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REVIEW ARTICLE

Combination therapy with parathyroid hormone analogs and antiresorptive agents for osteoporosis: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Combination therapy with parathyroid hormone (PTH) analogs and antiresorptive agents may be more effective than monotherapy for the treatment of osteoporosis. This study aimed to estimate the effectiveness and safety of this combination therapy for osteoporosis. MEDLINE, EMBASE, and Cochrane Library were searched from inception to May 1, 2018, including randomized controlled trials (RCTs) with a duration of at least 6 months on adults with osteoporosis treated with combination therapy versus monotherapy. Outcomes included fractures, bone mineral density (BMD) changes, and adverse events. A meta-analysis was performed using a random-effect model, to estimate risk ratios (RRs) for fractures, and mean differences (MDs) for BMD changes. A total of 19 RCTs and 2177 patients were included. Compared with monotherapy, combination therapy had an advantage of 36% (RR, 0.64; 95% confidence interval (CI), 0.42–0.98) regarding fracture risk reduction. It also appears to improve lumbar spine BMD by 4.06% (95%CI = 2.60–5.53) and total hip BMD by 1.89% (95%CI = 1.25–2.53). No RCT reported an increased risk of serious adverse events. Among patients with osteoporosis, combination therapy was superior to monotherapy regarding improvement of the lumbar spine and total hip BMD, without risk of serious adverse events. Combination therapy also had an advantage over monotherapy on fracture risk reduction. However, owing to the limited sample size, additional larger studies are required to confirm this benefit.

Keywords Anabolic · Antiresorptive · Bisphosphonates · Bone mineral density · Combination therapy · Denosumab · Osteoporosis · Teriparatide

Introduction

Osteoporosis is a common skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, causing an increase in bone fragility and susceptibility to fracture, which is currently considered a serious global public health problem [1]. During their lifetime, 30–50% of women and 15–30% of men suffer an osteoporosis-related fracture [2], which is associated with increased mortality and costs [3, 4]. The excess mortality during the first year after a hip fracture has been estimated at 8.4–36.0% and 1.9–42.0% after vertebral fractures [4]. The worldwide annual estimated excess cost of osteoporosis-related fractures is expected to rise to $25.3 billion by 2025 [5].

To date, a range of pharmacological interventions is available for the treatment of osteoporosis, including antiresorptive and anabolic agents. Antiresorptive agents such as bisphosphonates

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and denosumab inhibit both bone resorption and formation [6, 7], whereas anabolic agents—parathyroid hormone (PTH) and its analogs—promote both resorption and formation within the bone remodeling process [8, 9]. Theoretically, the "ideal" anti-osteoporosis drug would simultaneously increase new bone formation and inhibit bone resorption [10]. However, neither antiresorptive agents nor PTH analogs meet these criteria. Indeed, although the therapeutic options for osteoporosis have expanded greatly over the past 30 years [11], no currently approved therapy appears to restore normal bone integrity in most patients with established osteoporosis, and options for severe cases remain limited [12].

Combination therapy with anabolic and antiresorptive agents has been proposed as a surrogate for this "ideal" drug to improve the treatment efficacy, based on the hypothesis that if bone formation is stimulated by an anabolic agent while bone resorption is inhibited by an antiresorptive agent, the improvement of bone mass and strength would be greater than with either agent alone [13, 14]. During the past two decades, various anabolic and antiresorptive therapies have been combined [12, 15–19]. Although teriparatide or PTH (1–84) combined with antiresorptive agents could theoretically produce additive effects, clinical results have been mixed [20]. Some studies have determined combination therapy to be superior to monotherapy with antiresorptive agents, PTH analogs, or both [12, 17–19, 21–29], whereas others have failed to observe significant differences between combination therapy and monotherapy [30, 31], while still others have even suggested combination therapy could reduce the ability of anabolic therapy to increase bone mineral density (BMD) [16, 32, 33]. Based on early studies [16, 34], combination therapy with PTH analogs and antiresorptive agents was once discouraged [35–40]. Although more recent trials with positive results have emerged [12, 23, 27–29], the clinical value of the simultaneous use of PTH analogs and antiresorptive agents remains uncertain [10], and combination therapy is still not formally recommended to date.

As new trials continue to be published [25, 41], without a comprehensive review and evidence-based evaluation of this issue, we performed a direct comparison of the efficacy of combination therapy and monotherapy, incorporating these recent studies. This systematic review and meta-analysis of randomized controlled trials (RCTs) aims to provide an estimate of the effectiveness and safety of combination therapy with PTH analogs and antiresorptive agents compared with monotherapy in patients with osteoporosis.

Methods

This systematic review and meta-analysis was reported according to the Preferred Reporting Item for Systematic Review and Meta-Analysis checklist [42]. A formal protocol was developed and registered on the PROSPERO international prospective register of systematic reviews (CRD42017076702).

Study inclusion and exclusion criteria

RCTs eligible for inclusion had a duration of at least 6 months and assessed combination therapy (the concomitant use of PTH analogs and antiresorptive agents) compared with monotherapy (either PTH analogs or antiresorptive agents) among adults (age ≥ 18 years) with osteoporosis. Non-RCTs, duplicate reports, and trials that did not report on the outcomes of interest (fractures, BMD changes, and adverse effects) were excluded. Studies published as abstracts, editorials, or letters were also excluded.

Data sources and search strategy

Two independent authors (SHL and HCL) systematically searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception until May 1, 2018, without language restrictions. The search strategy was developed using MeSH terms and keywords associated with terms relevant to "osteoporosis," "teriparatide," "parathyroid hormone" together with "randomized controlled trial" (additional file S1). Reference lists of included RCTs and relevant reviews were scanned for additional RCTs. In addition, ClinicalTrials.gov (http://www.clinicaltrials.gov) was searched for RCTs that were registered as completed but not yet published.

Study selection and data extraction

Titles, abstracts, and full-text articles were screened independently by two authors (SHL and HCL), according to the inclusion criteria. For all eligible trials, data were extracted independently and in duplicate using a standardized electronic form (SHL and HCL). Discrepancies were resolved through consensus or consultation with a third independent reviewer (ZRL or PBY). The major categories of variables to be coded were (1) study characteristics, (2) participant characteristics, (3) type of intervention (agent, dose, duration), (4) outcome characteristics, and (5) risk of bias. When data were only presented graphically, GetData Graph Digitizer 2.26 software (http://getdata-graph-digitizer.com/) was used to digitize and extract the data. When the original data was not available, it was calculated through the available coefficients, according to the methods described in the Cochrane Handbook [43].

Risk of bias assessment

Two authors (SHL and HCL) independently assessed the risk of bias of RCTs using a modified Cochrane risk of bias tool whose response options were "definitely or probably yes"

(assigned a low risk of bias) or "definitely or probably no" (assigned a high risk of bias), an approach that has been validated previously [44, 45]. The tool addresses seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain is assigned a judgment relating to the risk of bias for that study: low risk, high risk, or unclear. Disagreements were resolved through discussion and sometimes with another reviewer (ZRL or PBY) if necessary.

Outcomes

The primary outcomes were fractures and BMD changes. Fractures were confirmed by X-ray radiography. Both vertebral and non-vertebral fractures were included. BMD changes were computed as the mean percent changes in BMD (measured by dual-energy X-ray absorptiometry, DXA) in the lumbar spine and total hip. When outcomes were presented at multiple time points, data belonging to the longest duration of treatment was included in the meta-analysis. The secondary outcome was the presence of adverse events related to combination therapy.

Data synthesis and statistical analysis

Continuous outcomes were expressed as weighted mean differences (WMDs) with a 95% confidence interval (95%CI). Dichotomous outcomes were expressed as risk ratios (RRs) and 95%CI. The meta-analysis was performed using the inverse variance weighted method, with a random-effects model to minimize the effects of study heterogeneity [46]. Cochrane's Q statistic and the I^2 statistic were used to assess heterogeneity, which was classified as unimportant heterogeneity ($I^2 \leq 40\%$), moderate to substantial heterogeneity ($I^2 >$ 40% and $< 75\%$), or considerable heterogeneity ($I^2 \geq 75\%$) [47]. In order to explore possible sources of heterogeneity in the instances of substantial heterogeneity ($I^2 \geq 50\%$) [47], sensitivity analyses were conducted using sequential omission of a single study from the total studies to evaluate the influence of each study on the pooled effect estimates. Random-effects meta-regression analyses were performed using the unrestricted maximum likelihood method to evaluate the association between treatment duration and outcomes. Moreover, owing to the different mechanisms of action of antiresorptive and anabolic agents, subgroup analyses were also performed based on the types of anti-osteoporosis drugs (antiresorptive or anabolic agents), regardless of the degree of heterogeneity. Publication bias was assessed using funnel plots and the Egger regression test [48]. The "trim and fill" method was used to adjust the effect size for potential publication bias [49]. All tests were two-tailed, and results were considered significant when $P \leq 0.05$. Statistical analyses were conducted with Review Manager (version 5.3) and Comprehensive Meta-Analysis (version 2.0) software.

Rating the quality of evidence

The quality of the evidence for the primary outcomes was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines [50], which use the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias in results.

Results

Search results

We identified 3391 relevant studies. After removal of 694 duplicates, the titles and abstracts of 2737 studies were reviewed, of which 2712 did not meet the inclusion criteria and were excluded. Next, 25 full-text articles were carefully assessed and reviewed, of which 6 studies were excluded due to not being about osteoporosis ($n = 2$) [51, 52] or using data from the same trials ($n = 4$) [12, 15, 19, 53]. Finally, 19 unique RCTs were found to be eligible and included in the systematic review and meta-analysis [16–18, 21–34, 41, 54]. The study selection process is shown in Fig. 1.

Study characteristics

A total of 2177 individuals were recruited in the 19 RCTs, with 923 and 1254 subjects in the combination therapy and monotherapy arms, respectively. The studies included were published between 1998 and 2017. The selected trials enrolled both females [16–18, 21–28, 30, 31, 33, 34, 41, 54] and males [29, 32], with the sample sizes ranging from 14 [34] to 412 subjects [17]. Except for 1 trial [34], all patients in the included trials received calcium and/or vitamin D supplementation daily. The RCTs used different types and doses of PTH analogs, including teriparatide 20 μg/day ($n = 8$) [17, 23, 25, 27–30, 41], teriparatide 25 μg/day ($n = 4$) [22, 26, 34], teriparatide 40 μg/day ($n = 3$) [31–33], PTH (1-38) 35 μg/day ($n = 1$) [34], or PTH (1-84) 100 μg/day ($n = 3$) [16, 33, 54]. The antiresorptive agents used in the RCTs included alendronate ($n = 6$) [16, 22, 23, 28, 32, 33], risedronate ($n = 1$) [29], zoledronate ($n = 1$) [17], ibandronate ($n = 1$) [54], raloxifene ($n = 4$) [18, 23, 28, 30], denosumab ($n = 3$) [25, 27, 41], and hormone replacement therapy (HRT) ($n = 5$) [21, 24, 26, 31, 34], with the recommended doses for the treatment of osteoporosis. The range of treatment duration ranged from 6 months [30, 54] to 36 months [21]. The main characteristics of the included trials are summarized in Table 1.

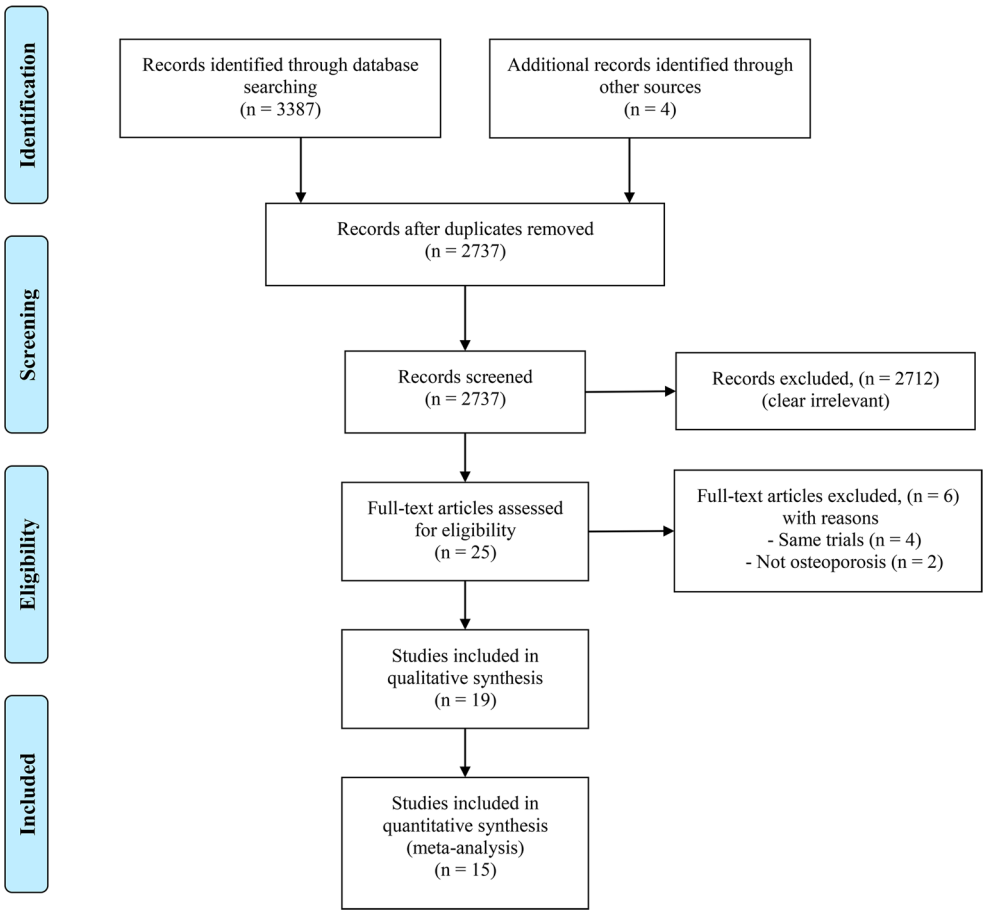

Fig. 1 Flow diagram showing the process of literature selection

Assessment of risk of bias

Out of all the studies included, some trials were characterized by lack of information about the random sequence generation ($n = 7$), allocation concealment ($n = 10$), and blinding of outcome assessment ($n = 4$); which rendered unclear. Owing to their open-label design, 13 studies (70%) had a high risk of bias for blinding of participants and personnel. In addition, 2 studies had a high risk for other biases due to unbalanced baselines [29] or eliminating data about men [41]. However, all evaluated studies showed a low risk of bias according to attrition bias and reporting bias. Details on the assessment of risk of bias are shown in Fig. 2.

Fractures

Nine trials [16, 17, 21–24, 26, 28, 29] assessed fractures. Combination therapy had a significant advantage over monotherapy, with a 36% reduction of fracture risk (RR = 0.64; 95%CI = 0.42–0.98; $I^2 = 0\%$; $P = 0.04$; 9 trials, Fig. 3). Our funnel plot and statistical test showed no evidence of publication bias (additional fig. S1, Egger's test $P = 0.23$). Tests for the subgroups found no statistical differences ($P = 0.66$ for interaction) between anabolic agents (RR = 0.71; 95%CI = 0.38–1.34; $I^2 = 0\%$; $P = 0.29$; 5 trials) or antiresorptive agents (RR = 0.59; 95%CI = 0.33–1.05; $I^2 = 0\%$; $P = 0.07$; 7 trials).

Lumbar spine BMD

Fifteen trials [16–18, 21–31, 41] assessed mean percent changes in the lumbar spine BMD (Fig. 4). Overall, when compared with monotherapy, combination therapy further improved lumbar spine BMD by 4.06% (95%CI = 2.60–5.53; $I^2 = 89.26\%$; 15 trials; Fig. 4). Our funnel plot and the statistical test showed no evidence of publication bias (additional fig. S2, Egger's test $P = 0.06$). Sensitivity analyses did not find any trials significantly affecting the pooled WMD (additional fig. S3). The meta-regression analyses did not show any statistically significant differences concerning treatment duration ($P = 0.24$ for slope, additional fig. S4).

As shown in the subgroup analyses, when compared with antiresorptive agents, combination therapy yielded a benefit of 6.14% lumbar spine BMD improvement (WMD = 6.14%; 95%CI = 4.07–8.22; $I^2 = 89.47\%$; Fig. 4). When compared with anabolic agents, combination therapy produced a benefit of 1.11% in lumbar spine BMD improvement (WMD = 1.11%; 95%CI = 0.26–1.96; $I^2 = 29.76\%$; Fig. 4). Findings

Table 1 Characteristics of the studies included in systematic review and meta-analyses

Study (year)	Sex	Experimental group (combination therapy)			Control group (monotherapy)			Duration (months)
		Number	Age (SD)	Intervention	Number	Age (SD)	Intervention	
Lane (1998)	Female	28	65.1 (9.6)	TPTD (25 μg/day) plus HRT	23	59.9 (10.2)	HRT	12
Reeve (2001)	Female	7	64.2 (10.9)	PTH 1-38 (35 μg/day) plus HRT	7	66.6 (7.8)	HRT	9
Cosman (2001)	Female	27	57.7 (8.8)	TPTD (25 μg/day) plus HRT	25	62.9 (7.5)	HRT	36
Black (2003)	Female	59	70.2 (6.8)	PTH 1-84 (100 μg/day) plus alendronate	60 119	70.7 (6.8) 69.4 (7.3)	Alendronate plus placebo PTH 1-84 (100 μg/day) plus placebo	12
Finkelstein (2003)	Male	25	58.0 (8.0)	TPTD (40 μg/day) plus alendronate	28 20	58.0 (7.0) 57.0 (9.0)	Alendronate TPTD (40 μg/day)	24
Deal (2005)	Female	69	66.6 (7.5)	TPTD (20 μg/day) plus raloxifene	68	66.1 (7.8)	TPTD (20 μg/day)	6
Cosman (2005)	Female	43	67.1 (7.6)	TPTD (25 μg/day) plus alendronate	40	67.4 (8.0)	Alendronate	15
Marie (2006)	Female	122	62.0 (7.6)	TPTD (40 μg/day) plus HRT	125	61.1 (7.4)	HRT	12
Cosman (2008)	Female	21	67.2 (9.6)	TPTD (25 μg/day) plus raloxifene	21	66.7 (7.9)	Raloxifene	12
Fogelman (2008)	Female	90	58.1 (6.2)	PTH 1-84 (100 μg/day) plus HRT	90	59.4 (6.8)	HRT plus placebo	24
Cosman (2009)	Female	47	68.3 (7.5)	TPTD (20 μg/day) plus raloxifene	49	68.6 (7.7)	TPTD (20 μg/day)	18
		52	67.8 (1.4)	TPTD (20 μg/day) plus alendronate	50	69.1 (1.4)	TPTD (20 μg/day)	
Finkelstein (2010)	Female	20	62.0 (7.0)	TPTD (40 μg/day) plus alendronate	29 20	64.0 (6.0) 65.0 (7.0)	Alendronate TPTD (40 μg/day)	24
Cosman (2011)	Female	137	65.0 (8.8)	TPTD (20 μg/day) plus zoledronate	137 138	66.1 (9.0) 63.8 (9.1)	Zoledronate TPTD (20 μg/day) plus placebo	12
Schafer (2012)	Female	22	62.7 (4.1)	PTH 1-84 (100 μg/day) plus placebo	22	61.2 (4.1)	3 months PTH 1-84 (100 μg/day) and 3 months ibandronate plus placebo	6
Muschitz (2013)	Female	37	69.7 (7.5)	TPTD (20 μg/day) plus raloxifene	47	71.7 (9.3)	TPTD (20 μg/day)	9
		41	71.6 (8.5)	TPTD (20 μg/day) plus alendronate				
Walker (2013)	Male	10	56.7 (15.5)	TPTD (20 μg/day) plus risedronate	10 9	54.0 (6.32) 51.6 (11.7)	Risedronate plus placebo TPTD (20 μg/day) plus placebo	18
Tsai (2014)	Female	30	65.9 (9.0)	TPTD (20 μg/day) plus denosumab	31 33	65.6 (7.9) 66.3 (8.3)	TPTD (20 μg/day) Denosumab	24
Idolazzi (2016)	Female	19	78.0 (5.0)	TPTD (20 μg/day) plus denosumab	20 20	76.0 (5.0) 76.0 (5.0)	TPTD (20 μg/day) Denosumab	12
Nakamura (2017)	Female	17	75.1 (7.4)	TPTD (20 μg/day/day) plus denosumab	13	75.5 (5.0)	Denosumab	24

SD standard deviation, *TPTD* teriparatide, *PTH* parathyroid hormone, *HRT* hormone replacement therapy

from the antiresorptive agent and the anabolic agent groups were significantly different ($P < 0.01$ for interaction).

Total hip BMD

Fifteen trials [16–18, 21–31, 41] assessed mean percent changes in total hip BMD (Fig. 5). Overall, combination therapy yielded a benefit of 1.89% total hip BMD improvement over monotherapy (WMD = 1.89%; 95%CI = 1.25–2.53; $I^2 = 74.26\%$; 15 trials; Fig. 5). The funnel plot and statistical test showed no evidence of publication bias (additional fig. S5, Egger's test $P = 0.33$). Sensitivity analyses did not find any trials significantly affecting the pooled WMD (additional fig. S6). The meta-regression analyses found statistically

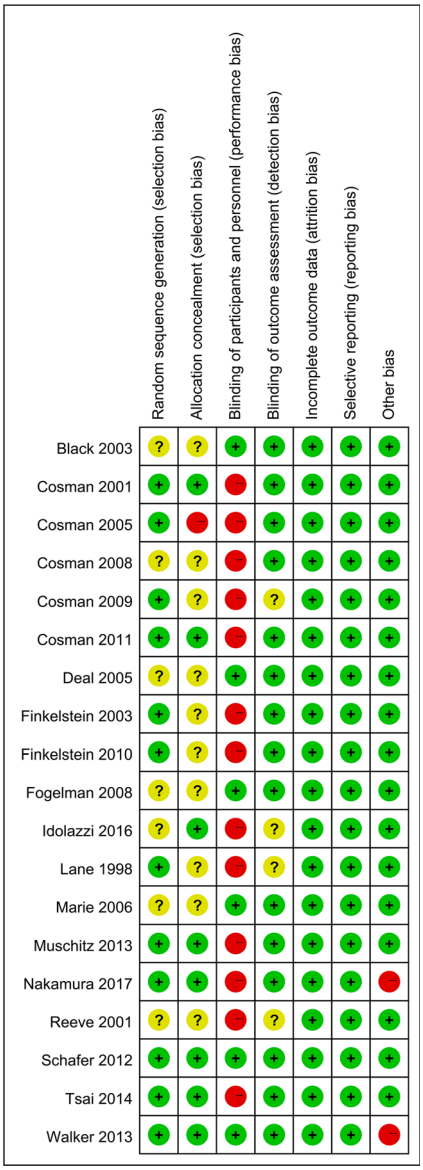

Fig. 2 The methodological quality of the RCTs. Risk of bias summary. "+" means low risk; "?" means unclear risk; "-" means high risk

significant differences in association with treatment duration ($P = 0.02$ for slope, additional fig. S7).

The subgroup analyses revealed that in comparison with anabolic agents, combination therapy increased total hip BMD by 2.27% (95%CI = 1.39–3.14; $I^2 = 68.36\%$; Fig. 5), while in comparison with antiresorptive agents, combination therapy could also increase total hip BMD by 1.46% (95%CI = 0.52–2.4; $I^2 = 75.45\%$; Fig. 5). No statistically significant differences were found between these two groups ($P = 0.22$ for interaction).

Adverse events

Out of the 19 RCTs of combination therapy for osteoporosis included in the pooled analyses, 17 publications reported assessment of adverse events, while the other 2 did not [25, 34]. Most of the included studies suggested the combination therapy to be well tolerated. The rate of total adverse events did not differ between treatment groups except for adverse events associated with PTH analogs such as headaches, injection-site tenderness, and nausea, which were statistically more common in patients on combination therapy than those receiving antiresorptive agents alone [22, 24, 31, 32] (Table 2).

Serious adverse events, assessed by nine studies, had no significant differences among groups in most of these trials [16, 23, 24, 30], were considered unrelated to the combination therapy [17, 27, 54], or were not reported in some studies [28, 31, 41] (Table 2).

Quality of evidence

The quality of evidence was judged as low regarding the association of combination therapy with fracture risk reduction, which was downgraded from high due to the risk of bias, reporting bias, and imprecision of results (additional table S1).

The quality of evidence was judged as low concerning the association of combination therapy with improvement of BMD (both in the lumbar spine and the total hip) in patients with osteoporosis, which was downgraded from high due to risk of bias and the inconsistency of results (additional table S1).

Discussion

We performed a review of 19 RCTs, involving a total of 2177 patients, providing low-quality evidence that in patients with osteoporosis, combination therapy with PTH analogs and antiresorptive agents was superior to monotherapy regarding fracture risk reduction and BMD improvement, without an increased risk of serious adverse events. Study heterogeneity may be partly explained by the type of anti-osteoporosis drugs and treatment durations implemented.

Early reviews [35–40] discouraged combination therapy since two key older studies [16, 32] suggested bisphosphonates appeared to blunt the anabolic action of PTH. There may be several possible explanations for this observation. Firstly, the type of PTH analog used might affect the effect of the combination therapy. Black et al. [16] used PTH 1-84 in combination with alendronate for 12 months, reporting no significant differences in BMD changes between the combination group and the alendronate alone group. Similarly, Fogelman et al. [24] implemented PTH 1-84 and HRT for 12 months, finding no differences between the combination group and the HRT group for BMD changes on the total hip and femoral neck. Unlike combination therapy of PTH 1-84 and antiresorptive agents, the combination of

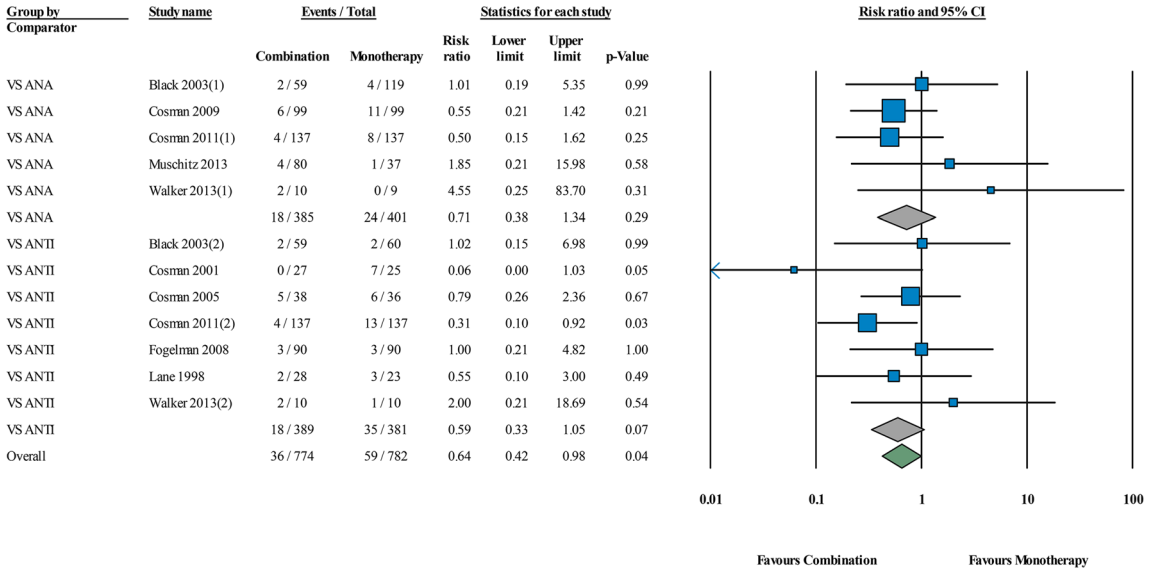

Fig. 3 Forest plot for the fracture events. ANA, anabolic agents; ANTI, antiresorptive agents

teriparatide (PTH 1-34) and antiresorptive agents appears to yield greater benefits for BMD changes than when compared with risedronate [29], denosumab [27, 41], alendronate [22], or HRT [21]. Thus, teriparatide (PTH 1-34) may be better suited than PTH 1-84 for use in combination therapy. On the other hand, the histories of anti-osteoporosis treatments might affect the impact of combination therapy. Two similar studies [32, 33] suggested that teriparatide 40 μg in combination with alendronate showed a statistical BMD reduction in both the lumbar spine and total hip when compared with teriparatide. It should be noted the design of these studies [32, 33] was different to the others, as they both were three-arm trials. According to their study design documentation [32, 33], "patients were assigned to receive alendronate alone (group 1), teriparatide alone (40 μg, group 2), or both (group 3). Alendronate was started at the baseline and continued for 30 months in groups 1 and 3. Teriparatide was started at the 6-month visit and continued for 24 months in groups 2 and 3.

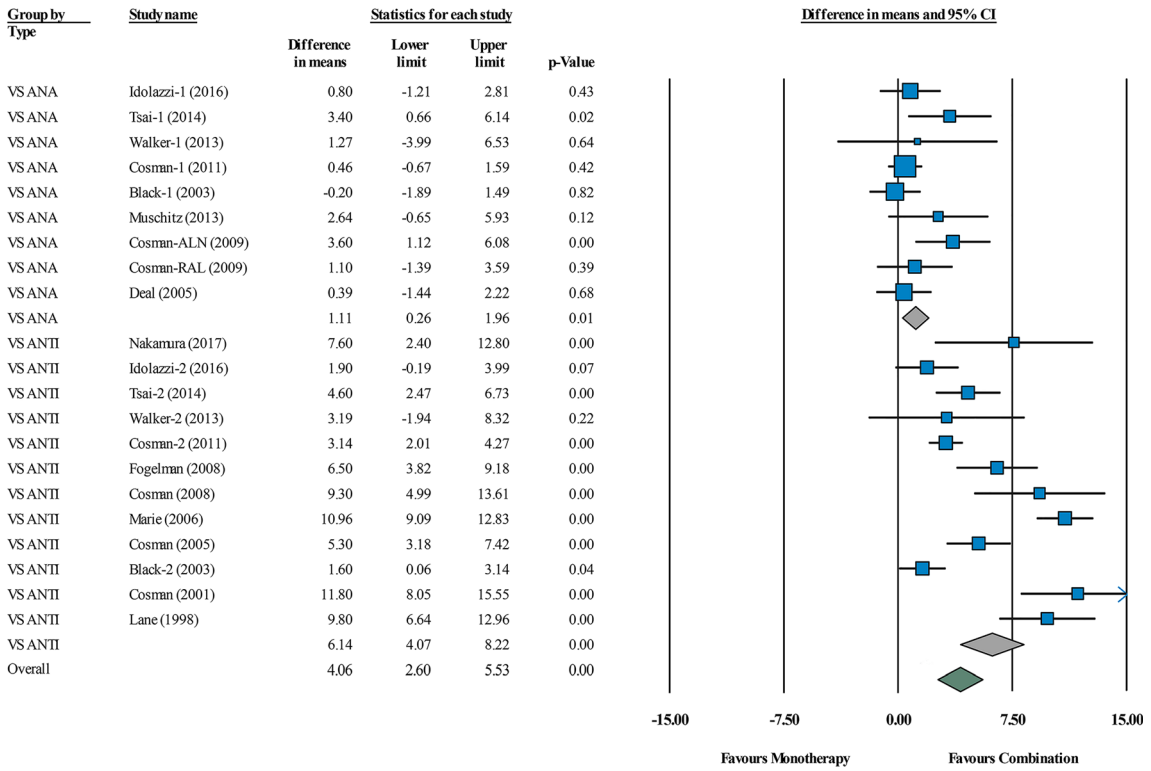

Fig. 4 Forest plot for the lumbar spine BMD changes. ANA, anabolic agents; ANTI, antiresorptive agents

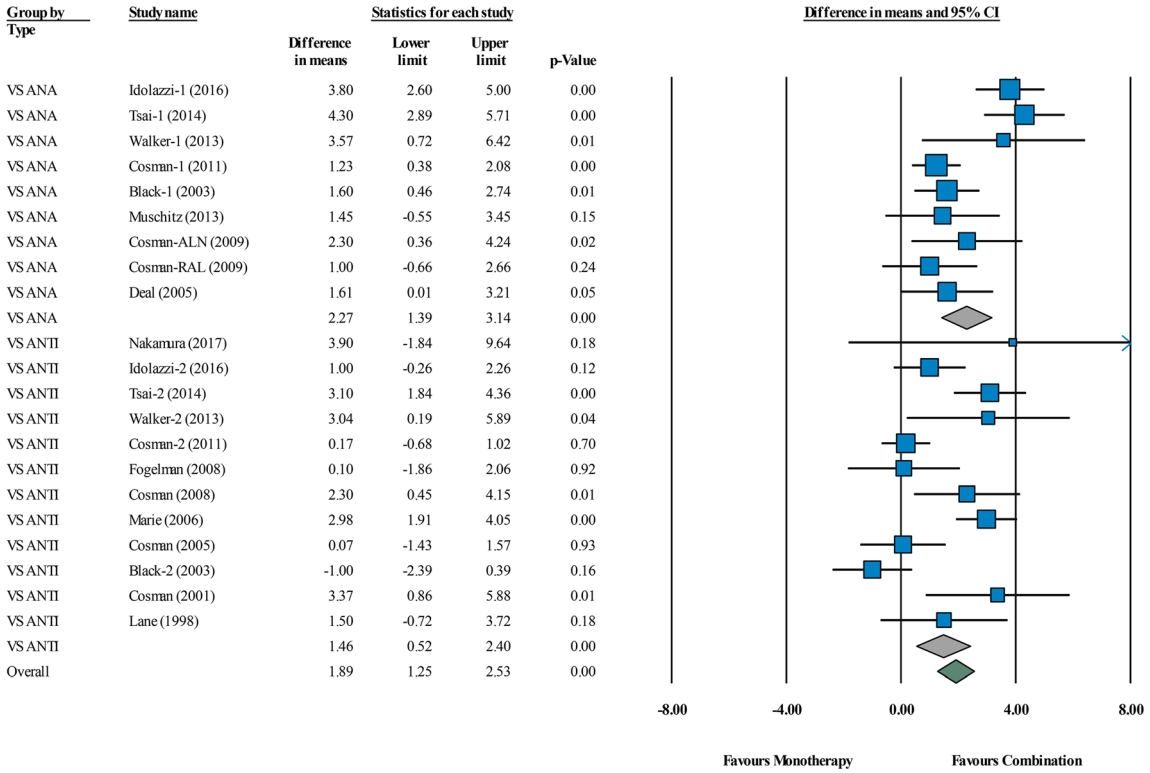

Fig. 5 Forest plot for the total hip BMD changes. ANA, anabolic agents; ANTI, antiresorptive agents

For group 3, BMD from months 0 to 30 were compared with group 1 and BMD from months 6 to 30 were compared with group 2." Based on this study design, group 3 had a 6-month prior antiresorptive treatment with no washout period. Because prior antiresorptive treatment may blunt the BMD response to teriparatide [22, 55], which may explain the statistically significant reduction in BMD reduction seen with teriparatide in comparison with the combination of teriparatide and alendronate. As data is limited in this regard, further studies are needed to clarify this phenomenon [32, 33].

Although recent reviews have acknowledged the additive effect of combination therapy [10, 20, 56–59], this is usually limited to superior total hip BMD and not superior lumbar spine BMD [56–58]. Owing to the greater number of eligible RCTs in our study, with rigorous pooled analyses, we were able to confirm the clinical value of combination therapy. We determined that not only hip BMD but also spine BMD could be further improved by combination therapy. Moreover, we determined combination therapy had an advantage on fracture risk reduction over monotherapy, which had not been reported in previous reviews.

We must, however, acknowledge the limitations of our study. First, there were methodological limitations in the quality of the original studies, such as unclear randomization methods and inadequate concealment of treatment allocation. The quality of evidence was downgraded due to these methodological limitations. Second, we cannot rule out the possibility of publication bias for some results, although no statistical evidence for it was detected. Third, although we made subgroup and meta-regression analyses to explore heterogeneity and used random-effects models to account for heterogeneity among studies, unexplained heterogeneity remained in the analyses of some outcomes. This may be explained by the utilization of different types of antiresorptive agents [20] and the different histories of anti-osteoporosis treatments [57, 58]. Finally, although our study determined combination therapy had an advantage over monotherapy in fracture risk reduction, the power of the pooled results might be not enough to evaluate anti-fracture efficacy due to the limited availability of studies. Therefore, future larger studies are needed to confirm this fracture-reduction benefit. Given these limitations, the results of this meta-analysis should be interpreted cautiously.

To improve knowledge about the advantages and disadvantages of combination therapy, some important research questions must be answered. First, since meta-regression analyses found a close association between treatment duration and BMD changes, long-term follow-up trials (18 to 24 months) are needed to identify the ideal duration for combination therapy. Second, among the included trials, only a few studies reported fracture data, but all of them were unpowered to detect differences of fracture endpoints. Although our study determined combination therapy had an advantage over monotherapy regarding fracture risk reduction, this should be interpreted with caution. Additional studies with larger sample size and longer follow-up are needed to evaluate the

Table 2 Adverse events reported of combination therapy for osteoporosis

Study (year)	Combination therapy		Monotherapy		Adverse events
	Sample size	Intervention	Sample size	Intervention	
Lane (1998)	28	TPTD (25 μg/day) plus HRT	23	HRT	Treatments were well tolerated; mild headaches and mild injection-site tenderness were reported
Cosman (2001)	27	TPTD (25 μg/day) plus HRT	25	HRT	Treatment were well tolerated, mild discomfort at injection sites and back pain were reported
Black (2003)	59	PTH 1-84 (100 μg/day) plus alendronate	60 119	Alendronate plus placebo PTH 1-84 (100 μg/day) plus placebo	The rates of adverse events did not differ according to treatment group; serious adverse events were not considered related to study treatments
Finkelstein (2003)	25	TPTD (40 μg/day) plus alendronate	28 20	Alendronate TPTD (40 μg/day)	Has a table of adverse effects by group; there were several differences among the treatment groups, such as joint pain, back pain, and dizziness, but these differences were generally small
Deal (2005)	69	TPTD (20 μg/day) plus raloxifene	68	TPTD (20 μg/day)	Except hot flushes were more frequently reported in the combination therapy group and vomiting was more frequently reported in the TPTD group, the rates of adverse events did not differ according to treatment group; muscle spasm was the only serious adverse event considered to be possibly related to study drug
Cosman (2005)	43	TPTD (25 μg/day) plus alendronate	40	Alendronate	Has a table of adverse effects by group; musculoskeletal symptoms and elevated urinary calcium were reported differences among the treatment groups
Marie (2006)	122	TPTD (40 μg/day) plus HRT	125	HRT	Except nausea, elevated serum calcium, and leg cramp were more frequently reported in the combination therapy group, the rates of adverse events did not differ according to treatment group; no serious adverse events were discovered during the study
Cosman (2008)	21	TPTD (25 μg/day) plus raloxifene	21	Raloxifene	Treatments were well tolerated
Fogelman (2008)	90	PTH 1-84 (100 μg/day) plus HRT	90	HRT plus placebo	Has a table of adverse effects by group; the overall incidence of adverse events was similar between the groups
Cosman (2009)	47 52	TPTD (20 μg/day) plus raloxifene TPTD (20 μg/day) plus alendronate	49 50	TPTD (20 μg/day) TPTD (20 μg/day)	In the alendronate stratum, asthenia and contusion were reported more frequently in the TPTD group; in the raloxifene stratum, sinusitis was reported more frequently in the combination therapy group; serious adverse events had no significant differences among groups
Finkelstein (2010)	20	TPTD (40 μg/day) plus alendronate	29 20	Alendronate TPTD (40 μg/day)	There were no significant differences in the frequency with which any adverse symptoms were reported (data not shown)
Cosman (2011)	137	TPTD (20 μg/day) plus zoledronate	138 137	TPTD (20 μg/day) plus placebo Zoledronate	There were no significant between-group differences in adverse event rates; serious adverse events were not considered related to study treatments
Schafer (2012)	22	PTH 1-84 (100 μg/day) plus placebo	22	6 months sequential therapy	There were no significant between-group differences in adverse events; serious adverse events were not considered related to study treatments
Muschitz (2013)	37 41	TPTD (20 μg/day) plus raloxifene TPTD (20 μg/day) plus alendronate	47	TPTD (20 μg/day)	The treatments were generally well tolerated; no serious adverse events were discovered during the study
Walker (2013)	10	TPTD (20 μg/day) plus risedronate	10 9	Risedronate plus placebo TPTD (20 μg/day) plus placebo	Has a table of adverse effects by group; therapies were well tolerated with no between-group differences adverse event frequency
Tsai (2014)	30	TPTD (20 μg/day) plus denosumab	31 33	TPTD (20 μg/day) Denosumab	The treatments were generally well tolerated; all serious adverse events were judged unrelated to the study treatments.
Nakamura (2017)	17	TPTD (20 μg/day/day) plus denosumab	13	Denosumab	Serious adverse events not reported during the study

TPTD teriparatide, *PTH* parathyroid hormone, *HRT* hormone replacement therapy

fracture-reduction efficacy of combination therapy. Third, although we did not find an increased risk of any new adverse events or other serious adverse events associated with combination therapy, a potential risk of more adverse events cannot be excluded based on our review. Future research should carefully track adverse events and clearly report them for further pooled analyses.

For osteoporosis, the treatment target should be an acceptably low risk of fracture, which should guide all clinical decisions [60–62]. Although using fracture risk reduction as a goal of treatment may be a better choice, more validated tools for fracture risk assessment are warranted [62, 63]. A T-score > − 2.5 to − 2.0 at the femoral neck, total hip, or lumbar spine by DXA was also recommended as the treatment goal [62, 64]. Notoriously, achieving these goals with currently approved monotherapy may not be possible for certain patients [64]. Our study provided evidence that combination therapy may be a more potent strategy for patients who are at high risk of fracture or have unsatisfying responses to monotherapy.

When using combination therapy as the treat-to-target strategy, clinicians should pay attention to the treatment sequence. For treatment-naïve patients, combination therapy should be

considered as the initial therapy if initial treatment with the current available monotherapy offers a low probability of reaching the target T-score of > − 2.5 to − 2.0 or reaching the goal of fracture risk reduction. On the other hand, for patients who are already on a bisphosphonate with an unsatisfying response, or if new fractures occur, switching to a more potent drug should be considered [64]. For these patients, the prevalent paradigm is to switch to an anabolic agent. However, trials suggest antiresorptive treatment may blunt the BMD response to anabolic agents [55, 65] and cause transient bone loss [66]. Thus, instead of anabolic agents alone, combination therapy may be an ideal alternative approach for patients who have failed previous treatment with antiresorptive agents. In addition, discontinuation of non-bisphosphonate drugs has been linked to a rapid decline in BMD [67]. Therefore, when clinicians consider stopping combination therapy, treatment should generally be continued with an agent to preserve BMD, possibly the antiresorptive agent used in the combination therapy [27].

Conclusion

Among patients with osteoporosis, combination therapy of PTH analogs and antiresorptive agents was superior to monotherapy in terms of BMD improvement at the lumbar spine and total hip, without an increased risk of serious adverse events. Combination therapy may also have an advantage over monotherapy regarding fracture risk reduction; however, additional larger studies are needed to confirm this finding.

Compliance with ethical standards

Conflicts of interest None.

Ethics approval and consent to participate Not applicable.

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