3 trials: n= 194 patients, Zoledronate vs Placebo or no treatment (MD: 4.60%; 95% CI: 2.89-6.32)Heterogeneity: I²: 33%, p &lt; 0.00001 Total: (MD: 2.84%; 95% CI: 2.11-3.57) Heterogeneity: I²: 67%, p &lt; 0.00001. Total after 96 weeks (MD: 6.76%; 95% CI: 4.98-8.54)</td>
</tr>
<tr>
<td></td>
<td>Femoral neck</td>
<td>One Trial: BMD at 96 weeks, no significant differences between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total hip after 48 weeks 3 trials: n= 157 patients, Alendronate vs placebo or no treatment. (MD: 2.26%; 95% CI: 1.45-3.07)Heterogeneity: I²: 36%, p &lt; 0.00001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 trials: n= 104 patients, Zoledronate vs Placebo or no treatment (MD: 1.74%; 95% CI: 0.43-3.06)Heterogeneity: I²: 42%, p &lt; 0.00001 Total: (MD: 2.12%; 95% CI: 1.43-2.81)Heterogeneity: I²: 28%, p &lt; 0.00001. Total after 96 weeks (MD: 3.2%; 95% CI: 1.52-4.88).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse Events No drug-related withdrawals were reported in the five randomized controlled trials assessing alendronate, whereas two patients out of 104 receiving zoledronate experienced acute-phase reactions.</td>
</tr>
</tbody>
</table>
### Evidence level: 1\*+

**Study type:** RCT

**Countries:** North America

**Centres:** 1 study centre

**Setting:** Shriners Hospital for Children in Montreal

**Funding sources:** "Funding for this study was provided by the Shriners of North America, the Network for Oral and Health Bone Research as well as the Fonds de Recherche du Québec — Santé.*

** Dropout rates:** 400 IU group: 2/30 (6.7%) 2000 IU group: 1/30 (3.3%)

**Study limitations:** - No data reflected on endogenous vitamin D synthesis, such as skin pigmentation or sun exposure.

- High proportion of participants received simultaneous treatment with IV bisphosphonates. Participants in previous retrospective studies on relationship between 250HD and aBMD had not received bisphosphonates. Bisphosphonates increase aBMD, possibly making it more difficult to identify any vitamin D related effects on aBMD. As bisphosphonate treatment is current standard of care in moderate to severe OI, concomitant use of such drugs could not be avoided. To minimize influence of bisphosphonate treatment on study outcomes, only patients on stable long-term bisphosphonate treatment included as well as stratification in randomization.

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. patients:</strong> 60 participants</td>
<td><strong>Patient characteristics:</strong> Age: 6.0 - 18.9 years Sex: 21/30 female in 400 IU group, 14/30 female in 2,000 IU group (difference not significant) OI type IV/III,V and VI: 12/117 in 400 IU group, 11/145/5 in 2,000 IU group. 72% of patients received bisphosphonates IV.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> (1) Patients of both sexes, (2) Age between 6 and 19 years, (3) Diagnoses of OI of any type.</td>
<td><strong>Exclusion criteria:</strong> (1) aBMD measurement of lumbar spine could not be performed. (2) Patients receiving bisphosphonate treatment for less than 2 years (to avoid the large fluctuation in LS-aBMD z-score that is commonly observed at the start of bisphosphonate treatment). (3) Pregnancy at any time during the study. (4) Any chronic disorder other than OI, or use of medication known to interfere with 250HD metabolism.</td>
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</tr>
</tbody>
</table>

| Notes: | |
| Allocation concealment not compiled but allocator not further involved in study. |

**Author's conclusion:** In conclusion, this one-year randomized controlled trial in children with OI found that supplementation of either 400 IU or 2000 IU of vitamin D translated into significant increases in serum 250HD concentrations. However, increases in serum 250HD concentrations that were already largely within the recommended range at baseline did not have a detectable effect on LS-aBMD z-scores.

### Outcome Measures/results

**Primary** Change in LS-aBMD z-score after 12 month

Change in serum 250HD, parathyroid hormone and collagen type I C-telopeptide relative to baseline after 12 month

**Secondary** Changes in cortical and trabecular volumetric BMD z-scores at the radius after 12 month

<table>
<thead>
<tr>
<th>Results: Change in LS-aBMD z-score:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No significant changes in the 400 IU and the 2000 IU treatment group: Mean change 0.0 (95% CI: -0.1, 0.2) vs 0.1 (95% CI: -0.1, 0.2); p = 0.63.</td>
<td></td>
</tr>
</tbody>
</table>

**Change in radius cortical BMD (z-score):** No significant changes in the 400 IU and the 2000 IU treatment group:

- Mean change -0.2 (95% CI: -0.6, 0.2) vs 0.0 (95% CI: -0.4, 0.4); p = 0.53.
- Change in radius trabecular volumetric BMD (z-scores): No significant changes in the 400 IU and the 2000 IU treatment group:
  - Mean change -1.0 (95% CI: -1.7, -0.3) vs -0.4 (95% CI: -1.0, 0.3); p = 0.22.
  - Changes in serum 250HD: Significant changes in the 400 IU and the 2000 IU treatment group: 15.2 nmol/L (95% CI: 6.4, 24.1) vs 30.5 nmol/L (95% CI: 21.3, 39.6); p = 0.02.

**Changes in serum parathyroid hormone:** No significant changes in the 400 IU and the 2000 IU treatment group:

- 0.0 pmol/L (95% CI: -0.3, 0.2) vs -0.2 pmol/L (95% CI: -0.4, 0.1); p = 0.39.
- Changes in serum CTX: No significant changes in the 400 IU and the 2000 IU treatment group: -0.03 ng/mL (95% CI: -0.14, 0.08) vs 0.02 (95% CI: -0.1, 0.13); p = 0.58.

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Rajatanavin, R. et al. The efficacy of calcium supplementation alone in elderly Thai women over a 2-year period: a randomized controlled trial. Osteopors Int. 24. 2871-7. 2013

### Evidence level

**Study details/limitations** | **Patient characteristics** | **Interventions**
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence level</strong></td>
<td><strong>Study details/limitations</strong></td>
<td><strong>Patient characteristics</strong></td>
</tr>
<tr>
<td>1*+</td>
<td>Allocation concealment not compiled but allocator not further involved in study.</td>
<td><strong>Author's conclusion:</strong> In conclusion, this one-year randomized controlled trial in children with OI found that supplementation of either 400 IU or 2000 IU of vitamin D translated into significant increases in serum 250HD concentrations. However, increases in serum 250HD concentrations that were already largely within the recommended range at baseline did not have a detectable effect on LS-aBMD z-scores.</td>
</tr>
</tbody>
</table>

**Primary** Change in LS-aBMD z-score after 12 month

Change in serum 250HD, parathyroid hormone and collagen type I C-telopeptide relative to baseline after 12 month

**Secondary** Changes in cortical and trabecular volumetric BMD z-scores at the radius after 12 month

<table>
<thead>
<tr>
<th>Results: Change in LS-aBMD z-score:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No significant changes in the 400 IU and the 2000 IU treatment group: Mean change 0.0 (95% CI: -0.1, 0.2) vs 0.1 (95% CI: -0.1, 0.2); p = 0.63.</td>
<td></td>
</tr>
</tbody>
</table>

**Change in radius cortical BMD (z-score):** No significant changes in the 400 IU and the 2000 IU treatment group:

- Mean change -0.2 (95% CI: -0.6, 0.2) vs 0.0 (95% CI: -0.4, 0.4); p = 0.53.
- Change in radius trabecular volumetric BMD (z-scores): No significant changes in the 400 IU and the 2000 IU treatment group:
  - Mean change -1.0 (95% CI: -1.7, -0.3) vs -0.4 (95% CI: -1.0, 0.3); p = 0.22.
  - Changes in serum 250HD: Significant changes in the 400 IU and the 2000 IU treatment group: 15.2 nmol/L (95% CI: 6.4, 24.1) vs 30.5 nmol/L (95% CI: 21.3, 39.6); p = 0.02.

**Changes in serum parathyroid hormone:** No significant changes in the 400 IU and the 2000 IU treatment group:

- 0.0 pmol/L (95% CI: -0.3, 0.2) vs -0.2 pmol/L (95% CI: -0.4, 0.1); p = 0.39.
- Changes in serum CTX: No significant changes in the 400 IU and the 2000 IU treatment group: -0.03 ng/mL (95% CI: -0.14, 0.08) vs 0.02 (95% CI: -0.1, 0.13); p = 0.58.
### Evidence level: 1++  
**Study type: RCT**

<table>
<thead>
<tr>
<th>Summary</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries:</strong></td>
<td>Thailand, Japan</td>
</tr>
<tr>
<td><strong>Centres:</strong></td>
<td>Single Center</td>
</tr>
<tr>
<td><strong>Setting:</strong></td>
<td>Ramathibodi Hospital, Faculty of Medicine, Bangkok</td>
</tr>
<tr>
<td><strong>Dropout rates:</strong></td>
<td>15.1% (verum 12.75%, placebo 17.5%)</td>
</tr>
<tr>
<td><strong>Study limitations:</strong></td>
<td>-</td>
</tr>
</tbody>
</table>

| **Total no. patients:** | N=404 |
| **Patient characteristics:** | Physically active healthy postmenopausal Women 50 years. |
| **Inclusion criteria:** | - lumbar spine BMD Tscore of 2.0 to 3.5 |
| **Exclusion criteria:** | - osteoporotic fracture; |
|  | - recent or long-term oral bisphosphonate treatment; |
|  | - intravenous bisphosphonate treatment; |
|  | - treatment with therapeutic doses of systemic corticosteroids, fluoride, strontium, or parathyroid hormone (PTH); |
|  | - metabolic bone disease other than primary osteoporosis; |
|  | - history of Bell’s palsy or other cranial nerve damage; |
|  | - cancer within the previous 5 years allergy to a monoclonal antibody. |

| **Interventions:** | 500 mg of elemental calcium in the form of calcium carbonate or placebo, once daily for 2 years. |

### Notes:
Primary and secondary outcomes not defined in the text. No study limitations described. No sample size calculation.

**Authors’ conclusion:** In conclusion, supplementation with elemental calcium 500 mg/day alone is able to decrease bone turnover and is effective in retarding bone loss at the lumbar spine and slowing bone loss at the femoral neck in elderly Thai women who had low dietary calcium intake. Dietary calcium augmentation should be recommended as a strategic option in helping to prevent early postmenopausal bone loss.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Not defined:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dietary calcium intake</td>
<td></td>
</tr>
<tr>
<td>- Biochemical measurement</td>
<td></td>
</tr>
<tr>
<td>- Bone mineral density</td>
<td></td>
</tr>
</tbody>
</table>

| Secondary | Not defined |

<table>
<thead>
<tr>
<th>Results:</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary calcium intake</td>
<td>- mean calcium intake 376±208 (SD)mg/day</td>
</tr>
<tr>
<td></td>
<td>- 99.4 % average daily calcium intake lower than 1,200 mg/day</td>
</tr>
<tr>
<td></td>
<td>- 3.8 % met reference intake for Thais (800 mg/day)</td>
</tr>
<tr>
<td></td>
<td>- mean dietary calcium intakes in the calcium-treated group vs placebo group 827.0±142.4 and 313.2±147.1 mg (p&lt;0.001).</td>
</tr>
<tr>
<td></td>
<td>- Calcium homeostasis and biochemical markers of bone turnover</td>
</tr>
<tr>
<td></td>
<td>- PTH value in the calcium-treated group significantly lower than placebo group at end of the study (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>- No changes in serum 25(OH)D levels in both groups</td>
</tr>
<tr>
<td></td>
<td>- No inverse relationship between change from baseline in serum 25(OH)D and change from baseline in plasma PTH (r=−0.073, p=0.14)</td>
</tr>
<tr>
<td></td>
<td>- CTX-I and PINP in the calcium-treated group significantly decreased from baseline. Placebo group did not change overtime.</td>
</tr>
<tr>
<td></td>
<td>- Bone mineral density</td>
</tr>
<tr>
<td></td>
<td>- Significant change in lumbar spine (L2-L4) BMD and femoral neck BMD calcium group vs Placebo (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>- Interaction between BMD and time since menopause: &gt; 10 years, the calcium group had significantly greater accretion of lumbar spine (L2-L4) and femoral neck BMD vs control group.</td>
</tr>
</tbody>
</table>

**Adverse Events:**
Calcium group not significantly different from the placebo group.

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**Evidence level:** 1++

**Study type:** RCT

<table>
<thead>
<tr>
<th>Summary</th>
<th>Details/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries:</strong></td>
<td>USA, Japan</td>
</tr>
<tr>
<td><strong>Centres:</strong></td>
<td>Multicenter</td>
</tr>
<tr>
<td><strong>Setting:</strong></td>
<td>13 sites in 5 countries</td>
</tr>
<tr>
<td><strong>Funding sources:</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Dropout rates:</strong></td>
<td>11.67%</td>
</tr>
<tr>
<td><strong>Study limitations:</strong></td>
<td>-</td>
</tr>
</tbody>
</table>

| **Total no. patients:** | N=120 |
| **Patient characteristics:** | Postmenopausal women between 45 and 85 years. |
| **Inclusion criteria:** | lumbar spine BMD Tscore of 2.0 to 3.5 |
| **Exclusion criteria:** | - osteoporotic fracture; |
|  | - recent or long-term oral bisphosphonate treatment; |
|  | - intravenous bisphosphonate treatment; |
|  | - treatment with therapeutic doses of systemic corticosteroids, fluoride, strontium, or parathyroid hormone (PTH); |
|  | - metabolic bone disease other than primary osteoporosis; |
|  | - history of Bell’s palsy or other cranial nerve damage; |
|  | - cancer within the previous 5 years allergy to a monoclonal antibody. |

| **Interventions:** | Blosozumab or Placebo |

**Notes:**
No study limitations described, no sample size calculation.

**Authors’ conclusion:** In conclusion, treatment of postmenopausal women with an antibody targeted against sclerostin resulted in substantial increases in spine and hip BMD. These results support further study of blosozumab as a potential anabolic therapy for osteoporosis.
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type: SR of 7 RCT and 3 CT</th>
<th>Included studies</th>
<th>Evidence details/limitations</th>
</tr>
</thead>
</table>

### Rijks, E. B. et al. Efficacy and Safety of Bisphosphonate Therapy in Children with Osteogenesis Imperfecta: A Systematic Review. Horm Res Paediatr. 84. 26–42. 2015

**Evidence level:** 2+

**Study type:** SR of 7 RCT and 3 CT

**Included studies:**
- Bishop N (2013)
- Lancellot Seikaly MG (2005)
- J Pediatr Orthop
- Rauch F (2009)
- J Bone Miner Res
- Ward LM (2011)
- J Clin Endocrinol Metab
- Latcha AD (2005)
- J Bone Miner Res
- Gatti D (2005)
- J Bone Miner Res
- Antoniazzi F (2006)
- J Pediatr Orthop
- Rauch F (2006)
- J Clin Endocrinol Metab
- Li M (2011)

**Countries:** The Netherlands, Canada (3 trials), Italy (2 trials), China, UK

**Centres:** Single- and multicenter

**Setting:** Not stated

**Funding sources:** Not stated

**Dropout rates:** Not stated

**Study limitations:** - 60% of included studies with poor methodological quality, which generates several types of bias.
- All studies with low risk of bias used oral BPs and all studies with a high risk of bias used intravenous BPs.
- Comparisons between studies difficult due to different follow-up periods.

**Patient characteristics:**
- Total no. patients: 519 children
- Patient characteristics: Mean age: 1 year
- 519 children with osteogenesis imperfecta (OI) participated in the studies with an average age of 7.9-11.9 years.
- Multiple OI types included: I, II, III, and IV

**Inclusion criteria:**
- Children with OI investigated.
- Randomized controlled trials (RCT) or nonrandomized controlled trials
- Children with OI

**Exclusion criteria:**
- Treatment periods <1 year.
- Historical matched controls.
- Comparison between effects of different dosages.
- Comparison between effects of different BPs.

**Interventions:**
- All patients were either supplemented with calcium and vitamin D or monitored and supplemented when necessary.
- Intravenous pamidronate (10 mg/m²/day) for 3 days every 3 months for 1 year.
- Intravenous pamidronate (10 mg/m²/day) for 3 years every 3 months.
- Intravenous pamidronate at 2.5 mg/kg of body weight every 3 months with treatment started just after diagnosis at birth for 18 months.
- Discontinuation of intravenous pamidronate treatment for 2 years.
- Intravenous ibandronate, 2 mg diluted in 250 ml isotonic saline, administered over 2 hours every 3 months for 24 months.

**Controls:**
- Placebo tablets
- Not further specified (4 of 9 children received recombinant growth hormone injections (50.06 mg/kg/day, 6 days/week).)

**Notes:**
- Thorough search strategy. No inclusion of grey/unpublished literature. No investigation of publication bias. Conflicts of interest not stated.

**Author's conclusion:** Treatment with oral or intravenous BPs in children with OI results in an increase in bone mineral density and seems to be safe and well tolerated.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Areal Bone Mineral Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: Areal Bone Mineral Density: 9 studies measured aBMD, 8 indicated significant increase in bone mineral density compared to placebo as a result of BP treatment. 1 study evaluated effects of discontinuation of...</td>
<td></td>
</tr>
</tbody>
</table>

Unclear 'of, Association Risk Effects Activity 1.00, 7 3 95.2984. Baltimore no other for other Intervention Hip fracture and wrist fracture most common fractures sites. Physical activity predominantly measured using a self-administered questionnaire, and the endpoint of fractures was confirmed by self-report diagnosis or medical record. Conclusions: prospective cohort study; investigated the association between physical activity and risk of fracture in older women; size effect evaluated using relative risk (RR), odds ratio (OR), or hazard ratio (HR) values with 95% confidence intervals (CIs), or sufficient data provided to calculate these values; and physical activity divided into at least 3 quantitative categories. Exclusion criteria: Studies conducted in a population with exposure to chronic disease (excluding osteoporosis) or drug consumption.}

Notes:
- Date of search not stated. No search for grey literature possibly introducing publication bias. Funnel plots for investigation of publication bias futile due to insufficient number of studies. Not stated of subgroup analysis was preplanned.
- Physical activity not defined and no description of included activities in studies.
- For investigation of associations, statistical measures of correlations might be more appropriate, especially regarding dose-response associations. Unclear, how association was calculated ("for every increase of 3 physical-activity units") - no description or time specified.
- Author's conclusion: Our results showed that increasing level of leisure physical activity reduced the risk of hip fracture, but not the risk of wrist fracture in older women.

Outcome Measures/results
- Primary: Association Between Physical Activity and Risk of Hip Fracture
- Secondary: Association Between Physical Activity and Risk of Wrist Fracture

Results: Primary: 9 studies included. Combined RR for every increase of 3 physical-activity units in each study: 0.93 (95% CI; 0.91, 0.96). Significant heterogeneity (Q=54.19, P<0.001; I²=85.2%). Combined RR in sensitivity analysis of 7 studies: 0.94 (95% CI; 0.93–0.96), with no significant heterogeneity (Q=5.52, P=0.479; I²=0%).
- Secondary: 3 studies included. Combined RR for every increase of 3 physical-activity units: 1.00 (95% CI; 0.98, 1.03). Significant heterogeneity (Q=10.53, P=0.005; I²=81.0%). Combined RR in sensitivity analysis of 2 studies: 1.01 (95% CI; 1.00, 1.03), with no significant heterogeneity (Q=0.460, P=0.500; I²=0%).

Interventions:
- Physical Activity: not further defined.
### Evidence level: 1++

**Study type:** RCT

| Countries: | European, Canada, Australia |
| Study details: | Study was supported by the 2014 General Medical and Health Research Plan of Zhejiang Province, China, Grant No. 2014KYA229. |
| Baseline enrollment: | n=870 |
| Baseline characteristics: | postmenopausal women aged ≥55 years |
| Inclusion criteria: | previously been prescribed alendronate therapy (stopped ≥1 month or demonstrating suboptimal adherence) |
| Exclusion criteria: | prior or current treatment with osteoporosis medication other than daily or weekly oral alendronate therapy |
| Outcomes: | - hormone replacement therapy - calcium and vitamin D (use of raloxifene or calcitonin prior to initiation of alendronate therapy was allowed) |
| Interventions: | 12 months - denosumab 60 mg subcutaneously (SC) every 6 months (Q6M) - risedronate orally (PO) 150mg once monthly (QM, one 75mg tablet on each of 2 consecutive days) both groups: ≥1000 mg elemental calcium and ≥800 IU vitamin D per day |

### Notes:
- In conclusion, in postmenopausal women who were previously taking alendronate with suboptimal adherence to denosumab was well tolerated and more effective to increase BMD and lower bone turnover than risedronate.
- Sample size calculation: 

### Outcome Measures/results

| Primary - Bone mineral density | Results: Bone mineral density |
| Change from baseline in total hip BMD at month 12 | Denosumab significantly increased BMD at the total hip at month 12 with a mean percentage change from baseline of 2.0% (95% CI: 1.8%, 2.3%); the difference in mean percentage change from risedronate was 1.6% (95% CI: 1.2%, 2.0%; p < 0.0001). - Denosumab also significantly increased BMD at the femoral neck and lumbar spine at month 12 with a mean percentage change from baseline of 1.4% (95% CI: 1.0%, 1.7%) and 3.4% (95% CI: 3.1%, 3.8%). Compared with risedronate, a difference in mean percentage change between the treatment groups of 1.4% (95% CI: 0.9%, 1.8%; p < 0.0001) and 2.3% (95% CI: 1.8%, 2.8%; p < 0.0001). - DXA scans for the least significant change (LSC) in BMD: month 12 BMD gains denosumab- vs risedronate-treated subjects ±LSC at total hip (49% vs 20%, p < 0.0001), femoral neck (24% vs 14%, p < 0.0001), lumbar spine (64% vs 32%, p < 0.0001) sCTX-1: significant decrease in both treatment groups at month 1. Significantly greater reduction denosumab vs risedronate: median (IQR) percentage change of −77.7% (−85.9%, −67.6%) vs −17.0% (−36.8%, −1.6%) (p < 0.0001) - Median reductions in sCTX-1 at month 6 greater in the denosumab vs risedronate group: median (IQR) percentage change of −60.6% (−77.0%, −48.8%) vs −22.5% (−41.9%, 11.4%) (p < 0.0001) - Subjects treated with denosumab significantly greater gains in lumbar spine BMD at month 12 at each tertile of baseline sCTX-1 (p < 0.01). - At all sites the magnitude of the BMD gain was significantly more pronounced in the middle and highest sCTX-1 tertiles (treatment-by sCTX-1 tertile interaction p-values < 0.01) |
| Secondary - mean percentage change in femoral neck and lumbar spine BMD at month 12 - median percentage change from baseline in sCTX-1 at month 1 - median percentage change from baseline in sCTX-1 at month 6 - Biochemical markers - Adverse Events |


| Evidence level: | 1- |
| Study type: | Systematic review and meta-analysis: 8 RCTs. |
| Funding sources: | This study was supported by the 2014 General Medical and Health Research Plan of Zhejiang Province, China, Grant No. 2014KYA229. |
| Dropout rates: | Dropout rates not reported in the study characteristics. Attrition bias was judged as low in all 9 studies. |
| Study limitations: | Firstly, the baseline of the patients included varied significantly in some studies. For example, the mean baseline folate level of the participants in the HOPE2 study was approximately 5 times higher than the participants in Sato’s study in Japan. Therefore, it might be possible that B vitamin supplementation might not generate additional benefits for patients who already have high serum B vitamin level. Among the 4 RCTs that assessed bone turnover markers in postmenopausal women, Sato’s study observed a reduction in bone turnover markers. In fact, the study population was highly selected and characterized as very high plasma Hcy level, severe disability, and an unusually (10-fold) high fracture risk rate compared to the average Japanese population of the same age. However, in a recent meta-analysis observed that fortification with certain B vitamins, such as folate, exert protective effects on Hcy-related cardiovascular risks and additional supplementation had no additive effect. Therefore, we cannot exclude the possibility that B vitamin supplementation might have some protective effects on bone health due to the homocysteine-lowering effects observed in countries without folate fortification, such as Japan. |
| Baseline demographic information: | Total no. patients: 26378. Patient characteristics: Mean age range 39-75 and 36-75 (IC); 17-100% of participants were female. |
| Inclusion criteria: | Study type-RCTs. Population not defined. |
| Intervention: | Vitamin B supplementation type and dose heterogeneous in the included studies: Folate + B6 + B12, or folate + B12, or folate only, or B6 + B12; Duration of treatment between 3 months and 5 years. |
| Comparison: | Placebo. Outcome: fracture risk or bone turnover indicators. |
| Exclusion criteria: | Case report, animal study, or review studies with detailed, but unextractable outcome data (RR of fracture or changes of... |
### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Fracture risk, plasma homocystein (Hcy).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>Bone turnover marker: Alkaline phosphatase ALP (serum), osteocalcin (unclear origin), beta crosslaps CTX (urine or serum).</td>
</tr>
</tbody>
</table>

### Results:

Based on the results of 4 RCTs, this meta-analysis failed to identify a risk-reducing effect of daily supplementation of B vitamins on osteoporotic fracture in patients with vascular disease and with relatively normal plasma Hcy. In addition, we also did not find any positive effects of B vitamin supplementation on bone turnover.

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<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1++</td>
<td>Systematic review and Meta-analysis (5 RCTs)</td>
<td>Included studies: Pfeifer M, et al. (2004) Am J Phys Med Rehabil, Pfeifer M, et al. (2011) Am J Phys Med Rehabil, Vorsanger GJ, et al. (2013) Pain Manag, Li M, S-w Law, et al. (2014) Prosth Orthot Int, Zhang TH, et al. (2013) Chin J Tissue Eng Res.</td>
<td>Total no. patients: 350. Participating 5 trials included a total of 350 participants, of which 318 were women and the mean age ranged from 66.7 years to 81.5 years in the trials. The number of patients in treatment groups ranging from 8 to 44.</td>
<td>Interventions: Spinal orthoses (SpinoMed) (3 trials), non-surgical medication (opioid), non-operative management options used to relieve back pain in patients with VCFs were for inclusion. Given the lack of consensus on pain management for people with VCFs, we focused on all types of analgesic medications, that are commonly used in VCFs, including: simple analgesics [e.g., NSAIDs], weak opioid (e.g., codeine), strong opioid (e.g., oxycodone) with or without analgesic adjuvants. Transdermal lidocaine was also used for a pain control. This method was used for all trials.</td>
</tr>
</tbody>
</table>

**Notes:**

Very limited available data and overall quality of data was judged as very low or low using PEDPro Scale and GRADE approach. The large variety of interventions and co-treatments complicates analysis. The main outcome of pain relief by orthosis use data only available from two studies that were partially or fully funded by pharmaceutical companies. PEDPro Scale reports only 10 out of 11 (missing eligibility criteria). Forest plots do not display p for overall effect.

**Author's conclusion:** There is only low- or very low-quality evidence on the efficacy of non-surgical treatment of symptoms of acute osteoporotic VCFs. Immediate- and short-term effects of opioids on pain were found inconsistent across trials with different comparators. Low-quality evidence supports immediate- and short-term effects of an NSAID on reducing pain intensity. There is low-quality evidence indicating the value of spinal orthoses for pain relief and disability at medium term. Low or insufficient statistical power of trials, additional interventions and possible conflict of interest might have influenced the results. At present, there is insufficient evidence to inform conservative care for acute pain related to VCF. Large, multinational, placebo/ sham-controlled trials to address this gap in evidence are needed.
Outcome Measures/results

Primary: Risk of hip fracture
Secondary: -

Results: 5 RCTs (n = 350) were identified including one placebo-controlled and 4 controlled trials examining analgesics (2 studies) and ortheses. PEDro scores ranged from 4 to 7. The overall quality of evidence ranged from very low to low. Pain reduction: In two trials, spinal orthoses provided significantly higher medium-term pain relief (SMD) = -1.47, 95 % confidence interval (CI) -1.82, -1.13; I^2 = 0 %) than no intervention. Immediate- and short-term pain effects of diclofenac (a non-steroidal anti-inflammatory drug) and tramadol (a strong opioid) were demonstrated when compared to a Chinese medicine. Non-significant effects were found for oxycodone and tapentadol (strong opioids) in a placebo-controlled trial. Low/insufficient statistical power, co-interventions and potential conflict of interest might have influenced the results.

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Evidence level: 2++
Study type: MA of 10 prospective cohort studies

Countries: 6 studies from Europe, 3 USA, 1 Canada.
Centres: N.r.
Setting: 8 studies population-based, 1 community-based, 1 Nurse Health Study.
Funding sources: N.r.
Dropout rates: N.r.

Study limitations: - Inconsistency among included studies in choice of adjustments. RRs of 6 studies adjusted in multivariable models, 2 studies not adjusted, 2 studies only adjusted with age.
- Misclassification of smoking habits could result in bias. Smoking classification in included studies ranging from current or former or never smoking status to more complicated ways of lifetime smoking by number and duration.
- Potential publication bias is likely to affect findings, yet little evidence of publication bias.
- Relatively strict inclusion criteria might have introduced selection bias.
- Dose-response analyses based on a limited number of studies. Results should be considered with cautions.
- Results of current analysis mainly based on data from American and European populations. Validity of extrapolation of association to other populations doubtful.

Total no. patients: 359,468 participants
Patient characteristics: Mean age (range): 20 - 93 years.
Distribution of male/ female not reported.

Inclusion criteria: (1) patients were prospectively enrolled and followed up; (2) studies reported relative risks (RR) and their corresponding 95% confidence intervals (95% CIs) of hip fracture by different smoking categories; and (3) studies included women both exposed and not exposed to cigarette smoking.

Exclusion criteria: (1) were letters, abstracts, review articles, meta-analyses, conference proceedings, case reports, retrospective studies or cross-sectional studies;
(2) were not written in English;
(3) did not report hip fracture or smoking status; and
(4) did not report data for women.

Interventions: Cigarette smoking

Notes: Final search query not stated. No search for unpublished literature. Sex of study participants not reported. The authors provide no p-values for estimates of meta-analysis.

Author's conclusion: Smoking is associated with an increased hip fracture risk in women. Cessation of smoking for 10 years had a decreased impact on risk of hip fracture. Given the inconsistency among the studies in the choice of adjustments, the associations between cigarette smoking and risk of hip fracture in women await further investigation.

Outcome Measures/results

Primary: Risk of hip fracture
Secondary: -

Results: Current smokers versus never smokers: Investigated in 7 studies. Statistically significant association between hip fracture for current smokers compared with never smokers. RR = 1.30 (95%CI; 1.16, 1.45). Dose-response analysis. Data provided in 3 studies. RR of hip fracture increased from 1.11 (95% CI; 0.89, 1.33) in low-dose smokers (less than 15 cigarettes per day) to 1.26 (95% CI; 1.02, 1.51) in high-dose smokers (more than 15 cigarettes per day).

Current smokers versus nonsmokers: Investigated in 3 studies. Current smokers with statistically significantly increased risk compared with nonsmokers (RR = 1.54; 95%CI; 1.20, 1.87)
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence level:</strong></td>
<td><strong>Study type:</strong></td>
<td><strong>RCT</strong></td>
</tr>
<tr>
<td><strong>Setting:</strong></td>
<td><strong>Not reported</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Funding sources:</strong></td>
<td><strong>A peer-reviewed grant from the Physicians' Services Incorporated Foundation funded this trial. Juvent Inc. supplied the WBV platforms and Jamieson Laboratories provided calcium and vitamin D supplements. None of these sources were involved in the study design, conduct, analysis, interpretation of the data, preparation of this manuscript, or decision to submit the manuscript for publication.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total no. patients:</strong></td>
<td><strong>202</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Project characteristics:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group:</strong></td>
<td><strong>2 Lost to follow-up. 1 Started hormone therapy.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Missing QUS measurements:</strong></td>
<td><strong>7 Missing QUS measurements.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Control group:</strong></td>
<td><strong>2 Lost to follow-up. 1 Started hormone therapy.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Dropout rates:</strong></td>
<td><strong>90-Hz WBV Group:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>2 Lost to follow-up.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Missing QUS measurements.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>30-Hz WBV Group:</strong></td>
<td><strong>3 Lost to follow-up.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Missing QUS measurements.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Control group:</strong></td>
<td><strong>2 Lost to follow-up. 1 Started hormone therapy.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Study limitations:</strong></td>
<td><strong>(1) Sample size and power calculations not based on calcaneal QUS outcomes, because they were collected as secondary endpoints. (2) Women and outcome assessor not blinded to control intervention, since sham WBV was not provided due to limited funding and a lack of effective masking of true WBV by a sham platform. (3) Control group participants were not instructed to stand still for 20 consecutive minutes every day, so it is unclear whether just standing on the vibration platform, regardless of WBV, could have contributed to the between-group differences in 12-month changes in BUA. (4) QUS outcomes missing in 12 % of participants and required replacements by use of multiple imputation models in primary analysis. (5) Numerous between-group comparisons performed during various statistical approaches, thus increasing the likelihood of chance findings.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Interventions:</strong></td>
<td><strong>90- and 30-Hz groups:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Whole-body vibration (WBV) platforms synchronously oscillating at a frequency of 90- or 30-Hz with a peak acceleration of magnitude of 0.3 g (peak-to-peak displacement of 0f 60 lm), provided by Juvent Regenerative Technologies Corporation, Riviera Beach, Florida. Participants instructed to stand erect on oscillating platform at home for 20 consecutive minutes daily for 12 months, with neutral postures at the neck, lumbar spine, and knees, wearing socks or barefoot, and without excessive foot or body movements.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Control group:</strong></td>
<td><strong>Participants asked not to use WBV therapies. Calcium and vitamin D supplements provided to all participants at baseline + 6 months.</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
Investigators could have been blinded, but were not. Test for baseline differences not described.

**Author's conclusion:** In conclusion, we found no beneficial effect of WBV on calcaneal QUS measurements in community-dwelling postmenopausal women receiving calcaneal BUA in two out of four multiple imputation models, per protocol analysis and subgroup analysis of 85 % adherent participants. This potential negative effect needs to be confirmed in future research. In the absence of any clear beneficial bone effects at hip, spine, distal tibia, and calcaneus, we do not recommend WBV therapy at this time for the prevention of bone loss in postmenopausal women with low bone density.

**Outcome Measures/results**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Calcaneal Quantitative Ultrasound Outcomes</th>
<th>Secondary</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results:</strong> Calcaneal Quantitative Ultrasound Outcomes: No improvement in BUA, SOS, or QUL in any of the WBV groups when compared to the control group in 2 out of 4 multiple imputation models analyses. Not statistically significant trend also for 90-Hz group. <strong>Adverse Events:</strong> No SAE related to WBV. Various adverse events reported regarding minor foot-related problems (including plantar foot pain, foot numbness, toe cramping) but no significant between-group differences.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence level

**Evidence level:** 2++

**Study type:** MA of 57 cross-sectional Studies

**Included studies:**
- Bachmann (2014)
- Bachrach (1991)
- Bertoli (2004)
- Bredella-Sanda (2010)
- Bredella (2008)
- Bredella (2009)
- Bredella (2012)
- Bredella (2014)
- DeAlvaro (2007)
- Diamanti et al. (2007)
- D’Vasta (2007)
- Dominguez (2007)
- Dostalova (2010)
- Faje (2014)
- Fazeli (2010)
- Fernandez-Garcia (2009)
- Fernandez-Soto (2013)
- Grinspoon (1999)
- Guo (2013)
- Iacopino (2003)
- Iketani (1995)
- Jacqanelli (2002)
- Kirike (1992)
- Kooh (1996)
- Lawson (2011)
- Legroux-Gerot (2007)
- Maimoun (2014)
- Marra (1997)
- Milos (2005)
- Misra (2007)
- Misra (2008)
- Misra (2013)
- Naessen (2006)
- Newton (1993)
- Olmos (2010)
- Poet (1993)
- Polito (1998)
- Pumarino (1992)
- Resch (2000)
- Rigotti (1984)
- Savvas (1989)
- Schneider (1998)
- Seeman (1992)
- Serafinowicz (2003)
- Stergioti (2013)
- Sundgot-Borgen (1998)
- Treasure (1986)
- van Marken Lichtenbelt (1997)
- Vestergaard (2002)
- Viapiana (2007)

### Study details/limitations

- **Countries:** Europe (studies = 30), North America (studies = 20), China, Hong Kong, Switzerland, Chile, Japan (studies = 2), Australia.
- **Setting:** In- and outpatients, community dwelling.
- **Funding sources:** None.
- **Study limitations:** Only cross-sectional studies included.
- **Dropout rates:** N.r.
- **Minimal data on BMD in BN and EDNOS participants.**
- **Indication of publication bias.**
- **High heterogeneity, potentially introducing a bias into our results.**
- **Some important moderators (e.g., nutritional intake) were unavailable for meta-analysis.**

### Patient characteristics

- **Total no. patients:** 21,607 participants
- **Patient characteristics:** Patients with eating disorders = 6.485; Healthy Controls (HC) = 15.122
  - 4,361 participants diagnosed with anorexia nervosa (mean age = 21.5 ± 8.1 years); average illness duration of 28.5 ± 27.2 months and mean BMI of 17.1 ± 10.8 kg/m².
  - 1,520 participants diagnosed with bulimia nervosa (mean age = 23.5 ± 5.5 years, illness duration = 60.1 ± 60.2 months, mean BMI = 22.4 ± 3.7).
  - 964 with eating disorders not otherwise specified (mean age = 24.6 ± 11.8 years, illness duration = 143 ± 72 months, mean BMI = 21.0 ± 3.2).

### Interventions

Mean age of HCs: 22.5 years with BMI of 22.2 ± 5.7 kg/m².

**Inclusion criteria:** Cross-sectional studies that
- (i) included participants of any age with a primary diagnosis of any eating disorder including anorexia nervosa (AN), bulimia nervosa (BN), eating disorder not otherwise specified (EDNOS) according to established criteria (e.g., DSM-III, DSM-IV, DSM-V, or ICD-10);
- (ii) assessed BMD using dual energy X-ray absorptiometry (DEXA) at one or more skeletal sites in a sample including ED and HC groups; and
- (iii) were published in a peer-review journal in English.

**Exclusion criteria:** -
Notes:

Search strategy only stated for PubMed. No search for grey/ unpublished literature.

STROBE criteria used for quality assessment of included studies and results reported in supplement.

Due to the anticipated heterogeneity, random effects meta-analysis (more conservative) utilized regardless of quantified heterogeneity.

Author's conclusion: People with AN have reduced BMD, increased odds of osteoporosis and risk of fractures. Proactive monitoring and interventions are required to ameliorate bone loss in AN.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measures/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Standardized mean difference (SMD) in BMD between ED participants and HCs at each skeletal site.</td>
</tr>
<tr>
<td>Secondary</td>
<td>Prevalence and odds ratio (OR) of osteopenia, osteoporosis (defined according to World Health Organization), fractures in ED participants versus HCs</td>
</tr>
</tbody>
</table>

Results: BMD: AN subjects with significantly lower BMD values at lumbar spine compared to HC (SMD = 1.51, 95% CI; 1.75, 1.27, studies = 42), total hip (SMD = 1.56, 95% CI; 1.84, 1.28, studies = 23), intertrochanteric region (SMD = 1.80, 95% CI; 2.46, 1.14, studies = 7), trochanteric region (SMD = 1.05, 95% CI; 1.44, 0.66, studies = 7), and femoral neck (SMD = 0.98, 95% CI; 1.12, 0.77, studies = 20). Reduced BMD moderated by ED illness duration and amenorrhoea (P < 0.05).

No difference in BMD was found between BN and EDNOS vs. HC.

Prevalence of osteoporosis: AN associated with an increased likelihood of osteoporosis (OR = 12.59, 95% CI; 3.30, 47.9, P < 0.001, studies = 4).

Fractures: AN associated with an increased likelihood of fractures (OR = 1.84, 95% CI; 1.17, 2.89, I² = 56%, studies = 6).


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type: Systematic review and Meta-analysis: 13 studies (8 RCTs, 5 NRCTs).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study details/limitations</td>
<td>Countries: China, Spain, Iran, Netherlands, Belgium, Australia, Denmark, Korea, Slovenia, Taiwan. Centres: n.a.</td>
</tr>
<tr>
<td>Setting: n.a.</td>
<td>Funding sources: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.</td>
</tr>
<tr>
<td>Dropout rates: Risk of bias assessment considered incomplete outcome reporting to be at low risk in 4 studies, unclear in 2 and high in 2 of the included RCTs. For the NRCTs the risk of bias due to loss of follow up was judged as reported, but inadequate in all 5 studies.</td>
<td></td>
</tr>
<tr>
<td>Study limitations:</td>
<td>(i) the demographics and co-morbidities of all of the included study participants were not reported; (ii) data on the specific segments of the secondary vertebral fracture sites were not well recorded in all of the included studies – thus, a comparison of the incidence of fractures at different levels was not possible; (iii) few RCTs and NRCTs comparing OVCF patients who underwent BKP alone with OVCF patients undergoing conservative treatment have been conducted, we therefore included only two trials investigating BKP among the analyzed studies; (iv) although we detected no statistically significant evidence of publication bias in the current meta-analysis, publication bias may have influenced our findings nevertheless.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type: Systematic review and Meta-analysis: 13 studies (8 RCTs, 5 NRCTs).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study details/limitations</td>
<td>Total no. patients: 1459. Patient characteristics: Participants with osteoporotic vertebral compression fractures (OVCF). Follow up ranging from 3 to 80 months. Mean age ranging from 65-80 years in the control group and from 66-80 years in the intervention group. Inclusion criteria: RCTs or NRCTs; (i) comparing vertebral augmentation techniques (either PVP or BKP or both) to conservative treatment in patients with OVCF; and (ii) reporting the number of patients in both groups and the number of patients who experienced secondary vertebral fractures during the final follow-up of both groups. When multiple reports from the same center or trial were found, we selected the most thorough publication.</td>
</tr>
<tr>
<td>Setting: n.a.</td>
<td>Exclusion criteria: The following studies were excluded: (i) retrospective studies, observational studies, and studies with no conservative treatment group or lacking key information; (ii) studies with no clear inclusion or exclusion criteria or with no clear description of the design; and (iii) studies including patients with severe cardiopulmonary co-morbidities, untreated coagulo- pathies, systemic or local spine infections, suspected underlying malignant diseases, spinal-cord compression syndromes, or contraindications for magnetic resonance imaging.</td>
</tr>
<tr>
<td>Dropout rates: Risk of bias assessment considered incomplete outcome reporting to be at low risk in 4 studies, unclear in 2 and high in 2 of the included RCTs. For the NRCTs the risk of bias due to loss of follow up was judged as reported, but inadequate in all 5 studies.</td>
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</tr>
</tbody>
</table>

Notes:

No mention of use of operators or Mesh terms for the literature search. Study characteristics provide no information regarding sex. Unclear whether data were extracted by two investigators. Weak definition regarding PICO and inclusion criteria, especially given the fact that part of the rationale was "Recent meta-analyses have compared the incidence of secondary vertebral fractures between patients treated with vertebral augmentation techniques or conservative treatment; however, the inclusions were not..."
In conclusion, no differences in the incidence of secondary fractures in patients who underwent vertebral augmentation techniques and patients who underwent conservative treatment were observed. Additional RCTs, especially trials comparing the incidence of secondary vertebral fractures at different levels, trials comparing BKP and conservative treatment and trials identifying risk factors for secondary fractures, should be conducted.


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence type: 1++</td>
<td>Study type: SR/MA of 16 RCT</td>
<td><strong>Countries:</strong> All studies but 2 conducted in multi-country populations. 2 remaining studies conducted in Germany and Japan. <strong>Centres:</strong> N.r.</td>
<td><strong>Total no. patients:</strong> 11.206 patients <strong>Patient characteristics:</strong> Middle-aged and elderly study populations, with mean age ranging from 45.9 years old to 59.5 years old. Proportion of female participants ranging from 32.1% to 76.2%.</td>
</tr>
<tr>
<td>Study limitations: - Conclusion needs to be interpreted with caution because a relatively low number of fracture cases were identified in meta-analysis and because that the durations of most trials were not sufficiently long to study the effects on bone fractures. - Age of study populations relatively younger than typical osteoporosis population, which might be an important bias in evaluation of drug effect on bone fractures. - Risk of GLP-1 RA on specific fracture sites could not be determined due to limited number of studies. - Risk of bone quality might be modified by patients’ concomitant medications such as statins, corticosteroids, estrogens, yet such information were generally not reported for individual studies. - Risk observed in meta-analysis</td>
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<td>Evidence level</td>
<td>Study type</td>
<td>Countries</td>
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<tr>
<td>1++</td>
<td>Systematic review and Meta-analysis</td>
<td>Spain, Australia, Iran, Austria, Belgium, France, Germany, Italy, Netherlands, Sweden, UK, Taiwan</td>
<td>n.a.</td>
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<td>RCTs</td>
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### Results

**Overall GLP-1 RA and risk of bone fractures:** 14 studies included with 5,040 patients (23 fracture cases) in intervention group and 3,410 (15 fracture cases) in comparator group. No significant association: OR = 1.05, 95 % CI: 0.59, 1.87. No significant heterogeneity: \( I^2 = 0 \%, P = 0.739 \). Observed risk effects not modified by age (\( P = 0.411 \)), BMI (\( P = 0.291 \)), and FrA1c (\( P = 0.786 \)) level at baseline.

**Ligand and risk of bone fractures:** 8 studies included with 7,377 patients (8 fracture cases) in intervention group and 3,175 (13 fracture cases) in comparator group. Treatment with ligand was associated with a significant reduced risk of bone fractures, compared with placebo or other active drugs (OR = 0.38, 95 % CI: 0.17, 0.87, no p-value stated). No significant heterogeneity: \( I^2 = 0 \%, P = 0.864 \). Excluding two studies using enoxistat as comparators led risk effect to be non-significant (OR = 0.49, 95 % CI: 0.19, 1.22).

**Exenatide and risk of bone fractures:** 10 studies included with 2,681 patients (20 fracture cases) in intervention group and 2,613 (7 fracture cases) in comparator group. Treatment with exenatide associated with a significant increased risk of bone fractures, compared with placebo or other active drugs (OR = 2.09, 95 % CI: 1.03, 4.21, no p-value stated). No significant heterogeneity: \( I^2 = 0 \%, P = 0.745 \). After exclusion of two studies with ligand as comparator arm, the pooled MHR was attenuated to 1.71 (95 % CI: 0.80, 3.67).

### Outcome Measures/results

**Primary** Risk of bone fractures  
**Secondary** -

- **Evidence**  
- **Study details/limitations**  
- **Patient characteristics**  
- **Interventions**


**Evidence level**  
**Study type**  
**Countries**  
**Centres**  
**Setting**  
**Funding sources**  
**Total no. patients**  
**Patient characteristics**  
**Interventions**

<table>
<thead>
<tr>
<th>Evidence level</th>
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<th>Countries</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>Systematic review and Meta-analysis</td>
<td>Spain, Australia, Iran, Austria, Belgium, France, Germany, Italy, Netherlands, Sweden, UK, Taiwan</td>
<td>n.a.</td>
<td>n.a.</td>
<td>The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 10/122/01. The protocol was agreed in October 2011. The assessment report began editorial review in August 2012 and was accepted for publication in December 2012. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have ensured the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report. This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC or the HTA programme or the Department of Health.</td>
<td>114 (not stated in the article).</td>
<td>Patients with osteoporotic vertebral compression fracture or non-osteoporotic vertebral fracture. 72-83% of the participants were female. Mean age range 72-80 years.</td>
<td>Percutaneous vertebroplasty or percutaneous balloon kyphoplasty.</td>
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<td>RCTs</td>
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### Notes

Unclear, whether data extraction was performed by two investigators.

Result of quality assessment with Jadad not presented one-to-one to studies, but as overall result instead.

**Author’s conclusion:** Our study demonstrated a divergent risk of bone fractures associated with different GLP-1 RA treatments. The current findings need to be confirmed by future well-designed prospective or RCT studies.
methodological problem was the lack of blinding in all studies except 2. Unblinding in surgical studies has been linked to a 25% overestimation of treatment effect. As Buchbinder and Kallmes have pointed out, the improvement in the treatment groups of the blinded trials was not dissimilar to that seen in the treatment groups of the unblinded trials. The assessment of BKP’s clinical effectiveness was particularly limited, as only one open-label RCT comparing BKP with non-surgical management was available, while the only study to compare BKP with PVP showed a number of potential sources of bias.

A further limitation of these findings was the use of pain as a primary outcome. As others have argued, pain measurement may be confounded by a number of factors, including pain threshold, analgesia and level of activity. Back pain-related disability and quality of life may provide more objective and clinically meaningful measures. However, these outcomes were measured in heterogeneous ways among the trials, precluding statistical aggregation of the data. Measures of vertebral body height and angular deformity may also be more useful clinical outcomes than pain, insofar as improvements could enhance mobility and stave off deterioration of cardiopulmonary function. 4 studies reported these outcomes, but it was not possible to aggregate their findings owing to the heterogeneous approaches that were taken to wedge angle and vertebral body height measurement.

Notes:
Article selection was not carried out by two investigators. Grey literature was not considered.

Author’s conclusion: For people with painful osteoporotic VCFs refractory to analgesic treatment, PVP and BKP perform significantly better in unblinded trials than optimal pain management (OPM) in terms of improving quality of life and reducing pain and disability. However, there is as yet no convincing evidence that either procedure performs better than OPLA. The uncertainty in the evidence base means that no definitive conclusion on the cost-effectiveness of PVP or BKP can be provided. Further research should focus on establishing whether or not BKP and PVP have a mortality advantage compared with OPLA and on whether or not these provide any utility gain compared with OPLA.

Outcome Measures/results
Primary Pain/analgesic use; Back-specific functional status/mobility; Vertebral body height (VBH) and angular deformity; Progression of treated fracture; Incidence of new vertebral fractures; Health-related quality of life.
Secondary All-cause mortality; Symptomatic and asymptomatic leakage of cement (egg into adjacent intervertebral discs); Periprocedural balloon rupture; Post-operative complications (including infection); Other adverse events; Resource utilisation; Cost utility.

Results: Quality of evidence: This body of literature was of variable quality, with the two double-blind, OPLA-controlled trials being at the least risk of bias. The most significant methodological issue among the remaining trials was lack of blinding for both study participants and outcome assessors. The volume of available evidence of clinical effectiveness is greater for PVP than for BKP, and the methodological quality of some of that evidence is also higher than that of any study of BKP.
Clinical effectiveness: In relation to PVP, the studies least at risk of bias found no significant differences between treatment groups in terms of change from baseline on the EQ-5D and OPLA at 1 month. This is consistent with the findings of the two double-blind, OPLA-controlled trials being at the least risk of bias. The most significant methodological issue among the remaining trials was lack of blinding for both study participants and outcome assessors. The volume of available evidence of clinical effectiveness is greater for PVP than for BKP, and the methodological quality of some of that evidence is also higher than that of any study of BKP.


Evidence level: 1+ Study: RCT
Countries: Germany
Centres: Siemens Betriebskrankenkasse, Centre for Muscle and Bone Research (Charité Universitätsmedizin)

Patient characteristics:
Total no. patients: ITT-population: 60 women; PP-population: 58 women.

Interventions: Intervention period: 9 months.
Joint resistive exercise: 2 training appointments per week in groups of max 10 participants. 15 min warm-up on a cycle ergometer followed by 30 min resistance exercise with increasing load.
Balance training (BAL): 15 min progressive proprioceptive and balance exercise program performed alone or when necessary with a partner.


Evidence level: 1+ Study: RCT
Countries: Germany
Centres: Siemens Betriebskrankenkasse, Centre for Muscle and Bone Research (Charité Universitätsmedizin)
Berlin) and Immanuel Krankenhaus Berlin

**Setting:** Training interventions local sports club (Sport-Gesundheitspark Berlin e.V.)

**Funding sources:** No funding received.

**Dropout rates:** 11 subjects dropped out of study. Distribution among groups not stated, only that the "drop out rate did not differ significantly between groups (χ² = 0.25, p = 0.61)."

**Study limitations:**
- Contribution of the resistive exercise on changes in current study unclear.
- Significant differences seen in response between groups indicate that additional training forms were driving factor behind changes seen in neuromuscular performance.
- Future work will need to consider issues of whole-body vibration training duration, intensity and frequency.

24.7 kg/m² (2.7)

Balance group: Mean age (SD): 65.3 (4.3) years; Mean BMI (SD): 23.8 (3.9) kg/m² (3.9)

**Inclusion criteria:** (1) a minimum of 8 years postmenopausal,
(2) no recent (last 6 months) involvement in whole-body vibration exercise, balance training or resistive exercise and
(3) a total hip or lumbar spine (L1–L4) T-score from ~2.0 to ~3.0 SD on dual energy X-ray absorptiometry (DXA).

**Exclusion criteria:** (1) any metal implants, known disturbance of the vestibular system, prior experience with the testing apparatus,
(2) bone fractures within the last year,
(3) neuromuscular and neurological diseases, acute thrombosis in the last 24 months, coronary heart disease, pacemaker, acute arthritis,
(4) smoking of more than 20 cigarettes per day and alcohol consumption of more than 14 g per day.

Notes:
- Allocation concealment mentioned but not described. Investigators could have been blinded but were not. No test for baseline differences mentioned but "no significant baseline differences stated."
- 8 participants were subsequently recruited after higher than expected drop-out rate. Baseline characteristics for these participants not stated. These subjects were excluded from ITT-analyses.

**Author’s conclusion:**
In conclusion, the results of the current study show that combining whole-body vibration with resistive exercise in postmenopausal women with low bone density is more effective in improving some aspects of neuromuscular performance than proprioceptive training with resistive exercise. The additional effect of whole-body vibration was seen most clearly in the countermovement jump test. The results support the implementation of whole-body vibration with resistive exercise in maintaining neuromuscular performance in post-menopausal osteopenic or osteoporotic women.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Countermovement jump power per unit body weight</th>
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<tbody>
<tr>
<td>Secondary</td>
<td>Multiple 1-leg hopping, Sit-to-stand test</td>
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</table>

Results: Countermovement jump: Peak power relative to body weight (W/kg): Significant change from baseline to 9 months in vibration group (27.9 [4.8] to 28.5 [5.0]; p<0.01). Adjusted Difference at 9 months (95% CI): 0.9 (0.3, 1.5), no p-value stated. Peak acceleration (g): Significant change from baseline to 9 months in balance and vibration group (2.0 [0.2] to 2.1 [0.2]; p<0.01 vs 2.1 [0.2] vs 2.2 [0.3]). Adjusted Difference at 9 months (95% CI): -0.04 (-0.12, 0.05), no p-value stated. Jump height (cm): Significant change from baseline to 9 months in balance group (25 [4] to 24 [4]; p<0.05). Adjusted Difference at 9 months (95% CI): 1.3 (0.3, 2.3), no p-value stated. Esslinger Fitness Index (%): Significant change from baseline to 9 months in vibration group (101 [15] to 109 [16]; p<0.001). Adjusted Difference at 9 months (95% CI): 3.2 (1.0, 5.5), no p-value stated. Jump efficiency (%): Significant change from baseline to 9 months in balance group (117 [16] to 111 [15]; p<0.01. Adjusted Difference at 9 months (95% CI): 6.9 (2.7, 11.1), no p-value stated.

Multiple 1-leg hopping: Hop force and acceleration significantly improved in both groups on left leg and in the VIB group also on the right leg. Adjusted Difference in hop force at 9 months (95% CI): 0.00 (-0.06, 0.06), no p-value stated. Adjusted Difference in acceleration at 9 months (95% CI): 0.01 (-0.08, 0.10), no p-value stated. Peak power relative to body weight (W/kg): Significant change from baseline to 9 months in balance group in both legs (left leg: 15.0 [3.1] to 14.0 [2.9]; p<0.05; right leg: 16.0 [3.3] to 14.0 [3.1]; p<0.001). Adjusted Difference at 9 months (95% CI): 0.4 (-0.6, 1.5) and 1.0 (-0.2, 2.2), no p-value stated.

**Sit-to-stand test:** Sit-to-stand duration and average acceleration both improved significantly in VIB-group, but not in the BAL-group. No significant change in average power per unit body weight.
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1++</td>
<td>Study type: RCT one-year open-label extension of DIRECT-study</td>
<td>Countries: Japan Centres: multicenter</td>
<td>Total no. patients: N= 810 (404 in the denosumab group and 406 in the placebo (cross-over) group)</td>
</tr>
<tr>
<td></td>
<td>Funding sources: Daiichi-Sankyo, Tokyo.</td>
<td>Patient characteristics: Generally, Healthy Japanese subjects with osteoporosis including postmenopausal women and men</td>
<td>Interventions: DIRECT study: for a period of 2 years, denosumab 60 mg given as a subcutaneous injection every 6 months, matching placebo, or open-label alendronate 35 mg taken orally every week.</td>
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<tr>
<td></td>
<td>Dropout rates: 3.71%, placebo 4.93%</td>
<td>Inclusion criteria: - Age ≥50 years - 1–4 prevalent vertebral fractures, and low bone mineral density (BMD) (T-score</td>
<td>During the open-label extension phase, all subjects received 60 mg denosumab subcutaneously every 6 months for 1 year with daily supplements containing at least 600 mg calcium and 400 IU vitamin D.</td>
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<td>Study limitations: The number of patients was relatively small and the extension did not have a placebo arm. Due to the small number of subjects, this study is considered to have inadequate power to detect adverse events with very low incidence such as atypical femoral fractures. Additionally, since all subjects received denosumab in the 12-month extension phase, it is difficult to rigorously investigate long-term vertebral fracture risk reduction.</td>
<td>Exclusion criteria: -</td>
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**Notes:** No information about sample size calculation or ITT

**Author’s conclusion:** Three-year denosumab treatment in Japanese subjects with osteoporosis showed a favorable benefit/risk profile.
<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary</th>
<th>Results</th>
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<tbody>
<tr>
<td>Vertebral and non-vertebral fractures, changes in BMD and BTMs, safety and tolerability of denosumab for 3 years.</td>
<td>Describe the efficacy including evaluation of the incidence of vertebral and nonvertebral fractures, and the changes in BMD and BTMs.</td>
<td>The 2-year incidence of new vertebral fractures was 2.2% in the denosumab (long-term) group and 8.6% in the placebo (cross-over) group, with the reduction in risk by 74.0% (p=0.0001), and the rate ratios comparing the number of new vertebral fractures for the denosumab group in year 1 and 2 with those for the placebo group were 0.44 (p=0.0937) and 0.14 (p=0.0001). In the long-term group, the cumulative incidences of new or worsening vertebral and new vertebral fractures at 36 months were 3.8% (95% CIs, 2.4; 6.1) and 2.5% (95% CIs, 1.4; 4.5). The annual rate of new or worsening vertebral and new vertebral fractures were 1.9 and 1.3%, in the first year, 1.6 and 0.9%, in the second year, and 0.3 and 0.3%, in the third year. In the cross-over group, the cumulative incidences of new or worsening vertebral and new vertebral fractures at 36 months were 11.8% (95% CIs, 9.1; 15.2) and 10.3% (95% CIs, 7.8; 13.5). The annual rate of new or worsening vertebral and new vertebral fractures in the first, second, and the third years were 2.7, 5.9, and 1.9%. BMD In the long-term group, increases from the baseline in BMD after 3 years of continued denosumab treatment were 11.0% at the lumbar spine, 5.3% at the total hip, 4.8% at the femoral neck, and 0.9% at the distal 1/3 radius (p&lt;0.001). From 24 months to 36 months BMD increased by 1.6% at the lumbar spine, 0.6% at the total hip, 0.8% at the femoral neck, and 0.4% at the distal 1/3 radius (p&lt;0.001). In the cross-over group, BMD changes at 36 months (1 year after the first dose of denosumab) were 5.4% at the lumbar spine, 1.4% at the total hip, 1.1% at the femoral neck, and 1.3% at the distal 1/3 radius from the baseline (p&lt;0.001). The BMD increased from 24 to 36 months by 5.3% at the lumbar spine, 2.6% at the total hip, 2.3% at the femoral neck, and 0.5% at the distal 1/3 radius (p&lt;0.001). BTMs In the long-term group, serum CTX-1 was greatly decreased by 70.9% at 1 month with relatively sustained reductions thereafter. Serum BSAP was reduced by 9.6% at 1 month and 50.2% at 3 months, and remained relatively stable thereafter. In the cross-over group, serum CTX-1 was greatly decreased by 77.9% at 25 months (1 month after the first dose of denosumab) and remained relatively stable thereafter. Serum BSAP was also reduced by 19.6% at 25 months and reached the same level as the long-term group at 36 months. Albumin-adjusted serum calcium and intact PTH In the long-term group, mean albumin-adjusted serum calcium was 9.09 and 9.14 mg/dL at month 1 and month 25, and median intact PTH was 54 pg/ml at 1 month and 44 pg/ml at month 25. In the cross-over group, mean albumin-adjusted serum calcium was 9.09 mg/dL at 25 months, and median intact PTH was 56 pg/ml at 25 months. These changes in albumin adjusted serum calcium and intact PTH had tendency to return to the baseline level during follow-up period. Safety No notable increase with longer denosumab treatment from 2 to 3 years, irrespective of the different duration of the observation periods. AEs in the long-term group were similar to those in the cross-over group.</td>
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Evidence

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Outcome

Med

for publication. Although we controlled for publication bias using statistical methods, publication bias could not be completely ruled out. Thus, the pooled effect measure may be overestimated.

Third, the degree of control for confounding variables, such as age, gender, body mass index and comorbidity, also varied between studies.

Fourth, in this meta-analysis, we were not able to investigate the effect of different opioid doses because relevant data were available in only a few studies.

Fifth, it was unfortunate that we were not able to define contributing factors because all of the included papers were from Western countries and all of the participants were Caucasian. Therefore, our results cannot be generalized to worldwide populations, especially non-Western populations.

Sixth, we were not able to determine the fracture timing, whether medication sedation effects would be more likely shortly after starting opioid therapy, or whether metabolic biomechanical reasons would be more likely the longer the medication is taken. Thus, further research into fracture timing is needed.

Finally, our meta-analysis is of good quality but is not the most comprehensive study because only cohort studies were included.

Notes:

No consideration of grey literature and listing of excluded studies. Study characteristics provide no information on participants age. Out of 8 studies mentioned in the tables 4 have no reference in the reference section, some are incorrectly referenced. Overall high heterogeneity can be observed in the main analysis, which is not due the influence of a single study as revealed by sensitivity analysis.

Author's conclusion: In summary, our meta-analysis of cohort studies demonstrates that opioids may play an important role in the development of fractures and that opioid use may significantly increase fracture risk. Further studies, including studies that are well-designed, international trials (especially prospective, non-Western studies), studies that examine the mechanisms responsible for the fractures due to opioid use and studies that aim to prevent these fractures from occurring are required to provide more convincing evidence for clinical practice and fracture prevention.

Outcome

Measures/results

Primary Fracture risk: pooled RR from the adjusted RR or HRs was computed.

Secondary Subgroup analysis specific to hip fractures.

Results: The meta-analysis indicated significant, positive associations between opioid use and overall fracture risk (RR 1.88, 95% CI 1.51–2.34). Substantial heterogeneity was observed (P=0.000, I²=85.6%).

Data on opioid use and hip fracture risk were available for 4 studies. The pooled results indicated that opioids contribute significantly to the risk of fracture (RR 2.00, 95% CI 1.84–2.19). No statistical heterogeneity was observed (P=0.266, I²=24.4%).

Evidence: type: Vitamin and fallers fractures participants Secondary call registered

Primary: Monthly reported falls: obtained from prospective fall diaries returned monthly via mail, and details of each registered fall ascertained by a telephone call. Fall defined as "an unexpected event in which the participant comes to rest on the ground, floor or lower level".

Secondary: Injurious falls (those for which participants sought medical care [nurse, doctor, physiotherapist, or hospital] and included bruises, abrasions, contusions, sprains, fractures, head injuries), the number of fallers and injured fallers, bone density, and physical functioning (muscle strength, balance, and mobility)

Results: Mean pill compliance: 98.1% (range, 42.6%-100%). Mean exercise compliance (measured as attendance at all offered training sessions for group and home training): 72.8% (range, 0%-97.4%) and 66.1% (0%-100%). Mean intensity of supervised training ranged from 1.6 METs (stretching or resting) to 5.6 METs. Individual maximal values were more than 7 METs.

Fail: No interaction was found vitamin D and exercise. Overall: 928 falls and 281 fallers, no between-group differences. Hazard ratios for injured fallers lower in both exercise groups compared with the placebo without exercise group. Placebo + exercise group: HR = 0.47 (95% CI: 0.23, 0.99). Vitamin D + exercise group: HR = 0.38 (95% CI: 0.17, 0.83). No significant difference between vitamin D without exercise group and placebo without exercise group. Results similar for the incidence rate ratios of injurious falls. No. of multiple fallers distributed similarly across the groups (n = 190 and n = 117).

Bone density: Femoral neck BMD declined in all groups. Decline was greatest in placebo without exercise group (Mean change at 24 months: -1.22 [95% CI: -4.75, 2.45]) and differed significantly from that in all other study groups (vs Vitamin D without exercise P = 0.02; vs. Placebo + exercise P = 0.01; vs. Vitamin D and exercise P = 0.04). Lumbar spine BMD did not change significantly in any group. Vitamin D increased trabecular bone density at the tibia slightly but significantly between the vitamin D and exercise group and the placebo without exercise group (Change at 24 months: -0.49 [95% CI: -3.77, 2.80] vs. 0.19 [95% CI: -3.04, 3.42]; P = 0.02).

Physical functioning: Normal walking speed maintained in placebo + exercise group compared with placebo without exercise group (P = 0.007), while declining more significantly in other groups. Chair stand time improved in exercise groups, showing more 6% improvement compared with the placebo without exercise group but reaching statistical significance only in the placebo and exercise group (P = 0.03). TUG time deteriorated significantly more in vitamin D without exercise group compared with the placebo without exercise group (P = 0.01). Other groups did not differ from placebo without exercise group. Backward walking improved significantly among exercisers. Difference compared with placebo without exercise group statistically significant in placebo and exercise group (P = 0.001) and in vitamin D and exercise group (P = 0.03). Irrespective of vitamin D, exercise increased muscle strength, while vitamin D alone had no effect. Predicted mean increase in lower limb extension strength was almost 15% in both exercise groups and differed significantly from placebo without exercise group (P < 0.001).


Evidence level: 2-

Evidence: type: Countries: Europe, North America, Asia, Australia.

Study type: Settings: Dialysis uni, In- or Out-patients.

Total no. patients: 670810

Interventions: Vitamin K
Several outcomes of DXA and BMD were considered in the included studies. Our findings indicate that VKAs are associated with significant differences in BMD compared to controls, regardless of treatment with VKAs or MCs. However, the studies did not account for potential confounders, such as age, sex, and body mass index (BMI), which could affect the results.

**Funding sources:** n.a.

**Dropout rates:** n.a.

**Study limitations:** Considering BMD parameters, we failed to find significant differences between VKAs and MC or HC groups, except for significantly lower spine T-score values [30] and a higher prevalence of osteoporosis [23] compared with HCs in one study each. In contrast with the first meta-analysis published on this topic [10], we also failed to find any significant association between VKAs and low radius BMD values. This finding is likely to be due to the different inclusion criteria used in the previous meta-analysis, such as the inclusion of studies without a control group, or studies using different methods other than DXA that is considered the best approach for investigating BMD [3,9]. Thus, results of the previous meta-analysis could have been affected by the remarkable differences in bone composition investigation methods. However, independent of these considerations, the findings of both meta-analyses suggest a non-significant effect of VKAs on BMD, since the significant differences in BMD in our and in the previous meta-analysis are limited to outcomes including single studies with a small number of subjects.

Several limitations of our study need to be considered. First, many of the included studies did not use any matching, thereby not controlling for the potential confounders between the VKA-treated and the control groups. Although some individual studies that did not match samples adjusted their analyses for relevant covariates and potential confounders [8,19], these adjustments could not be used in this meta-analysis, as only patient level data would be able to do so. By contrast, in meta-analyses, unadjusted group means or group rates are pooled in the analyses.

**Patient characteristics:**

**Intervention:** Patients treated with vitamin K antagonists (VKA)

- n=79663.

**Comparison:** Medical illness (MC), or healthy controls (HC), n=597348 controls in total.

**Inclusion criteria:** Cross-sectional and longitudinal studies comparing data on osteoporosis, fractures, BMD, and T-scores (deviation from the bone mass of an average healthy 30-year-old adult) between patients treated with VKAs vs. controls. Included were only studies that (i) reported on BMD or fractures, (ii) included patients treated with VKAs, and (iii) compared patients treated with VKAs with HCs or MCs.

**Exclusion criteria:** Studies were excluded if they (i) did not specify the type of VKAs used, (ii) measured only in-vitro parameters or used animal models, (iii) did not compare patients treated with VKAs vs. a control group, or (iv) reported only laboratory data and not data about BMD or fractures. We also contacted authors asking for further information when (i) data could not be meta-analyzed (i.e., no mean and SD or equivalent for BMD or no data on fractures or osteoporosis provided for both treated and control group) and (ii) other relevant information (e.g., age, percentage of females, or parameters related to anticoagulation therapy, etc.) was missing.
Sato Y, et al. (1997)
Stroke
Cerebrovasc Dis
Stenova E, et al.
(2011) Bratisl Lek
Listy
Woo C, et al. (2008)
J Am Geriatr Soc

Notes:
Inconsistency regarding comparison of VKA with healthy (HC) and medical (MC) group. The abstract describes that the comparison of three CS studies with HC. The results section describes the comparison with MC, so does the figure heading. The same goes inconsistency applies to the longitudinal studies as well. This aggravates interpretation of the results and lowers overall confidence in the study results. Excluded studies are not listed.
Funnel plots for the investigation of publication bias is not particularly meaningful if less than 10 studies are included. No COI of the included studies are mentioned.

Author's conclusion: In conclusion, the use of VKAs seems to neither significantly increase fracture risk when matching on confounding factors nor reduce BMD beyond effects of medical illness. Since the use of VKA treatment, as well as osteoporosis and fractures, are continuously increasing particularly in older people, future studies using appropriate matching procedures, following patients for sufficiently long periods and including newer oral anticoagulants are needed to clarify the short-and long-term effects of VKAs on bone health.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary</th>
<th>Prevalence or incidence of fractures; characteristics of BMD parameters.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Results: 21 studies were eligible, including 79663 individuals treated with VKAs vs. 597 348 controls. Compared with HCs, VKA-treated individuals showed significantly higher fracture risk in cross-sectional (3 studies; RR=1.24; 95% CI: 1.12–1.39, P=0.0001) and longitudinal studies (7 studies; RR=1.09; 95% CI: 1.01–1.18, P=0.03) and more incident hip fractures (4 studies; RR=1.17; 95% CI: 1.05–1.31, P=0.003).
Analyzing studies that matched VKA participants with HCs (4 studies), both these findings in longitudinal studies became non-significant. Notably, the VKA and MC group had similar BMD values at all investigated sites. Compared with HCs, a single study showed significantly lower spine T-scores in the VKA-treated group (standardized mean difference=0.45; 95% CI:0.75, 0.14, P=0.004).


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2-</td>
<td>Countries: n.a.</td>
<td>Total no. patients: 3807</td>
<td>Risk factors (predictors of the outcome), Age, shortening, volar comminution, loss of radial inclination, presence of a volar hook, AO type 3</td>
</tr>
<tr>
<td>Study type: Systematic review and Meta-Analysis (8 Meta-Analyses).</td>
<td>Centres: n.a.</td>
<td>Patient characteristics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setting: n.a.</td>
<td>Age range 18-97.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Funding sources: The authors received no financial support for the research, authorship, and/or publication of this article.</td>
<td>Inclusion criteria: Adults (≥18 years); with distal radius fractures initially treated with plaster</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dropout rates:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study limitations: The majority of studies that we included focused primarily on secondary displacement.</td>
<td></td>
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<tr>
<td></td>
<td>Consequently, these studies only described patients who were treated conservatively. Patients treated initially with an operation were probably not included. This last group is likely to include the most unstable fractures. In our opinion, this limitation mostly applies to studies performed after the introduction of volar locking plates in 2000. Conversely, some patients might have been treated operatively who would have achieved excellent results with conservative treatment. Unfortunately, the decisions to perform primary surgical fixation and exclude these patients were only reported in a few studies. Intra-articular involvement, volar fracture displacement or</td>
<td></td>
<td></td>
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</tbody>
</table>
Arch Orthop Trauma Surg

Notes: No description of the search string. Study characteristics table does not inform the reader regarding gender distribution. No investigation of publication bias.

Author's conclusion: This systematic review provides a comprehensive overview of all known predictors and non-predictors of secondary displacement in patients with distal radius fractures. We have demonstrated that, despite their popularity as predictors of secondary displacement, distal radius fractures with an associated ulna fracture, a dorsal angulation >15° or >20° from neutral and intra-articular fractures do not have an increased risk of secondary displacement. We did find a significantly increased risk of secondary displacement for patients older than 60–65, women and fractures with dorsal comminution.

| Outcome Measures/results | Primary Risk (as OR) for secondary displacement in distal radius fractures. | Secondary n.a. | Results: Female gender, age >60–65 years and dorsal comminution were significant predictors of secondary displacement. An associated ulnar styloid fracture, intra-articular involvement, dorsal angulation >15° from neutral and dorsal angulation >20° from neutral were not significantly associated with secondary displacement |


Evidence level Evidence level: 2- Study type: Systematic review and Meta-analysis: 8 studies (1 RCT, retrospective, 3 prospective cohort studies and 1 case control trial)

Evidence summary: Study details/limitations Countries: China, Germany, Taiwan, Iran, Singapore. Centres: n.a. Setting: n.a.
Funding sources: There was no external funding in the preparation of this manuscript.
Dropout rates: Study limitations: The limitations of this meta-analysis include statistical efficacy can be improved by more studies, low evidence based non-RCT articles and likely to induce various types of bias, and no accurate definition of short-term and long-term outcome time points.

Patient characteristics Total no. patients: 845. Patient characteristics: 845 participants with osteoporotic vertebral fractures (OVCF): 231 Men an 614 women. Mean age range 64-77 in the PKP and 62-77 in the PVP group. Follow up periods between 6 and 24 months.

Inclusion criteria: Study design: randomized controlled trials (RCT) or prospective or retrospective comparative studies. Population: patients with VCFs due to osteoporosis.

Intervention: Percutaneous balloon kyphoplasty (PKP) comparing vertebroplasty (PVP).

Outcomes: subjective pain perception, quality of life evaluation, incidence of new adjacent vertebral fracture, bone cement leakage, and post-operative kyphotic angle.

Exclusion criteria: Articles were excluded in our meta-analysis if they had a neoplastic etiology (i.e., metastasis or myeloma), infection, neural compression, traumatic fracture, neurological deficit, spinal stenosis, severe degenerative diseases of the spine, previous surgery at the involved vertebral body, and PKP or PVP with other invasive or semi-invasive intervention treatment.
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level:</td>
<td>Countries: USA, Canada, the Netherlands, Sweden.</td>
<td>Total no. patients: 977493 participants and 102488 cases.</td>
<td>Interventions: Non interventional study design.</td>
</tr>
<tr>
<td>2+</td>
<td>Centres: n.a.</td>
<td>Patient characteristics: Follow up duration ranges between 6-37 years. No overall information on male or female participants (both mixed and single gender cohorts are included). No information on participants age.</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Setting: n.a.</td>
<td>Inclusion criteria: Articles that assessed the risk of vertebral fracture comparing diabetic with non-diabetic individuals, excluding articles that were irrelevant or contained overlapping data.</td>
<td></td>
</tr>
<tr>
<td>Systematic review and Meta-analysis of cohort studies: 8 studies, both retrospective and prospective.</td>
<td>Funding sources: n.a.</td>
<td>Exclusion criteria: n.a.</td>
<td></td>
</tr>
<tr>
<td>Included studies:</td>
<td>Dropout rates: n.a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melton LJ 3rd, et al. (2008) J Bone Miner Res</td>
<td>Study limitations: Firstly, the source of heterogeneity is not fully clear, though subgroup analysis indicated follow-up duration as one element; however, other undetected factors still exist, and absence of original data limit our further analysis of that issue. Secondly, there was no description in the articles selected that described medical attention patients received, including use of orally administered hypoglycemic agents and the use of insulin, which might be part of the causal pathway of the studied relationship. Thirdly, we did not conduct a subgroup on diabetes type; some reports indicate that different diabetes types affect bone to varying degrees and by varying mechanisms. Finally, geographical distribution was limited to Western countries and lacked data from Asian and other regions.</td>
<td></td>
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<tr>
<td>Schneider AL, et al. (2013) Diabetes Care</td>
<td></td>
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<tr>
<td>Ma CC, et al. (2011) Arch Osteoporos</td>
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<tr>
<td>Holmberg AH, et al. (2006) Osteoporos Int</td>
<td></td>
<td></td>
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<tr>
<td>Schwartz AV, et al. (2001) J Clin Endocrinol Metab</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bonds DE, et al. (2006) J Clin Endocrinol Metab</td>
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</tbody>
</table>
Notes: Weak definition of inclusion and exclusion criteria. Grey literature was not considered in the article. Excluded studies are not listed. Assessment of publication bias with less than 10 studies is questionable, but the effort is commendable. Study characteristics provide no information on age. No reported COI of included studies.

Significant and substantial of heterogeneity in the primary analysis ($I^2=60\%$ $p=0.008$) indicates substantial differences in study design. These are likely partly caused by differences in follow up length (which the authors investigated) and might also be influenced by diabetes type. I am not certain the subgroup analyses by follow up were planned a priori.

Author’s conclusion: In conclusion, our meta-analysis strongly supports the relationship between diabetes and risk of vertebral fracture in both male and female diabetic patients. Based on the meta-analysis, diabetes should be regarded as an independent risk factor of vertebral fracture. However, more information from future studies is necessary in order to implement prevention strategies.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary</th>
<th>Vertebral fracture relative risk (RR).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary</td>
<td>Subgroup analyses by sex, follow up length, and study design.</td>
</tr>
</tbody>
</table>

Results: Meta-analysis of 8 studies showed that the pooled RR of vertebral fracture for diabetic individuals was 2.03 (95 % CI 1.60–2.59; $p<0.0001$). Subgroup analysis by gender showed that the corresponding RRs for male and female were 2.70 (95 % CI 1.34–5.43; $p=0.005$) and 1.93 (95 % CI 1.18–3.13; $p=0.008$), respectively. Subgroup analysis by study design showed that the corresponding RRs for prospective design and retrospective design were 1.81 (95 % CI 1.19–2.75; $p = 0.006$) and 2.23 (95 % CI 1.60–3.10; $p<0.0001$), respectively. Subgroup analysis by time of follow-up showed that the RR of vertebral fracture for patients with >20 and <20 years of follow-up were 2.23 (95 % CI 1.98–3.62; $p<0.0001$) and 1.67 (95 % CI 1.29–2.16; $p < 0.0001$), respectively.


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2+</td>
<td>Countries: Denmark, 2; Finland, 2; France, 1; Japan, 1; Norway, 1; and USA, 3.</td>
<td>Total no. patients: 217,295 participants and 26,525 OF cases</td>
<td>Interventions: Exposure: Parity</td>
</tr>
<tr>
<td>Study type: SR/MA of 10 prospective cohort studies.</td>
<td>Centres: N.r.</td>
<td>Patient characteristics: Age range: min: 32 years; max: 99 years</td>
<td></td>
</tr>
<tr>
<td>Included studies: Bjornerem A (2011) J Bone Miner Res</td>
<td>Setting: N.r.</td>
<td>Inclusion criteria: (1) the exposure of interest was parity; (2) the outcome was OF; and (3) the investigators reported relative risk (RR) (or hazard ratio (HR)) with 95 % confidence intervals (CIs).</td>
<td></td>
</tr>
<tr>
<td>Cauley JA (2007) J Bone Miner Res</td>
<td>Funding sources: “The work has been supported by the National Science Foundation of China (grant no. 81573235), Fundamental Research Funds for the Central Universities (grant no. HUST:2014TS048), Health and Family Commission of Wuhan Municipality (grant no. WG15D20), and Wuhan Jiangan District Science and Technology Bureau (grant no. 201141111904). [...] The funding sources had no role in the study design, data collection, analysis, data interpretation, or the writing of the report.”</td>
<td>Exclusion criteria: Reviews, editorials and nonhuman studies, letters</td>
<td></td>
</tr>
<tr>
<td>J Bone Miner Res</td>
<td>Study limitations: - Since only a few studies reported HF risk associated with grand parity (e.g., over five parities), the accuracy of HF risk decrease related to grand parity is worth reconsidering in future studies. - The association of parity with risk of OF on skeletal sites other than hip cannot be confirmed yet due to insufficient reports available for pooled analysis. - No prospective studies of parity and OF risk among women from regions other than Europe and USA (except for one in Japan) identified,</td>
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<tr>
<td>Honkanen FA (2000) J Bone Miner Res</td>
<td></td>
<td></td>
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<tr>
<td>Hundrup YA (2005) Eur J Epidemiol</td>
<td></td>
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<tr>
<td>Evidence Measures</td>
<td>Outcome Measures/results</td>
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<tr>
<td>Kauppi M (2011)</td>
<td>Primary Osteoporotic fracture risk</td>
<td></td>
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<tr>
<td>Osteoporos Int</td>
<td>Secondary Dose-response association</td>
<td></td>
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<tr>
<td>(1991) J Womens Health (Larchmt)</td>
<td></td>
<td></td>
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<td>Petersen HC (2002)</td>
<td></td>
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<tr>
<td>Ann Epidemiol</td>
<td></td>
<td></td>
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<tr>
<td>Tremoliers FA (2010)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J Bone Miner Res</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Notes:** Final search query not stated. Published search terms possibly missed relevant hits. Unclear, whether 2 persons selected studies. No search for unpublished studies.

**Author's conclusion:** This meta-analysis revealed that increasing number of parity (range of zero to five live births) is associated with linearly reduced HF risks among women. The large statistical heterogeneity, source of which is the study location, must be of concern, however. More studies to populations from identical study locations may help increase the certainty of our findings in the future. The association between parity of six or more live births and HF risks should be studied further, as well as the association between parity and risk of osteoporotic fracture on other skeletal sites than hip.

**Results:** Risk of fracture in parous women compared to nulliparous women: Investigated in 9 studies with 19 study samples. Parous women at significantly lower risk of OF: pooled RR = 0.89 (95%CI; 0.80, 0.97).

Significant and high level of statistical heterogeneity: $I^2 = 77.1\%$ ($p<0.001$). Pooled RR of OF in relation to one or more parity compared to nulliparous women = 0.81 (95% CI; 0.67, 0.95; $I^2=68.9\%$, $p=0.001$) and 0.95 (95% CI; 0.85, 1.05; $I^2=73.6\%$, $p=0.001$) for women from Europe and USA.

**Hip fracture risk in parous women compared to nulliparous women:** Investigated in 6 studies. Women with one or more live births were less likely to incur HF than nulliparous women: pooled RR = 0.74 (95% CI; 0.65, 0.83; $I^2=19.5\%$, $p=0.287$).

**Dose-response association between parity and osteoporotic fracture risk:** Statistically significant nonlinear dose-response association between parity (range of 0–6) and OF risk (overall $p=0.001$; $p_{\text{nonlinearity}}=0.0163$) based on 9 studies. Compared with null parity, the pooled RRs of OF = 0.89 (95 % CI; 0.85, 0.94) for one live birth, 0.81 (95 % CI; 0.74, 0.89) for 2 live births, 0.78 (95 % CI; 0.71, 0.85) for 3 live births, 0.76 (95 % CI; 0.69, 0.84) for 4 live births, 0.75 (95 % CI; 0.67, 0.84) for 5 live births, and 0.84 (95 % CI; 0.64, 0.85) for 6 live births. Evidence of large between-study heterogeneity ($I^2=79.7\%$, $p<0.001$).

**Dose-response association between parity and hip fracture risk:** Significant linear dose-response association between parity (range of 0–5) and HF risk (overall $p=0.001$; $p_{\text{nonlinearity}}=0.054$) based on 6 studies. Reduction of HF risk = 12 % (95% CI; 9, 15 %) for each live birth increase among women. Evidence of large between-study heterogeneity ($I^2=6.5\%$, $p=0.001$).

Evidence level: 1-
Study type: SR/MA of 7 RCT
Included studies:
- Reid IR (2001) Lancet
- Bone HG (2007) Clin Endocrinol
- Metab
- Chueungsammarn S (2010) Bone
- Zhao C (2013)
- Zhonghua yi xue za zhi
- Chen ZG (2014) Arch Gerontol Geriatr
- Pena JM (2014) JAMA Intern Med

Countries: Australia, Denmark, USA, Thailand, China, 1 study from 26 countries
Centres: N.r.
Setting: Diverse study populations: Patients with myocardial infarction or unstable angina, postmenopausal women with and without osteoporosis or osteopenia, patients with dyslipidemia with and without osteoporosis or osteopenia, and men with osteoporosis or osteopenia

Funding sources: "The authors have no funding and conflicts of interest to disclose."

Dropout rates: N.r.

Study limitations: - Number of RCTs regarding to association of statins use with BMD and fracture risk is very small, which has limited subgroup analysis and further limited to identify subgroup population who were more susceptible to statins therapy on both dyslipidemia and osteoporosis.

- Most of included studies conducted in females, which have limited the generality of the results to male patients.

Notes: No search for unpublished literature.

Because of the high, unexplained heterogeneity in meta-analysis on BMD (I² = 99.2%), the author's confident conclusion can not be supported. Funnel plots produced despite insufficient No. of studies.

Author's conclusion: These findings provide evidence that statins could be used to increase BMD other than decreasing fracture risk in patient with dyslipidemia. In addition, further trials with the primary outcome of bone health-related measurements in subpopulation are warranted to ensure the effect of statins use.

Outcome Measures/results

Primary Bone mineral density (BMD) change
Secondary Fracture risk

Results: Primary: Investigated in 5 studies. Significant increase in BMD in intervention group compared with control group: Mean change = 0.030 g/cm² (95% CI: 0.006, 0.053; P<0.001; I² = 99.2%).

Secondary: Investigated in 2 studies. No difference between intervention group compared with control group: HR = 1.00 g/cm² (95% CI: 0.87, 1.15; P = 0.396; I² = 0%).


Evidence level: 1-
Study type: RCT

Evidence level Study details/limitations Patient characteristics Interventions

Evidence level: 1-
Study type: RCT

Evidence level Study details/limitations Patient characteristics Interventions

Evidence level: 1-
Study type: RCT

Evidence level Study details/limitations Patient characteristics Interventions

Evidence level: 1-
Study type: RCT

Evidence level Study details/limitations Patient characteristics Interventions

Evidence level: 1-
Study type: RCT

Evidence level Study details/limitations Patient characteristics Interventions
cardiovascular diseases, acute infections or fever, iritis or an acute attack of polyarthritis. 
(2) Participants should not have used hormone replacement therapy or any other therapy affecting the bone metabolism during the last 12 months before enrollment.

Notes:
No reason stated for exclusive recruiting of working married couples. Results might not be directly applicable for other patient groups. Test for baseline differences not stated.

Author's conclusion: In conclusion, the combined exercise and thermal bath intervention regimen applied to an apparent healthy population as included in this study revealed marked and unexpectedly sustained changes in humoral regulators and markers of bone turnover as well as self-reported somatic complaints and pain. These factors certainly indicate a delicate and complex physiological interplay of central, systemic and local regulators of bone metabolism which needs to be unraveled. However, given the changes of the primary outcome parameters OPG, RANKL and the OPG/RANKL ratio, it is feasible to assume that the overall bone metabolism is tuned toward an anabolic condition. Moreover, these effects are accompanied by significant improvements of perceived quality of life and pain. Although low-dose radon hyperthermia baino treatment does not significantly outweigh conventional thermal water treatment in this study, borderline significant differences of RANKL and the OPG/RANKL ratio indicate a possible additive effect of radon baino treatment on the achieved biological effects. Mountain hiking is a popular form of exercise in the alpine region and a low cost non-pharmacologic intervention. Even though men develop osteoporosis later than women, as a matter of fact age-related bone loss begins at the age of fifty in both sexes (Campion and Maricic 2003). The immense and continuously rising costs caused by osteoporosis make a preventive intervention as performed in this study worth considering and useful for both men and women.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary OPG, RANKL and OPG/RANKL ratio</th>
<th>Secondary Somatic complaints (Beschwerdenliste, von Zersen 1976)</th>
<th>Quality of life (Qualeffo-41)</th>
</tr>
</thead>
</table>

**Results:** OPG: No absolute change of values reported, only model analysis of relative change. Increases of OPG from T1 to T2, T3 to T2 in placebo and radon group. OPG concentration decreased approximately to the baseline levels after 6 months (T5). RANKL: No absolute change of values reported, only model analysis of relative change. RANKL concentrations declined in entire study population from T1 to T2. OPG/RANKL ratio: Significantly elevated OPG/RANKL ratio from time T1 to T2 and subsequent decrease from T4 to T5 in both groups.

**Complaints list and quality of life:** Results not quantified but stated as "significant decline in self-reported health complaints [...] after Treat-1 (p ≤ 0.000, T2) and Treat-2 (p ≤ 0.004, T4), which remained reduced until T5 (day 240; p<0.0004)". No significant difference between groups (p = 0.1923). Qualeffo-41 showed significant reduction (p = 0.042) of pain (domain Qualeffo-Pain) in the whole study population 6 months after treatments (T5) (data not shown).

### Wright, E. et al. Bisphosphonates and evidence for association with esophageal and gastric cancer: a systematic review and meta-analysis. BMJ Open. 5. e007133. 2015

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Study type</th>
<th>Study type</th>
<th>Study type</th>
<th>Country</th>
<th>Study details/limitations</th>
<th>Patient ns characteristics</th>
<th>Intervention ns characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Systematic Review of 11 retrospective, control (6) and cohort (5) studies (and Meta Analysis of n= 5 )</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Total no. patients: cohort studies between 30.606 - 55.090 cases of cancer case control: between 116-5364 cases</td>
</tr>
<tr>
<td>41</td>
<td>Systematic Review of 11 retrospective, control (6) and cohort (5) studies (and Meta Analysis of n= 5 )</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Interventions: association between bisphosphate prescribing and esophageal and gastric cancer</td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
(1) the study used a case-control or cohort design; (2) the study examined bisphosphonates and the risk of esophageal and/or gastric cancer; (3) the risk estimate was reported as an OR, HR or relative risk; (4) the 95% CI for the risk estimate.

Vestergaard P. Occurrence of gastrointestinal cancer in users of bisphosphonates and other antiresorptive drugs against osteoporosis. Calcif Tissue Int 2011;89:434–41


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2-</td>
<td>Countries: 9 studies conducted in the United States and Canada, 2 in Europe, 1 in Asia.</td>
<td>Total no. patients: 407.104 participants</td>
<td>Interventions: Protein consumption; Total protein consumption, animal protein, vegetable protein.</td>
</tr>
<tr>
<td>Study type: SR/MA of 12</td>
<td>Centres: N.r.</td>
<td>Patient characteristics: Age (range): 20 – 89 years.</td>
<td></td>
</tr>
<tr>
<td>prospective cohort studies</td>
<td>Setting: N.r.</td>
<td>Study recruited women only, 1 study men only, 7 studies with mixed populations.</td>
<td></td>
</tr>
<tr>
<td>Included studies: Mussolino ME (1998) J Bone Miner Rese</td>
<td>Funding sources: &quot;This work is funded by National Natural Science Foundation of China (81372014, 81371988); and Ximiniao talent plan of Zhejiang Province (2014R413053). The funders had no role in the design, execution, and writing of the study.&quot;</td>
<td>Inclusion criteria: 1) Designed as a prospective cohort study;</td>
<td></td>
</tr>
<tr>
<td>(1998) J Bone Miner Rese</td>
<td>Dropout rates: N.r.</td>
<td>2) Exposure of interest is (animal or vegetable/plant) protein consumption;</td>
<td></td>
</tr>
<tr>
<td>Beasley JM (2014) Am J Clin Nutr</td>
<td>Study limitations: - No meta-analysis on vertebral fractures possible because of only one study reporting risk of vertebral fracture. - Meta-analysis on subgroups and dose-response apart from hip fracture not possible due to insufficient data. - Significantly heterogeneity in most subgroup analysis.</td>
<td>3) Primary outcome of interest is any fractures/ hip fracture/ vertebral fracture/ limb fracture;</td>
<td></td>
</tr>
<tr>
<td>Meyer HE (1997)</td>
<td></td>
<td>4) the relative risk (RR) estimates with 95% confidence intervals (CI)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Unclear, whether study selection and data extraction was performed by 2 reviewers. **Author’s conclusion:** This is the fourth and most detailed meta-analysis on this topic. We have not identified any compelling evidence for a significantly raised risk of esophageal cancer or gastric cancer in male and female patients prescribed bisphosphonates. **Results:** Esophageal cancer and all bisphosphonates - no significant association between use of bisphosphonates and esophageal cancer, OR 1.11 (0.97 to 1.27) - sensitivity analyses: different combinations of CPRD: all non-significant Gastric cancer and all bisphosphonates - no significant association between use of bisphosphonates and gastric cancer, OR 0.96 (95% CI 0.82 to 1.12) - Esophageal cancer and alendronate - no increased risk, OR 0.98 (0.87 to 1.11), of esophageal cancer in alendronate users - sensitivity analyses: all non significant - Gastric cancer and alendronate - no increased risk of gastric cancer with alendronate, OR 0.99 (95% CI 0.71 to 1.38) - Cohort studies—UGI cancer and all bisphosphonates no significant association, OR 1.32 (95% CI 0.81 to 2.13) - Case—control studies—UGI cancer and all bisphosphonates no significant association, OR 1.06 (95% CI 0.93 to 1.22).
Final search query not stated. No search for unpublished studies.

Weight given to studies in meta-analysis not reported.

Restriction to include studies which only investigated fractures as the primary outcome might have screened out relevant publications.

P-values for results of meta-analysis not shown.

Analysis of "all fracture" does not include results from studies on hip and limb fractures.

Unexplained sources of heterogeneity in most subgroup analysis.

Flaws in the translation of this study might compromise the absolute reproducibility of presented results.

Author's conclusion: Total dietary protein consumption may be decrease the risk of hip fracture, but not for all fractures and limb fracture. No current evidence shows the animal or vegetable protein could decrease or increase the risk of fracture.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary</th>
<th>Risk of fracture.</th>
<th>Secondary -</th>
</tr>
</thead>
</table>

Results: All fractures: 3 studies analysed. Results from studies on hip/limb fractures not included.

No significant association for total dietary protein consumption: RR = 0.99 (95% CI: 0.97, 1.02).

Hip fracture: 6 studies included. Higher protein consumption associated with statistically significant reduction: RR = 0.89 (95% CI: 0.82, 0.97).

Limp fractures: 2 studies analysed. No significant association for total dietary protein consumption: RR = 1.05 (95% CI: 0.81, 1.37).


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2++</td>
<td>Countries: Italy, Australia, USA, Japan, England, Sweden, Netherlands. Centres:</td>
<td>Total no. patients: 34840 Patient characteristics: Inclusion criteria: Prospective and population-based design, reporting of risk of fracture as the outcome of interest and included hs-CRP measurements as a risk factor; reporting estimate effects with 95% confidence intervals, or sufficient data to calculate these values. For the dose–response analysis, at least three quantitative categories of hs-CRP levels and the number of participants and fracture cases had to be reported. Exclusion criteria: unavailable data on CRP or fracture, wrong study design (not prospective), study population with particular disease, absence of controls, and review articles.</td>
<td>Interventions: Measurement of high sensitivity C-reactive protein (hsCRP).</td>
</tr>
<tr>
<td>Study type: Systematic review (8 prospective cohort studies).</td>
<td>Setting: Funding sources: n.a. Dropout rates: Study limitations: First, a meta-analysis is not able to solve problems related to etiologic analysis or confounding factors that could be inherent in the included studies. Inappropriately adjusted for confounders may exaggerate or underestimate the risk estimates. However, most of the prospective studies on hs-CRP levels adjusted for major potential confounders, including age, history of diabetes, body mass index, physical activity, medication use, smoking, alcohol use, and BMD. Second, moderate heterogeneity was observed among the studies; however, it disappeared when the study of Schett et al. [16] was excluded, which was the only study that did not adjusted for bone turnover markers or BMD. Third, publication bias is a potential concern for meta-analysis based on data from published reports. No evidence of publication bias was reported or could be calculated with reported data.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Arch Intern Med
Nakamura K, (2011) Osteoporosis Int J
Eriksson AL, (2013) J Bone Miner Res
Oei L, (2013) Osteoporosis Int
Ahmadi-Abhari S, (2013) Bone

Outcome Measures/results
Primary Risk of fracture.
Secondary n.a.

Notes:
No inclusion of grey literature.

Author's conclusion: In summary, the present analysis showed that the relationship between CRP concentrations and subsequent fracture risk is still inconsistent. The positive association cannot completely explain the existing evidence, and further larger prospective cohorts with more power are needed to demonstrate the shape of the association, especially for the relatively low CRP concentrations, such as less than 3 mg/L.

Results: Eight prospective cohort studies involving 34,840 participants and 3,407 incident fracture events were eligible for the present analyses. A meta-analysis of 6 showed that the overall risk for incident fracture in a comparison of individuals in the top tertile with those in the bottom tertile of baseline hs-CRP levels was 2.14 (95% CI 1.51–3.05, I^2 = 62.3 % p=0.021). The moderate heterogeneous disappeared when one study was excluded. However, the remaining two studies reported inconsistent results. One study with the biggest sample size showed a U-shaped association for CRP and fracture risk (the association was positive when CRP>1 mg/L). Similarly, another study reported that per doubling of CRP was positive only when CRP>3 mg/L.

Xiao, F. et al. Association between loop diuretic use and fracture risk. Osteoporos Int. 26. 775-84. 2015

Evidence level
Evidence level: 2++
Study type: MA of 13 studies (4 cohort studies, 9 case-control studies)

Included studies:
- Rashiq S (1986) BMJ
- Tromp A (2000)

Study details/limitations
- Countries: 5 from USA, 7 from Europe, 1 from Australia
- Centres: N.r.
- Setting: N.r.
- Funding sources: "This study was supported by the National Nature Science Foundation of China (Grant No. 31170901), the Fund for Key National Basic Research Program of China (Grant No. 2012CB619101), and the Major Basic Research of Science and Technology Commission of Shanghai Municipality (Grant No. 11DJ1400303). The funding sources had no role in the study design, collection, analysis, or interpretation of the data, or in the writing of the report."
- Dropout rates: N.r.
- Study limitations: - Quality of individual studies varied; several included studies had limited adjustment for potential statistical confounding, including three studies without clear adjustment. Present study was subject to confounding factors within the selected studies, which is an innate limitation of all observational studies and meta-analyses.
- Not all articles involved prospective cohort studies. However, sensitivity analyses and subgroup analyses show that different types of study designs were not the main sources of heterogeneity.
- High degree of heterogeneity among included studies, which might have reduced the

Patient characteristics
Total no. patients: 842.644 participants

Inclusion criteria: (1) were observational studies (case-control or cohort),
(2) involved an adult population,
(3) investigated the association between loop diuretic use and the risk of fractures, and

Interventions: Loop diuretics:
- No information on dose regimen or duration of use provided.

Evidence level | Study details/limitations | Patient characteristics | Interventions
--- | --- | --- | ---
Evidence level: 2+ | **Countries:** n.a.  
**Centres:** n.a.  
**Setting:** n.a.  
**Funding sources:** n.a.  
**Dropout rates:** Dropout rate in the included studies was judged as acceptable risk of bias (>20%) in 17 out of 19 included studies and as a high risk of bias in 2 studies (>20%).  
**Study limitations:** This meta-analysis has several limitations, and we should regard the present outcomes with caution: firstly, the relatively small number of participants restricted the statistical power. Secondly, the poorly designed non-RCTs are more likely to suffer from various biases. Besides, the inclusion of longer-term follow-up data, when available, may change the result of subsequent fractures.  
**Total no. patients:** 1,787  
(887 received PVP and 900 received BKP) | **Patient characteristics:** 1787 patients with osteoporotic vertebral compression fractures (OVCF). Mean age range 57-77 in both intervention and comparison groups. Follow up range from 6-42 months  
**Inclusion criteria:** (1) comparative studies (including randomized and non-randomized controlled trial) on PVP versus BKP for treating OVCFs, (2) studies enrolling ≥20 patients, and (3) studies reported complications (secondary fractures or cement) | **Interventions:** Balloon kyphoplasty (BKP) or percutaneous vertebroplasty (PVP).
Osteoporosis Int
(Philadelphia 1976)
Kumar K, et al. (2010)
Neurosurgery
Li X, et al. (2012)
J Spinal Disord Tech
Pflugmacher R, et al. (2005) Rofo
Frankel BM, et al. (2007) Spine J

**Exclusion criteria:** (1) diagnosis of OVCFs was not clinically established (patients with traumatic, or cancer-related vertebral fractures), (2) patient had infection, neurological deficits, or spinal stenosis, (3) single-arm studies, (4) no relevant data could be extracted and (5) systematic review and meta-analysis.
Differences in the follow-up periods of the included studies range from 6-42 months (follow-up times were not pre-specified). The loss to follow up was not reported in 11 of the 19 studies, but it was considered as low risk of bias (not unclear risk of bias) in 17 out of 19 studies. No listing of excluded studies or inclusion of grey literature. No investigation of publication bias. Conflict of interest for the primary studies are not reported.

**Author's conclusion:** Based on this meta-analysis, we have the following conclusions: the two procedures suffer from equal risk of subsequent spinal fractures; PVP has a significant higher cement leakage rate compared to BKP, mainly caused by a higher paravertebral leakage, hence, patients with extremely poor pulmonary function or unstable haemodynamic are better candidates for BKP. To confirm the present assessments, high-quality RCT should be conducted.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Incidence of adjacent vertebral fractures; Incidence of non-adjacent vertebral fractures. Cement leakage into disk spaces, or into paravertebral areas or total cement leakage rate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>-</td>
</tr>
</tbody>
</table>

### Evidence level

- **Evidence type:** MA of 9 studies (3 cohort studies, 6 case-control studies)
- **Included studies:**
  - Jha RM (2010) BMC Musculoskelet Disord
  - Kanis J (1999) Osteoporos Int
  - Zeng FF (2013) J Clin Endocrinol Metab

**Notes:**

- Final search query not stated. Unclear, whether 2 person selected studies. No search for unpublished/ grey literature.

### Results:

19 studies encompassing 1,787 patients in total, of whom 887 received PVP and 900 received BKP, met the inclusion criteria. Fractures: For subsequent fractures, our meta-analysis detected no significant difference between the two procedures, both for adjacent fractures (p = 0.29) and non-adjacent fractures (p = 0.37). Cement leakage: For cement extravasations, there was no significant difference between the two interventions if considering disc spaces extravasations only (p = 0.24), while considering total extravasations and paravertebral extravasations, the cement leakage rate in the PVP group was significantly higher than the BKP group (total: p<0.01; paravertebral: p<0.01).

### Evidence:

- **Evidence level:** 2-

**Study type:** MA of 9 studies (3 cohort studies, 6 case-control studies)

**Included studies:**

- Jha RM (2010) BMC Musculoskelet Disord
- Kanis J (1999) Osteoporos Int
- Zeng FF (2013) J Clin Endocrinol Metab

**Notes:**

- Final search query not stated. Unclear, whether 2 person selected studies. No search for unpublished/ grey literature.

### Patient characteristics

- **Total no. patients:** 147,950

**Patient characteristics:** Mostly female patients. Largest study with 91,465 patients with female patients only.

Patients of varying ages included (range: 19 - 100 years).

**Inclusion criteria:**

1. The association between tea consumption and risk of fractures was evaluated;
2. a cohort or case-control study design;
3. the value of relative risk (RR), odds ratio (OR) with 95% confidence intervals (CI) or enough data to calculate these.

**Exclusion criteria:**

1. Fractures caused by other reasons, such as injury, trauma, and etc.
2. Patients who consumed the tea only for a few days or months, or with intervals.

**Interventions:** Varying categories of tea consumption: No drinking/drinking, Former drinking/current drinking or never, 1-2 cup/day, 3 cup/day, ≥4 cup/day.
Various differences between studies, e.g. regarding population (range of included ages: 19 - 100 years), outcomes (wrist fractures, hip fractures, osteoporotic fractures) and exposure to tea (black or green tea and categories of former drinking/ current drinking or ≤ 3 cup/day and up to ≥ 4 cup/day).

References not correct.

**Author's conclusion:** In conclusion, tea consumption might not be associated with the risk of fracture. However, these conclusions should be considered with cautions because the inherent limitations in this meta-analysis. More large-sample and well-designed studies are required to confirm the existing conclusions or detect the covered significant association in this meta-analysis.

<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary Risk of fractures</th>
<th>Secondary -</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results:</strong> Incidence of fractures not significantly related to tea consumption (OR = 0.89; 95% CI: 0.78, 1.04). No significant association in any subgroup. High and significant heterogeneity ($I^2 = 73.6%$; $P &lt; 0.001$).</td>
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</table>


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level:</td>
<td>Countries: UK (n = 2), US (n = 2). Denmark</td>
<td><strong>Total no. patients:</strong> 314.146</td>
<td><strong>Interventions:</strong> Exposure: Subclinical hypothyroidism (defined as elevated TSH values in the presence of normal FT4 values) and subclinical hyperthyroidism (defined as lower TSH values in the presence of normal FT4 levels).</td>
</tr>
<tr>
<td>Study type: SR/MA of 5 population-based cohort studies</td>
<td>Centres: N.r. Setting: N.r. Funding sources: N.r. Dropout rates: N.r.</td>
<td><strong>Patient characteristics:</strong> Mean age of participants older than 60 years including men and women. Follow-up period ranged from 4.5 to 13 years. Lower limit of TSH cutoff value from 0.4 to 0.55 mU/L used to diagnose subclinical hyperthyroidism, and upper limit of TSH cutoff value ranged from 4.0 to 4.78 mU/L for subclinical hypothyroidism. 5 studies reported whether patients were taking thyroid-associated drugs or not. <strong>Inclusion criteria:</strong> Full-text, published, longitudinal cohort studies that - measured thyroid function of both TSH and FT4, - followed participants prospectively assessed the risk of fracture, and - provided sufficient data to calculate risk estimates associated with subclinical thyroid dysfunction compared with normal thyroid function. <strong>Exclusion criteria:</strong> -</td>
<td></td>
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<tr>
<td>Included studies:</td>
<td>Flynn RW (2010) J Clin Endocrinol Metab Lee JS (2010) Arch Intern Med Thenmalar V (2011) J Clin Endocrinol Metab Waring AV 2013 J Bone Miner Res Abrahamson B (2014) J Bone Miner Res</td>
<td>- Mean age of participants in all included studies greater than 60 years old, thus relationship between the risk of fracture and subclinical thyroid dysfunction in middle-aged and young patients remains unclear. - Different TSH cutoff levels (4.0–4.78 mU/L for subclinical hypothyroidism; 0.4–0.55 for subclinical hyperthyroidism) in studies included might have different influence on risk of fracture.</td>
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<tr>
<td>Notes:</td>
<td>No search for unpublished studies. No discussion of publication bias. 1 included study not listed correctly in references (Thenmalar et al. quoted as Vadiveloo et al.)</td>
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<tr>
<td>Author's conclusion:</td>
<td>Despite heterogeneity across the studies, data suggest that subclinical hyperthyroidism is associated with an increased risk of fracture in the population older than 60 years. No evidence could prove a definite association between subclinical hypothyroidism and the risk of fracture yet.</td>
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<table>
<thead>
<tr>
<th>Outcome Measures/results</th>
<th>Primary Associations between subclinical thyroid dysfunction and fracture</th>
<th>Secondary -</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results:</strong> Subclinical hypothyroidism and fracture: 3 studies provided multivariable-adjusted data. No significant association: RR = 1.20, 95 %CI; 0.7, 2.04; $P$ for heterogeneity = 0.000, $I^2=87.4%$). Sensitivity and subgroup analyses without significant results. Subclinical hyperthyroidism and fracture: 5 studies provided multivariable-adjusted data. Significantly increased risk of fracture (RR = 1.25, 95 %CI; 1.11, 1.41; $P$ for heterogeneity = 0.169, $I^2=37.9%$).</td>
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</table>

Author's conclusion cannot be supported. "we can conclude that pain relief after kyphoplasty is significantly greater than that achieved with vertebroplasty." F.e. in VAS score meta-analysis: The baseline results cross the 0 threshold and are non significant. The follow up datasets for VAS display high heterogeneity with $I^2$ 79-97% (significant in all cases), despite this a fixed effects model was used! Publication bias was mentioned investigation using funnel plots was mentioned but not shown. COI statements for primary studies or review authors are absent.

Author's conclusion: Based on the result of this meta-analysis, we can conclude that pain relief after kyphoplasty is significantly greater than that achieved with vertebroplasty. The benefits can be sustained for at least 2 years. Kyphoplasty can improve the vertebral height and kyphosis angle much more than vertebroplasty with lower occurrence of cement leakage.

**Outcome Measures/results**

**Primary Clinical outcomes:** pain visual assessment scale VAS
- Radiographic outcomes: vertebral height (mm), kyphosis angle.
- Complications outcomes: adjacent new vertebral fractures and cement leakage.
- Secondary Per-operative outcomes: volume of cement and operative time.
- Clinical outcomes: Oswestry Disability Index (ODI), and Euro Quality of Life-5 Dimensions (EQ-5D).
- Radiographic outcomes: vertebral height rate (%) (it was expressed as the percentage of the vertebra height for the fractured vertebra compared with the height for the adjacent normal vertebral).
### Funding sources:
This research was supported by grants from Technology Development Project of Taian city of China (2014–498) and Natural Science Foundation of Shandong Province of China (ZR2015HL028).

### Drop-out rates:
N.r.

### Study limitations:
- Findings primarily based on results derived from observational studies, which was subject to unmeasured confounding and other potential biases.
- Substantial heterogeneity across studies, especially for women subgroup.
- Inverse associations of MetS with fracture risk could be attributed to adoption of healthy lifestyles by subjects after being diagnosed MetS. However, four of five studies adjusted for physical activity, three adjusted for smoking and drinking.
- Absence of uniform diagnostic criteria of MetS increased likelihood of wrongly estimating the associations.
- Duration of MetS or its components may also have an impact on fracture risk. Impossible to establish how long MetS or its components had existed prior to baseline.
- Possibility of publication bias could not be excluded.

### Notes:
Final search query not stated. No search for unpublished studies. References partly not correct.

### Author’s conclusion:
In summary, our analysis indicated that MetS was associated with a lower risk of fractures in men but not in women. However, the results should be interpreted with caution given the limited number of studies and the non-significant difference between the gender subgroups. Future well-designed cohort and intervention studies are warranted to confirm our results and explore whether the associations differ by gender and menopause.

### Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Fractures: 2 studies did not specify the type of fracture and other 2 studies only had non-vertebral fracture as study endpoint.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
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</table>

### Results:
Association between MetS and the risk of any fracture: 5 studies with 48,637 participants. Inverse relationship of MetS with fracture risk: RR = 0.76, 95%CI: 0.59, 0.97, P<0.026. Moderate heterogeneity existed among the studies (I²=63.8%).

Subgroup analysis by gender: Protective effects of MetS on fractures observed in men (RR = 0.66, 95%CI: 0.51, 0.86, P = 0.002) but not in women (RR = 0.96, 95%CI: 0.60, 1.54, P = 0.866). Test of interaction showed that difference between the two subgroups was not statistically significant (Z = -1.34, p = 0.179). No evidence of statistical heterogeneity in male subgroup (P=0.235, I²=27.90%) but substantial heterogeneity in female subgroup (P=0.002, I² = 83.4%).

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<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| Evidence level: 2+ | Countries: 1 Denmark, 1 France, 1 Korea, 1 Japan  
Centres: N.r.  
Setting: N.r.  
Funding sources: N.r.  
Dropout rates: N.r.  
Study limitations: - Possibility of uncontrolled | Total no. patients: 57,259  
Patient characteristics: N.r. in detail.  
1 studies stratified age in 70 > age ≥ 35 and ≥ 70. Remaining studies with age > 50, ≥ 60 and average ≥ 74 years.  
Inclusion criteria: - Observational studies that reported on | Interventions: BP  
types: Risedronate.  
Alendronate and n.r.  
PPI types: Rabeprazole; omeprazole; lansoprazole; |
control study) confounders, and individual studies did not adjust for fractures associated with BP or and PPI exposure.パンツオロプラズモ；

Included studies: potential risk factors in a consistent way. The lack of control or controlled cohort (prospective or retrospective) studies that evaluated the association of fracture risk with concomitant BP or and PPI exposure. observational studies: randomized controlled trials, case-

Bone Miner Metab
resulted in a slight overestimation of the OR.

Lee J (2013) J Gastroenterol
- Only studies in English included, some relevant studies reported in other languages might not be included in the results (OR/RR/HR) for bone fractures, or that reported sufficient raw data to allow for calculation of OR.

Roux C (2012) Osteoporos Int
- Only four studies including five comparisons, reducing the power of findings.

Abrahamsen B (2011) Arch Intern Med
- Number of patients included in BP group and BP+PPI group not well matched (43974 BP users vs 13285 BP/PPI users).

Notes:
No search for grey/ unpublished literature. Characteristics of patients in included not reported in detail. Observational studies listed as inclusion criteria, but randomized controlled trials, case-control or controlled cohort defined as such. Interventions not described (e.g. dose regimen).

Author’s conclusion: In summary, the findings of this meta-analysis suggest that there is an interaction associated with increased fracture risk (particularly for spine and Asian race) between BP and PPI use. Clinicians should carefully evaluate such risk factors for osteoporosis in patients taking BPs, before routinely prescribing PPIs, and make a careful judgment as to whether PPIs may be safe for patients at high risk of fractures.


Evidence level: * Study type: Prospective cohort study

Evidence level: Study
Countries: Australia
Centres: Orthopaedic fracture clinic
Setting: Outpatient setting
Funding sources: Funded by grant from Servier Laboratories Australia
Dropout rates: N.r.
Study limitations: - Modest patient number and single centre limits generalizability to other hospitals.
Cohort predominately female.
- Individuals with hip fractures excluded by recruitment criteria.

Patient characteristics
Total no. patients: 107 in analyses of Osteoporosis Policy, 203 in evaluation of FLS
Patient characteristics: Only reported for participants in evaluation of FLS:
Mean Age (SD): 67 (11) years, 77% female. Fractures: 39% wrist, 18% humerus, 11% ankle, 44% with DXA criteria met for osteoporosis, 40% with osteopenia.

Inclusion criteria: Male and female patients > 50 years old with low-trauma fractures.
Exclusion criteria: -

Interventions details/limitations
Interventions: Orthopedic Osteoporosis Policy:
Policy advising doctors to perform DXA, serum 25OHvitD, calcium, RFTs for all patients > 50 years with low-trauma fractures. Dietary advice or supplementation when necessary. Letter recommending osteoporosis-specific therapy to patient’s general practitioner.
Fracture liaison service (FLS): Introduced after implementation of policy described above. All patients > 50 years with low-trauma fractures referred to endocrinologist. All patients prescribed an osteoporosis-specific medication received follow-up appointment 3 months later, assessing medication tolerance and adherence before discharge to care of GP.

Notes:
Potential impact of study results on delivery of health care discussed briefly.
No justification of study design offered. Limitation resulting from “Before-After-Comparison” not discussed: major problem is difficulty of attributing any changes purely to the new treatment (high risk of confounding). Calculation of QALYs not described in detail.
Sensitivity analyses performed for assumption o fracture risk rate. Baseline characteristics of participants not shown.
Author’s conclusion: This FLS model improves uptake of osteoporosis intervention guidelines, is popular among patients, and improves cost-effectiveness. Thus, it has the capacity to substantially improve health in a cost-effective way.

Outcome Measures/Results
Outcome Measures: Performance of FLS: clinic database review performed by independent investigator and 13-point patient questionnaire.
Results: At baseline (n = 49), 2% of ambulatory patients who had sustained fragility fractures underwent dual-energy X-ray absorptiometry (DXA) and 6% received osteoporosis-specific medication. After introduction of an osteoporosis policy (n = 58), 28% were investigated with DXA (p < 0.0001). However, treatment rates were unchanged. An FLS was introduced, reviewing 203 new patients over the inaugural 2 years. Osteoporosis medications were prescribed to 61% patients (risedronate: 22%, alendronate: 16%, strontium ranelate: 13%, zoledronic acid: 8%, other: 2%). Eighty-five of 90 questionnaire respondents were very satisfied or

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
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<tbody>
<tr>
<td>2++</td>
<td>Countries: USA (n = 7), Finland (n = 2), Germany, UK, China, Sweden, Korea Centres: N.r. Setting: N.r. Funding sources: “The authors have no support or funding to report.” Dropout rates: N.r. Study limitations: - Meta-analysis based on observational studies, half of included studies controlled some confounding factors, such as age and gender. Other confounding factors (estrogen level, total calcium intake, diet, and level of fluoride exposure) difficult to control in epidemiological studies. - Few evidence of publication bias observed but statistical power for these tests limited because of relatively small number of included studies. - Significant heterogeneity detected in meta-analysis. Heterogeneity between studies should not be ignored even if it is highly common in the meta-analysis. Sensitivity analyses and meta-regression performed to determine sources of heterogeneity, but heterogeneity still observed. - Majority of studies used different methods to assess and categorize fluoride exposure among studies. Findings are likely to be influenced by misclassification of exposure. In cohort studies, this misclassification would likely be non-differential if exposure variable was dichotomous, and thereby result in an underestimate of true association, whereas the influence of a misclassification on results in case-control studies is less predictable. Potential for misclassification of exposure to fluoride may contribute to heterogeneity.</td>
<td>Total no. patients: 73,411,368 + 7 individuals. 1 study did not report No. of subjects. Patient characteristics: 3 studies with small study samples investigated only women, 11 studies investigated women and men. Age: Median only reported in 3 studies (62.8, 62.8 and 74.2 years). Range: 20-89 years. Inclusion criteria: (1) evaluating the association between fluoride exposure in drinking water and hip fracture risk with obtainable full text; (2) providing adjusted and/or unadjusted hazard ratios (HRs), odds ratios (ORs), and relative risks (RRs) with corresponding 95% confidence interval (CI) or raw data for calculating crude HRs, ORs, or RRs. Exclusion criteria: Letters, comments, correspondences, conference reports, or laboratory studies; or did not contain enough data for risk estimates calculation.</td>
<td>Exposure to water fluoridation (categorized between ≤ 0.1 mg/l - 7.97 mg/l or simple nonfluoridated vs. fluoridated). Average follow-up ranged from 2 years to 16.8 years. Patients followed up over five years in majority of the studies (64.3%).</td>
</tr>
</tbody>
</table>


Notes: No search for grey/unpublished studies.

Author’s conclusion: In conclusion, limited evidence suggests that chronic fluoride exposure from drinking water does not significantly increase the risk of hip fracture. Although these findings are encouraging, the results of this meta-analysis should be explained with caution because of potential confounding factors, heterogeneity, and exposure misclassification. Further large-scale and well-designed trials on this topic are needed.

Outcome Measures/results

<table>
<thead>
<tr>
<th>Primary</th>
<th>Hip fracture risk</th>
</tr>
</thead>
</table>

Results: RR estimates for each study pooled to determine total estimates of risk using random-effects

Cost-effectiveness of FLS: Costs based on 2012 Australian Medicare Benefits and Pharmaceutical Benefits Schedules. satisfied with the FLS. With the treatment prescribed over 5 years, we conservatively estimated that this FLS would reduce nonvertebral refractures from 59 to 50, improving QALYs by 0.054 and costing $1716 per patient (incremental cost-effectiveness ratio: $31749).
### Evidence level

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>SR/MA</td>
<td>Countries: Sweden (n = 2), UK (n = 3), USA (n = 2), Japan (n = 2), Taiwan (n = 2), Germany (n = 1).</td>
<td>Total no. patients: 512,214 stroke patients</td>
<td>Interventions: Exposure: Stroke. Not further detailed.</td>
</tr>
<tr>
<td></td>
<td>of 13 cohort studies</td>
<td>Centres: N.r.</td>
<td>Patient characteristics: Mean age of stroke survivors at baseline ranged from 58 to 79 years. Mean/median follow-up durations varied between 1.3 and 25 years. Proportion of incident of hip fracture in stroke survivors ranged from 0.5% to 18.2%.</td>
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</tr>
<tr>
<td></td>
<td>(6 prospective, 7 retrospective)</td>
<td>Setting: N.r.</td>
<td>Inclusion criteria: (1) observational studies using cohort (both prospective and retrospective) study design, (2) adult population, and (3) incidence of hip fracture in stroke survivors.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Included studies:</td>
<td>Funding sources: &quot;None.&quot;</td>
<td>Exclusion criteria: -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rammemark A (1998)</td>
<td>- Large amount of heterogeneity between studies, which was not explained by subgroup analyses. - Adjustment for for potential confounding factors not possible because of the use of raw data from original studies. - No attempt was made to include unpublished data and some eligible published studies may have missed. - Types of stroke (ischaemic or hemorrhagic) and degree of function loss (hemiplegia or total loss of function) may influence the outcome and were not differentiated in included studies. - Half of included studies with retrospective cohort design (n = 7 studies).</td>
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</table>

### Notes:

- Final search query not presented. No search for unpublished studies. Unclear, if subgroup analyses were pre planned. A high number of subgroup analyses as in this review increases the chance of significant findings by chance.
- Source of high heterogeneity was not explored. Confident authors' conclusion can not be supported by study results.
- The performance of a meta-regression analysis would have improved trust in results.
- **Author's conclusion:** In conclusion, the present meta-analysis shows that stroke survivors were at high risk of hip fracture, and had 1.5-fold increase risk compared to stroke-free men and women of the same age. Hip fractures often occur in ageing and female stroke patients. Prevention of bone loss and falls in stroke survivors may be the most important way to prevent hip fracture.

### Outcome Measures/results

- **Primary** Prevalence of hip fracture in stroke survivors.
- **Secondary** Relative risk (RR) (compared with population controls) of hip fracture in stroke survivors.

### Results:

- **Pooled prevalence of hip fracture** = 4.87 % (95 % CI, 4.05 to 5.68 %) in stroke patients with high, significant heterogeneity (I² = 99.3 %, p = 0.000). Based on analysis of 13 studies.
- **Risk of hip fracture**: Reported in 5 studies. Unadjusted risk of hip fracture RR = 1.54 (95 % CI; 1.06, 2.25, no p-value stated) with high, significant heterogeneity.
Zhang, X. et al. Alcohol consumption and hip fracture risk. Osteoporos Int. 26, 531-42. 2015

Evidence level | Study details/limitations | Patient characteristics | Interventions
--- | --- | --- | ---
Evidence level: 2- | Countries: USA, Europe, Australia, Canada, Japan
Centres: N.r.
Setting: N.r.
Funding sources: This study supported by the Fund for Key National Basic Research Program of China (grant no. 2012CB619101 and 81401852), Natural Science Foundation of Science and Technology Commission of Shanghai Municipality (14ZR1424000), Major Basic Research of Science and Technology Commission of Shanghai Municipality (grant no. 11DJ1400303). The funding sources had no role in the study design, collection, analysis, or interpretation of data, or writing of the report.
Dropout rates: N.r.
Study limitations: - Moderate heterogeneity in terms of moderate alcohol consumption observed (P=0.021; $I^2=55.6$%), which was likely attributed to variation in study designs as well as quality of analyzed studies.
- Certain factors, such as lifetime exposure to alcohol, not included in meta-analysis since very few studies reported on these factors.
- Heterogeneity may have been introduced by methodological differences among studies. Most causes of heterogeneity could not be explored, and inadequate controls of confounding factors may have resulted in an exaggeration or underestimation of risk estimates of biases in results, and reduced strength of conclusions.
- One study included more than three million participants, and this study may thus have heavily influenced results; hence, findings should be interpreted with caution.
Total no. patients: 3,730,424 participants
Patient characteristics: 8 studies recruited male and female participants, 4 recruited only men, and the remaining 6 recruited only women.
Age of participants was ≥20 years in all studies.
Study length ranged from 3 to 30 years.
Inclusion criteria: (1) prospective cohort design,
(2) adult population,
(3) exposure of interest: alcohol consumption,
(4) outcome of interest: hip fracture,
(5) follow-up was ≥2 years and cohort size was >1,000, and
(6) risk estimates such as relative risks (RRs), odds ratios, hazard ratios, or another measure that could be transformed into RRs with 95% confidence intervals (CI).
Exclusion criteria: -
Interventions: Alcohol exposure: All information on alcohol consumption obtained from self-administered questionnaires for daily alcohol consumption or health records. Three exposure levels to alcohol: light (0.01–12.5 g/day), moderate (12.6–49.9 g/day), and heavy (≥50 g/day).

Notes: Final search query not stated. Search for unpublished studies not described in detail. Undeclare, how many people selected the included studies, only stated as "the reviewers".
Funnel plots for assessment of publication bias not shown.
No quality assessment of included studies.
Random-effects models used throughout the whole analysis regardless of quantified heterogeneity.

Author's conclusion: Overall, our meta-analysis found a nonlinear association between alcohol consumption and the risks of hip fracture. We found ($I^2=97.6\%$, $p=0.000$).

Subgroup analysis indicated age (RR = 1.21; 95% CI; 1.12, 1.30, $p=0.000$) and female sex (RR = 1.70; 95% CI; 1.44, 1.96, $p=0.032$) as influencing variables. Both analyses with significant heterogeneity (Age: $I^2=97.8\%$, $p=0.000$. Sex: $I^2=66.0\%$, $p=0.032$).
Measures

Outcome

Primary

Hip fractures: Fractures identified using self-reports of fracture experience, radiologic diagnoses, or medical records.

Secondary -

Notes

Study

Evidence

Table:<br>

<table>
<thead>
<tr>
<th>Evidence level:</th>
<th>Study details/limitations</th>
<th>Patient characteristics</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>Countries: China</td>
<td>Total no. patients: n=219</td>
<td>12 months ALN/D5600 (Fosamax® Plus D, alendronate 70 mg/vitamin D3 5600 IU) once weekly as a combination tablet vs calcitriol (Rocaltrol®, calcitriol 0.25 µg) 0.25 µg daily. Calcium supplements (500mg/daily)</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>Centres: 13</td>
<td>Patient characteristics: Postmenopausal (at least 1 year) women ≥55 years</td>
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<tr>
<td></td>
<td>Setting: -</td>
<td>inclusion criteria: - BMD T-scores ≥2.5 in at least one anatomic site (lumbar spine, total hip, or femoral neck) or - prior non-pathological fragility fracture (of the spine, wrist, humerus, or clavicle) and - BMD T-scores ≥1.5 in at least one of the same anatomic sites; 25(OH)D levels ≥28 ng/mL (20 nmol/L) or - no prior hip fracture, no history of clinical significance (no pronounced medical history other than osteoporosis) - no treatment with specific drugs for specified time periods - no contraindications to alendronate, calcitriol, or vitamin D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Funding sources: MSD China Holding Co., Ltd., China</td>
<td>Exclusion criteria: -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dropout rates: 4.5% in ALN/D5600 group, 3.7% in Calcitriol group</td>
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<td></td>
<td>Study limitations: Open-label design which may have introduced bias. In addition, although BMD was measured by either Hologic (Hologic Corporation) or GE Lunar (GE Medical Systems) DXA machines and individual sites followed quality control procedures recommended by the manufacturers, there was no independent central BMD quality control/quality assessment program. However, because the study was not large enough to compare fracture incidence, central adjudication of events such as fractures was not performed by either an internal or an external committee. Moreover, the study was not designed to distinguish the relative contributions of ALN and vitamin D3 in reducing bone loss and increasing BMD.</td>
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</tbody>
</table>

Notes:

sample-size calculation not reported

Author’s conclusion: In summary, ALN/D5600 showed significantly greater increases in BMD at the lumbar spine and significantly greater decreases in bone turnover markers compared with calcitriol in Chinese postmenopausal women with osteoporosis. The study did not evaluate whether the greater increase in BMD resulted in fewer fractures. ALN/D5600 was also generally well tolerated in Chinese patients with a safety profile consistent with previous studies across various regions and races.

Outcome

Measures/results

Primary

Percent change from baseline in lumbar spine BMD at month 6.

- percent change from baseline in the biochemical markers of bone turnover procollagen type 1 N-terminal propeptide (P1NP) serum C-telopeptides of type 1 collagen (s-CTX)
- percent change from baseline in total hip, femoral neck, trochanter BMD
- proportion of patients with serum 25(OH)D <20 ng/mL;
- proportion of patients with serum 25(OH)D <15 ng/mL;

Results: Lumbar spine BMD

Month 6

- percent change (least squares LS) from baseline: ALN/D5600 3.5 % (95 % CI 2.7, 4.4; standard error (SE), 0.42) vs Calcitriol 1.6 % (95 % CI 0.8, 2.4; SE 0.41) between treatment difference of 2.0 % (95
- change from baseline in mean serum 25(OH)D level. At month 12
- percent change from baseline in lumbar spine, total hip, femoral neck, trochanter BMD
- percent change from baseline in the biochemical markers of bone turnover P1NP and s-CTx
- proportion of patients with serum 25(OH)D <20 ng/mL
- proportion of patients with serum 25(OH)D <15 ng/mL
- change from baseline in mean serum 25(OH)D level

The safety and tolerability of ALN/D5600 once weekly

\[-\text{change from baseline in mean serum 25(OH)D level at month 12} -\text{percent change from baseline in lumbar spine, total hip, femoral neck, trochanter BMD} -\text{percent change from baseline in the biochemical markers of bone turnover P1NP and s-CTx} -\text{proportion of patients with serum 25(OH)D <20 ng/mL} -\text{proportion of patients with serum 25(OH)D <15 ng/mL} -\text{change from baseline in mean serum 25(OH)D level}\]

\- The safety and tolerability of ALN/D5600 once weekly

\text{The safety and tolerability of ALN/D5600 once weekly}

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study</th>
<th>Patient characteristics</th>
<th>Interventions details/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1+</td>
<td>Study type: SR of 6 RCT</td>
<td>Countries: 2 UK, 2 Japan, 1 Finland, 1 US</td>
<td>Interventions: Jumping exercise interventions. All studies prescribed high-impact exercise (jumping) with one exercise plus lower or lower/upper body resistance exercise and one exercise combining stamping, running, and walking. Study duration ranged from 6 to 12 months, with a training frequency of two to three times per week in most interventions. Two exercise protocols were conducted six or seven times per week, but the intensity of training was relatively low, and the total training volume was similar to other studies. Three control groups were asked to maintain their usual diet and lifestyle. Two control groups performed mild arm exercises or stretching and balance exercises. Specific information was not available on one of the control groups.</td>
</tr>
<tr>
<td>Funding sources:</td>
<td></td>
<td></td>
<td>Details linked to the study drug.</td>
</tr>
<tr>
<td>This article was based on work funded by the Zhejiang Provincial Natural Science Foundation of China under grant numbers Y2110954 and LY14H070001.</td>
<td></td>
<td></td>
<td>Details linked to the study drug.</td>
</tr>
<tr>
<td>Dropout rates:</td>
<td>Not quantified. Study limitations:</td>
<td>Inclusion of only 6 studies; - Highly selective samples of premenopausal women of varying ages; - Future studies should include both traditional resistance exercises and high impact intervention studies to examine the optimal exercise for improving premenopausal bone health.</td>
<td>Details linked to the study drug.</td>
</tr>
<tr>
<td>Notes:</td>
<td>No search for grey literature possibly introducing publication bias. Mislabeled interpretation of funnel plots by authors (&quot;asymmetry... indicating positive treatment effect&quot;). Instead, funnel plots indicate publication bias, resulting in an overestimation of treatment effect and its direction. However, funnel plots futile due to insufficient number of studies. Primary Outcomes (Absolute changes in BMD) not reported. Author’s conclusion: Based on meta-analysis of existing studies, the sensitivity of skeletal response to jumping exercise in premenopausal women is significant and site-specific, with significant benefit from high-impact exercise noted, especially at the hip.</td>
<td></td>
<td>Details linked to the study drug.</td>
</tr>
<tr>
<td>Outcome Measures/results:</td>
<td>Primary</td>
<td>Absolute changes in BMD and its standard deviation (SD) at femoral neck, trochanter, and lumbar spine, as assessed by dual-energy X-ray absorptiometry (DXA).</td>
<td>Details linked to the study drug.</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>Weighted mean difference (WMD) between exercise and control groups pooled SDs of mean difference between exercise and control groups.</td>
<td>Details linked to the study drug.</td>
</tr>
</tbody>
</table>


| Evidence level | Study type: MA of 24 studies (19) | Total no. patients: postmenopausal women | Interventions: All of the included trials were based on high-intensity resistance training with study durations ranging from 6 months to 12 years, with a training frequency of 2-3 times per week in most |}

---

**Evidence level**: 2+

**Study type**: MA of 24 studies (19)

**Countries**: USA, Brazil, Australia, Canada, Germany, UK, Belgium

**Patient characteristics**: Healthy postmenopausal women.

**Interventions**: All of the included trials were based on high-intensity resistance training with study durations ranging from 6 months to 12 years, with a training frequency of 2-3 times per week in most.
### Funding sources
This material was based upon the work funded by Zhejiang Provincial Natural Science Foundation of China under Grant No. LY14H070001.

### Inclusion criteria
- Study design: Controlled or randomized controlled trials; 1-year intervention; 10 or more participants in each group; 20% inclusion rate (range: 0% - 52.3% in intervention groups, 0% - 41.2% in control groups); no study with no statement regarding dropout rates.

### Notes
- High-quality study design and sample size included.
- Highly selected samples of postmenopausal women of varying ages included studies.
- Relatively low quality of the included studies.
- Studies included that reported findings of the same program might potentially impact the results of pooling intervention effects.

### Process of study selection
- No search for grey literature. No investigation of publication bias because “the subjective nature of visual interpretation of funnel plots seems to have limited use in the examination of publication bias in the current meta-analysis”.

### Author’s conclusion
The general conclusions of the present meta-analysis were that progressive high-intensity resistance training tended to be effective for improving or preserving hip and spine BMD in postmenopausal women. However, skeletal adaptation was dependent on training modes, as the combined protocols that integrated resistance training with high-impact or weight-bearing exercises showed significant beneficial effects on postmenopausal bone loss, while resistance-alone protocols did not. Although the number of training-related injuries reported in the included studies was very low, caution is advised when resistance training is performed at home or without supervision because the resistance exercise conducted by the participants in the clinical trials was usually performed with special training equipment and under supervision. The poor quality of several trials reminds us that well-designed studies with large sample sizes are still needed. Further studies are also needed to characterize both material and structural changes to determine exercise-induced gains in bone strength. Nevertheless, combined resistance training protocols furnish a feasible nonpharmacological strategy for preventing postmenopausal bone loss.

### Outcome Measures/Results

<table>
<thead>
<tr>
<th>Primary areal BMD (BMD g/cm²) assessed by dual X-ray absorptiometry (DXA) or dual photon absorptiometry (DPA)</th>
<th>Secondary -</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Notes:</strong></td>
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<tr>
<td>Process of study selection not described. No search for grey literature. No investigation of publication bias because “the subjective nature of visual interpretation of funnel plots seems to have limited use in the examination of publication bias in the current meta-analysis”. Adverse events not investigated.</td>
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</tr>
<tr>
<td><strong>Authors’ conclusion:</strong> The general conclusions of the present meta-analysis were that progressive high-intensity resistance training tended to be effective for improving or preserving hip and spine BMD in postmenopausal women. However, skeletal adaptation was dependent on training modes, as the combined protocols that integrated resistance training with high-impact or weight-bearing exercises showed significant beneficial effects on postmenopausal bone loss, while resistance-alone protocols did not. Although the number of training-related injuries reported in the included studies was very low, caution is advised when resistance training is performed at home or without supervision because the resistance exercise conducted by the participants in the clinical trials was usually performed with special training equipment and under supervision. The poor quality of several trials reminds us that well-designed studies with large sample sizes are still needed. Further studies are also needed to characterize both material and structural changes to determine exercise-induced gains in bone strength. Nevertheless, combined resistance training protocols furnish a feasible nonpharmacological strategy for preventing postmenopausal bone loss.</td>
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<tr>
<td><strong>Results:</strong> Overall analysis of resistance training impact: Resistance training interventions resulted in significantly increased femoral neck BMD: $\text{SMD} = 0.303$ (95% CI: 0.127, 0.479, $p = 0.01$; $I^2 = 46.5$%) and lumbar spine BMD: $\text{SMD} = 0.311$ (95% CI: 0.115, 0.507, $p = 0.002$; $I^2 = 62.3$%). Combining resistance versus resistance-alone protocols: Combined resistance training protocols significantly affected both the hip BMD: $\text{SMD} = 0.411$ (95% CI: 0.176, 0.645, $p = 0.001$; $I^2 = 48.3$%) (analyses is for femoral neck) and spine BMD: $\text{SMD} = 0.431$ (95% CI: 0.159, 0.702, $p = 0.002$; $I^2 = 71.3$%). Resistance-alone protocols had no significant effects on the preservation of femoral neck BMD: $\text{SMD} = 0.212$ (95% CI: $-0.043$, 0.468, $p = 0.104$; $I^2 = 45.6$%) or lumbar spine BMD: $\text{SMD} = 0.180$ (95% CI: $-0.09$, 0.456, $p = 0.203$; $I^2 = 48.3$%). Differences between combined resistance and resistance-alone groups not significant: $p = 0.149$ for femoral neck BMD and $p = 0.253$ for spine BMD.</td>
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</tbody>
</table>
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