Systematic Review and Meta-Analysis

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The effect of sequential therapy for postmenopausal women with osteoporosis

A PRISMA-compliant meta-analysis of randomized controlled trials

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Abstract

Background: Osteoporosis, more likely to occur in postmenopausal women, is a chronic condition that usually requires a long-term treatment strategy, but the use of either antiresorptive or anabolic drugs should be limited to 18 to 24 months. Discontinuing antiosteoporosis drugs may result in rapidly declining bone mineral density (BMD). Therefore, many patients are treated with the sequential use of 2 or more drugs. However, whether switching treatment from anabolic to antiresorptive drugs or the reverse could maintain or further increase BMD; and whether the sequential therapy could outperform the monotherapy under the same treatment duration still remains unclear. Nowadays, no firm conclusions were drawn.

Methods: We searched Medline, Embase, and Cochrane Library from January 1, 1974 until February 1, 2016 to identify all randomized controlled trials for evaluating the effectiveness of sequential therapy of antiresorptive and anabolic drugs in postmenopausal osteoporosis women with the BMD changes of lumbar spine, femoral neck, and total hip as the outcomes. We evaluated the methodological quality and abstracted relevant data according to the Cochrane Handbook.

Results: Eight trials involving 1509 patients were included. The pooled data showed that after switching treatment, the alternative drugs maintained the BMD and significantly increased the percentage change in BMD at the lumbar spine (MD, 3.59; 95% CI, 2.26–4.93), femoral neck (MD, 1.44; 95% CI, 0.60–2.27), and total hip (MD, 1.24; 95% CI, −0.12 to 2.60), although change in BMD was not significantly increased at the total hip. The sequential therapy significantly increased BMD from baseline at the lumbar spine (SMD, 0.59; 95% CI, 0.26–0.91), femoral neck (SMD, 0.22; 95% CI, 0.06–0.37), and total hip (SMD, 0.28; 95% CI, 0.01–0.56).

Conclusions: After switching treatment, sequential therapy further increased BMD. The sequential therapy showed a more significant improvement in BMD compared with any anti-resorptive drug given for the same treatment duration and was as effective as anabolic drugs. Thus, sequential therapy may be recommended as an effective treatment for osteoporotic women. However, more randomized controlled trials are still needed to determine the best sequence and the most appropriate drugs of sequential therapy.

Abbreviation: BMD = bone mineral density, CI = confidence interval, MD = mean difference, PTH = parathyroid hormone, RCT = randomized controlled trials, SMD = standard mean difference.

Keywords: anabolic drugs, antiresorptive drugs, osteoporosis, sequential therapy

Editor: Pricivel Carrera.

SL and HL contributed equally to this work.

Author Contributions: PT conceived and designed the experiments, and reviewed the draft. SL and HL performed the experiments, analyzed the data, wrote the paper, prepared figures and tables, and reviewed the draft. GW, ZL, and LZ performed the experiments and analyzed the data. ML and LZ contributed to design the search strategy, prepared figures and tables, and reviewed the draft.

This meta-analysis received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2016) 95:49(e5496)

Received: 30 May 2016 / Received in final form: 9 October 2016 / Accepted: 4 November 2016

http://dx.doi.org/10.1097/MD.0000000000005496

1. Introduction

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue.[1] Due to the high mortality and morbidity, osteoporosis-related fractures have become a formidable public health threat, especially in postmenopausal women.[2–4] Currently, medications approved for the treatment of osteoporosis are mainly divided into 2 categories, including antiresorptive and anabolic drugs.[4]

The most common medications approved for the treatment of postmenopausal osteoporosis are antiresorptive drugs, including bisphosphonates, raloxifene (selective estrogen receptor modulator), and denosumab (receptor activator of nuclear factor κB ligand inhibitor). Anti-resorptive drugs could increase bone mineral density (BMD) and reduce the risk of fractures by inhibiting bone resorption.[5] However, antiresorptive drugs cannot fully restore bone mass or structure. Alternatively, anabolic drugs could stimulate bone formation and resorption,[6,7] improve trabecular and cortical microarchitecture,[8,9] and reduce the risk of vertebral and nonvertebral fractures.[6] Anabolic drugs, including parathyroid hormone (PTH), teriparatide, and the recombinant full-length molecule PTH, are considered second-line treatment for osteoporosis,[10,11] specifically in patients with incident fractures under antiresorptive drugs or intolerance to antiresorptive drugs.

Osteoporosis is a chronic condition that usually requires a long-term management and its first-line strategy is the use of antiresorptive drugs.[12,13] However, chronic administration of antiresorptive drugs might cause an increased risk of atypical femoral fracture,[14,15] osteonecrosis of jaw,[16,17] fatal strokes, and venous thromboembolic events.[18] A study about the potential higher risk of osteosarcoma in rats[19] indicated treatment of anabolic drugs is limited to 24 months. Current guidelines recommend that long-term use of either antiresorptive or anabolic drugs should be limited to 18 to 24 months.[20,21] Discontinuation of antiosteoporosis drugs, however, results in a rapid decline in BMD.[22–25]

Thus, a sequential use of several drugs may be required due to the required short duration of monotherapy with antiresorptive or anabolic drugs. Nevertheless, it is unclear whether switching treatment from anabolic to antiresorptive drugs or the reverse could maintain or further increase BMD and whether the sequential therapy could outperform the monotherapy under the same treatment duration. To uncover these 2 questions, we performed a meta-analysis of randomized controlled trials (RCTs), comparing the different effects between sequential therapy and monotherapy, in postmenopausal osteoporosis women with the BMD changes of lumbar spine, femoral neck, and total hip as the outcomes. Postmenopausal osteoporosis women were defined as women aged >45 years with postmenopausal osteoporosis. Women with secondary osteoporosis, suffering from chronic kidney disease, malignancy, or other known metabolic bone diseases, were not included. We hypothesized that after switching treatment, sequential therapy may maintain or further increase BMD, and the sequential therapy may dramatically improve the BMD compared with any antiresorptive drug given for the same treatment duration, and may even be as effective as anabolic drugs.

2. Methods

This meta-analysis was performed according to the Cochrane Handbook recommendations and was reported on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] There was no registered protocol. This study was not a human or animal experiment, so no ethical approval was needed.

2.1. Search strategy

We searched Medline, Embase, and Cochrane Library from January 1, 1974 until February 1, 2016, with terms relevant to "osteoporosis," "bisphosphonates," "denosumab," "raloxifene," "teriparatide," "parathyroid hormone," together with either "randomized controlled trial" or "controlled clinical trial." We also searched ClinicalTrials.gov registry (www.clinicaltrials.gov) and screened the references of both retrieved articles and relevant reviews to further identify potentially eligible trials. Two authors (SL, GW) independently searched the literatures with no language restriction and in duplicate. The full search strategies used in MEDLINE, EMBASE, and Cochrane Library databases are provided in Supplemental Digital Content (SDC) 1, http://links.lww.com/MD/B458.

2.2. Study selection

Two authors (SL, HL) independently screened the full texts of potentially relevant studies in accordance with the inclusion criteria. Any discrepancy was resolved by discussion and consensus.

The inclusion criteria were as follows: postmenopausal women with osteoporosis were defined as postmenopausal women aged >45 years with a high risk of fracture. High fracture risk is defined as follows: T score ≤ -2.5 at the spine, hip, or femoral neck; T score ≤ -2.0 with at least one BMD-independent risk factor; or T score ≤ -1.0 with a history of fragility fracture; at least 1 of 3 outcomes was reported: changes in BMD at the lumbar spine, femoral neck, or total hip; BMD should be measured by dual-energy X-ray absorptiometry; RCTs relevant to the sequential therapy of anabolic and antiresorptive drugs. The active treatment arm should be a sequential therapy including switching treatment from antiresorptive to anabolic drugs, from anabolic to antiresorptive drugs, from single drug to combined drugs, or from combined drugs to single drug. The control treatment arm should be a placebo therapy or a monotherapy with any single antiosteoporosis drug. In addition, trials comparing the effects of different sequential therapies were also included. In this study, switching treatment from anabolic to antiresorptive drugs or to combined drugs was defined as the active treatment arm, while other methods were defined as the control treatment arm.

Patients with secondary osteoporosis suffering from chronic kidney disease, malignancy, or other known metabolic bone diseases were excluded. Case-control studies, cohort studies, case series, nonrandom designed trials, repeated reports, and trials without the outcomes of interest or enough information were excluded as well.

2.3. Data extraction

Information was carefully extracted from all eligible publications by 2 authors independently (SL, HL or GW). One author (SL) extracted the data that were double-checked by a second author (HL or GW). Discrepancies were resolved through discussion. The following characteristics were extracted from each study: first author, year of publication, number of patients, study design, interventions, and outcomes. The extracted data were entered into a standardized Excel file (Microsoft Corporation; 15700 NE 39th St Redmond, WA 98052). We also sought supplementary

appendixes from the included trials or contacted the authors to verify the extracted data and obtain the missing data. The predefined primary outcome was the change in BMD from switching at the lumbar spine, femoral neck and total hip, and the secondary outcome was the change in BMD from baseline at the lumbar spine, femoral neck, and total hip.

When there were multiarm trials in the included trials, we divided the multiarm trials into several two-pairwise trials according to the meta-analysis requirements. When there were various methods of sequential therapy in the included trials, the switching treatment from anabolic to antiresorptive drugs or to combined drugs was defined as the experiment group and other methods as the control group.

2.4. Risk-of-bias assessment

Two authors (SL, LZ) independently assessed the risk of bias using the Cochrane risk-of-bias tool.[27] Seven categories of bias were specified: random-sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias. Each category included 3 levels: low risk, unclear risk, and high risk.

2.5. Grading quality of evidence

Two authors (SL, LZ) independently evaluated the quality of evidence for primary and secondary outcomes according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[28] for risk of bias, inconsistency, indirectness, imprecision, and publication bias. The assessment results were classified as very low, low, moderate, or high. Summary tables were constructed with GRADE Profiler 3.6.

2.6. Statistical analysis

Data were pooled using mean differences (MDs) and 95% confidence intervals (CIs). Data in different units were pooled using standard mean differences (SMDs) and 95% CIs. The heterogeneity of results from individual studies was assessed using Cochran Q statistic, I^2 statistic (I^2 >50% indicates significant heterogeneity), and P values (P<0.10 indicates significant heterogeneity).[29] A fixed-effect model was applied in the meta-analysis, but in case of significant heterogeneity, a random-effect model was used.[30] Publication bias was assessed from a visual inspection of funnel plot. All tests were 2-tailed and P<0.05 was deemed significant. All statistical analyses were performed with RevMan 5.3 (Nordic Cochrane Centre).

3. Results

3.1. Search results

A total of 1172 articles were obtained through electronic and hand searches. We excluded 1160 irrelevant articles after screening titles and abstracts, and thus retrieved 12 articles, all written in English, for further assessment. Finally, 8 studies[31–38] fulfilled our inclusion criteria. Four trials were excluded due to report of repeated data,[39] nonrandomization[40,41] or failure in matching to the aim of our study.[42]Figure 1 illustrates the selection process.

3.2. Characteristics of included trials

The main characteristics of the included trials are summarized in Table 1. These trials were published from 2000 to 2015 and involved in total 1509 patients, with the sample sizes ranging from 60 to 329. Six trials[31–34,37,38] had more than 2 groups. All patients received oral calcium and vitamin D supplements daily. The anabolic drugs included teriparatide and PTH, with the doses ranging from 20 to 100 μg. The antiresorptive drugs included tibolone, raloxifene, salmon calcitonin, clodronate, risedronate, alendronate, and denosumab. Four trials[31,32,34,37] included combined drugs (defined as concomitant use of anabolic and antiresorptive drugs) in the sequential therapy switching from single drug (anabolic or anti resorptive drugs) to combined drugs or the reverse.

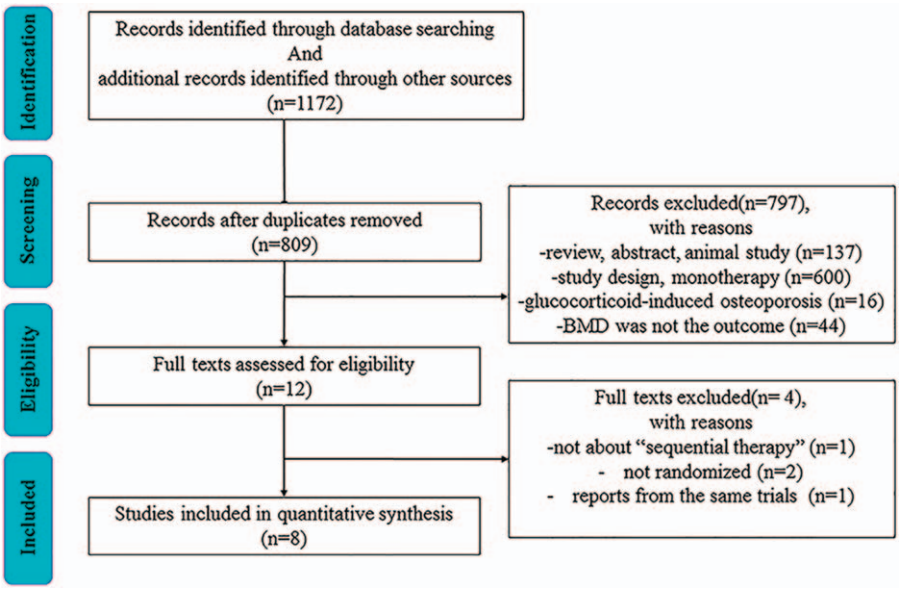

Figure 1. Flow diagram shows the process of literature selection.

Table 1

Characteristics of included randomized controlled trials.

Study (Year)	Sex	Age (SD)	Design	No. of each arm	Basic intervention	Intervention of each arm			
						First stage	Time (mo)	Second stage	Time (mo)
Rittmaster 2000	Female	64 (5)	4 arm	12	Calcium 500 mg; vitamin D 400 IU daily	50 μg PTH daily	12	Switch to 10 mg alendronate daily	12
				17		75 μg PTH daily		Switch to 10 mg alendronate daily	
				18		100 μg PTH daily		Switch to 10 mg alendronate daily	
				19		Placebo		Switch to 10 mg alendronate daily	
Black 2005	Female	69 (7)	4 arm	60	Calcium 500 mg; vitamin D 400 IU daily	Full-length PTH 100 μg daily	12	Switch to placebo	12
				59		Full-length PTH 100 μg daily		Switch to 10 mg alendronate daily	
				59		PTH+alendronate		Switch to 10 mg alendronate daily	
				60		10 mg alendronate daily		Continued to 10 mg alendronate daily	
Gonnelli 2006	Female	71 (7)	2 arm	30	Calcium 1000 mg; vitamin D 400 IU daily	Antiresorptive treatment	At least 12	Switch to 20 μg teriparatide daily	12
				30		Antiresorptive treatment		Continue the antiresorptive treatment	
Adami 2008	Female	67 (6)	2 arm	172	Calcium 500 mg; vitamin D 400 to 800 IU daily	20 μg teriparatide daily	12	Switch to 60 mg raloxifene daily	12
				157		20 μg teriparatide daily		Switch to placebo	
Cosman 2009	Female	68 (9)	4 arm	50	Calcium 500 mg; vitamin D 400 to 800 IU daily	10 mg alendronate daily	At least 18	Switch to 20 μg teriparatide daily	18
				52		10 mg alendronate daily		Add to 20 μg teriparatide daily	
				49		60 mg raloxifene daily		Switch to 20 μg teriparatide daily	
				47		60 mg raloxifene daily		Add to 20 μg teriparatide daily	
Eastell 2009	Female	69 (7)	3 arm	305	Calcium 500 mg; vitamin D 400 to 800 IU daily	20 μg teriparatide daily	12	Continued to 20 μg teriparatide daily	12
				100		20 μg teriparatide daily		Switch to 60 mg raloxifene daily	
				102		20 μg teriparatide daily		Switch to no active treatment	
Christian 2013	Female	71 (9)	3 arm	47	Calcium 1000 mg; vitamin D 800 IU	20 μg teriparatide daily	9	Continued to 20 μg teriparatide daily	9
				41		20 μg teriparatide daily		Add to 10 mg alendronate daily	
				37		20 μg teriparatide daily		Add to 60 mg raloxifene daily	
Leder 2015	Female	66 (7)	3 arm	27	Calcium and vitamin D daily	20 μg teriparatide daily	24	Switch to 60 mg denosumab every 6 months	24
				27		60 mg denosumab every 6 months		Switch to 20 μg teriparatide daily	
				23		Teriparatide +denosumab		Switch to 60 mg denosumab every 6 months	

PTH = parathyroid hormone.

3.3. Risk-of-bias assessment

Figures 2 and 3 summarize the details of risk of bias. Random sequence generation was adequately reported in all trials. Allocation concealment was adequately reported in 3 trials[32,33,37] but was unclear in the remaining trials.[31,34–36,38] Seven trials[31–36,38] were open-label design, which might cause performance bias. However, the effects whether or not the participants and investigators were blind on the change in BMD were limited. Blinding of outcome assessment was adequately reported in 6 trials[31,33,35–38] and unclear in 2 trials.[32,34] Inadequate information was found to assess the presence of other bias in the included trials.

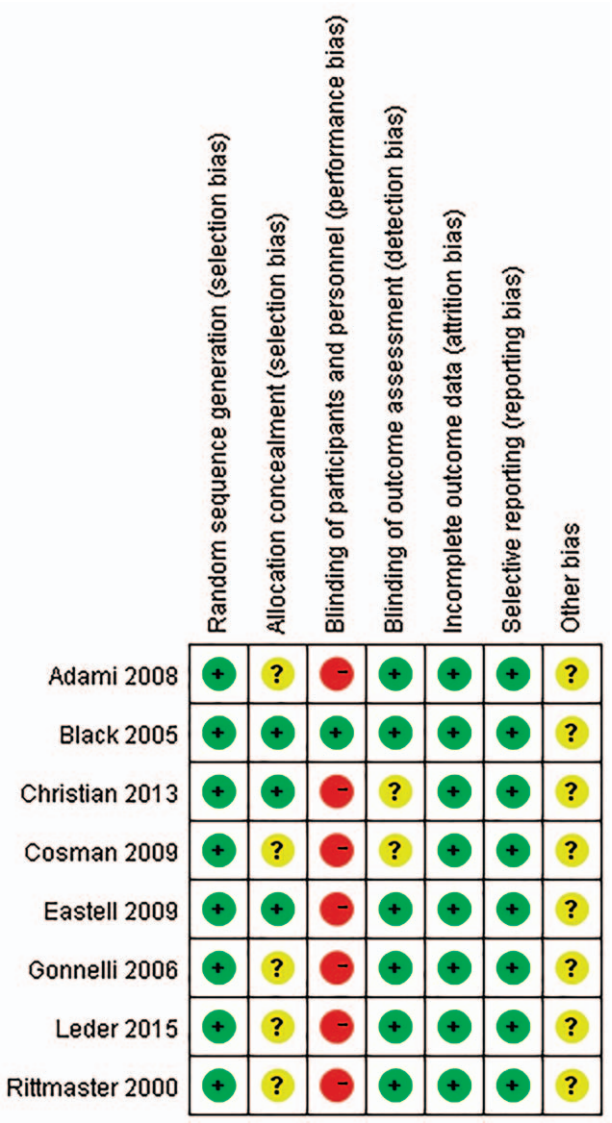

Figure 2. Risk of bias graph. Risk of bias summary. "+" means low risk; "?" means unclear risk; "−" means high risk.

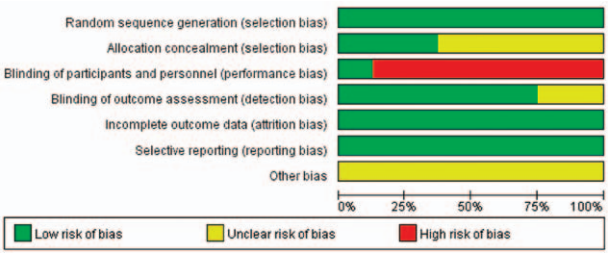

Figure 3. Risk of bias summary.

3.4. Percentage change in BMD from switching

This analysis involved 6 trials[32–37] with a total of 931 patients. After switching treatment, the alternative drugs maintained the BMD and significantly increased the change in BMD at the lumbar spine (MD, 3.59; 95% CI, 2.26–4.93; $I^2=72\%$; $P<0.01$), femoral neck (MD, 1.44; 95% CI, 0.60–2.27; $I^2=27\%$; $P<0.01$), and total hip (MD,1.24; 95% CI, −0.12 to 2.60; $I^2=73\%$; $P=0.07$), although did not significantly increase the change in BMD at the total hip (Fig. 4).

As $I^2=72\%$ indicates significant heterogeneity, we further performed a sensitivity analysis and found 1 trial[37] significantly affected the pooled MD at the lumbar spine, after it was omitted, there was no significant heterogeneity (MD, 2.93; 95% CI, 2.26–3.64; $I^2=9\%$; $P<0.01$). Similarly, at the total hip, $I^2=73\%$ indicates significant heterogeneity, and a sensitivity analysis was performed as well. One[36] trial significantly affected the pooled MD, after omitting it, there was no significant heterogeneity (MD, 1.80; 95% CI, 0.81–2.80; $I^2=41\%$; $P<0.01$).

Furthermore, subgroup analyses of BMD changes at both the lumbar spine (Fig. 5) and total hip (SDC 2) from switching were performed based on the different methods of sequential therapy. Results showed that the alternative drugs maintained the BMD and significantly increased the change in BMD at the lumbar spine after switching treatment to antiresorptive drugs (MD, 3.96; 95% CI, 1.82–6.11), or to anabolic drugs (MD, 5.6; 95% CI, 2.86–8.34), even to combination of antiresorptive and anabolic drugs (MD, 2.43; 95% CI, 0.89–3.98). Similarly, the results showed that the alternative drugs maintained the BMD and significantly increased the change in BMD at the total hip after switching treatment to antiresorptive drugs (MD, 2.33; 95% CI, −0.02 to 4.68) or to combination of antiresorptive and anabolic drugs (MD, 1.44; 95% CI, 0.38–2.50), but not to anabolic drugs (MD, −2; 95% CI, −3.86 to −0.14).

3.5. Percentage change in BMD from baseline

The analysis involved 6 trials[31–33,35,37,38] with a total of 1248 patients. The sequential therapy of switching treatment from anabolic to antiresorptive or combined drugs, compared with the control group, significantly increased BMD from baseline at the lumbar spine (SMD, 0.59; 95% CI, 0.26–0.91; $I^2=81\%$; $P<0.01$), femoral neck (SMD, 0.22; 95% CI, 0.06–0.37; $I^2=24\%$; $P<0.01$), and total hip (SMD, 0.28; 95% CI, 0.01–0.56; $I^2=63\%$; $P=0.04$) (Fig. 6).

A sensitivity analysis showed that 1 trial[33] significantly affected the pooled SMD at the lumbar spine, after it was omitted, there was no significant heterogeneity (SMD, 0.69; 95% CI, 0.53– 0.84; $I^2=0\%$; $P<0.01$). Similarly, after 1 trial[31] was omitted, there was no significant heterogeneity at the total hip (SMD, 0.29; 95% CI, 0.05–0.52; $I^2=46\%$; $P=0.02$).

Then subgroup analyses of the BMD change from baseline at the lumbar spine (Fig. 7) and total hip (SDC 3) were performed based on the different interventions. The switch from anabolic to antiresorptive drugs seemed superior and significantly increased BMD at the lumbar spine (SMD, 0.84; 95% CI, 0.57–1.11) and total hip (SMD, 0.58; 95% CI, 0.03–1.13) compared with the

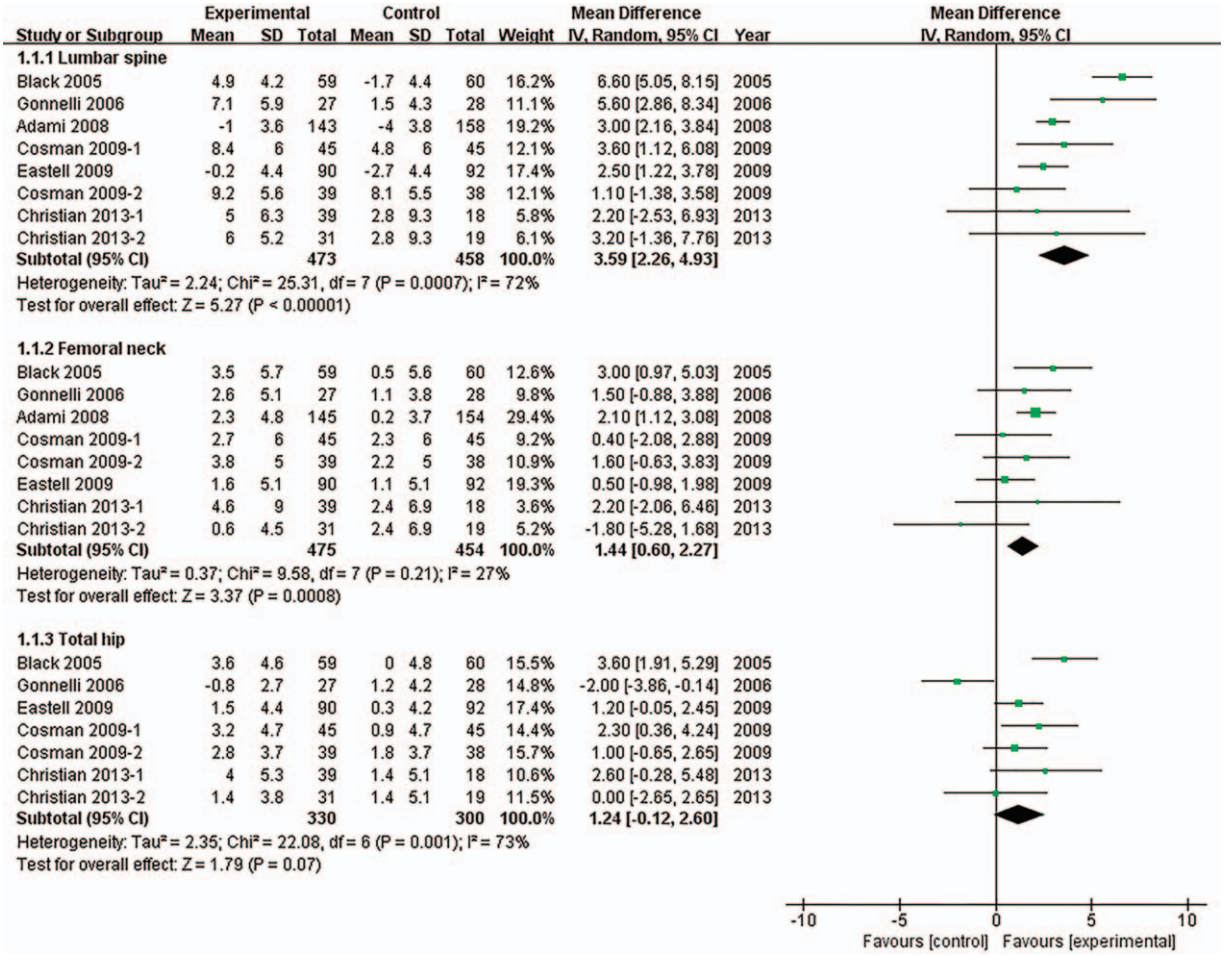

Figure 4. Forest plot for the change in BMD from switching. BMD = bone mineral density.

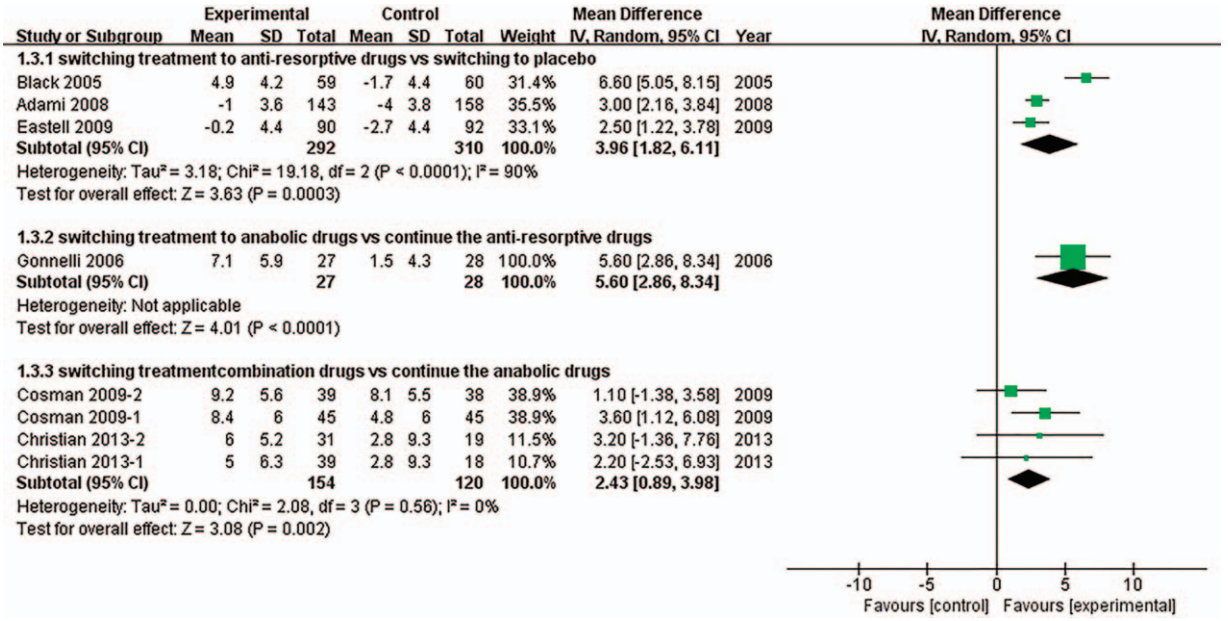

Figure 5. Subgroup analysis for the lumbar spine BMD change from switching.

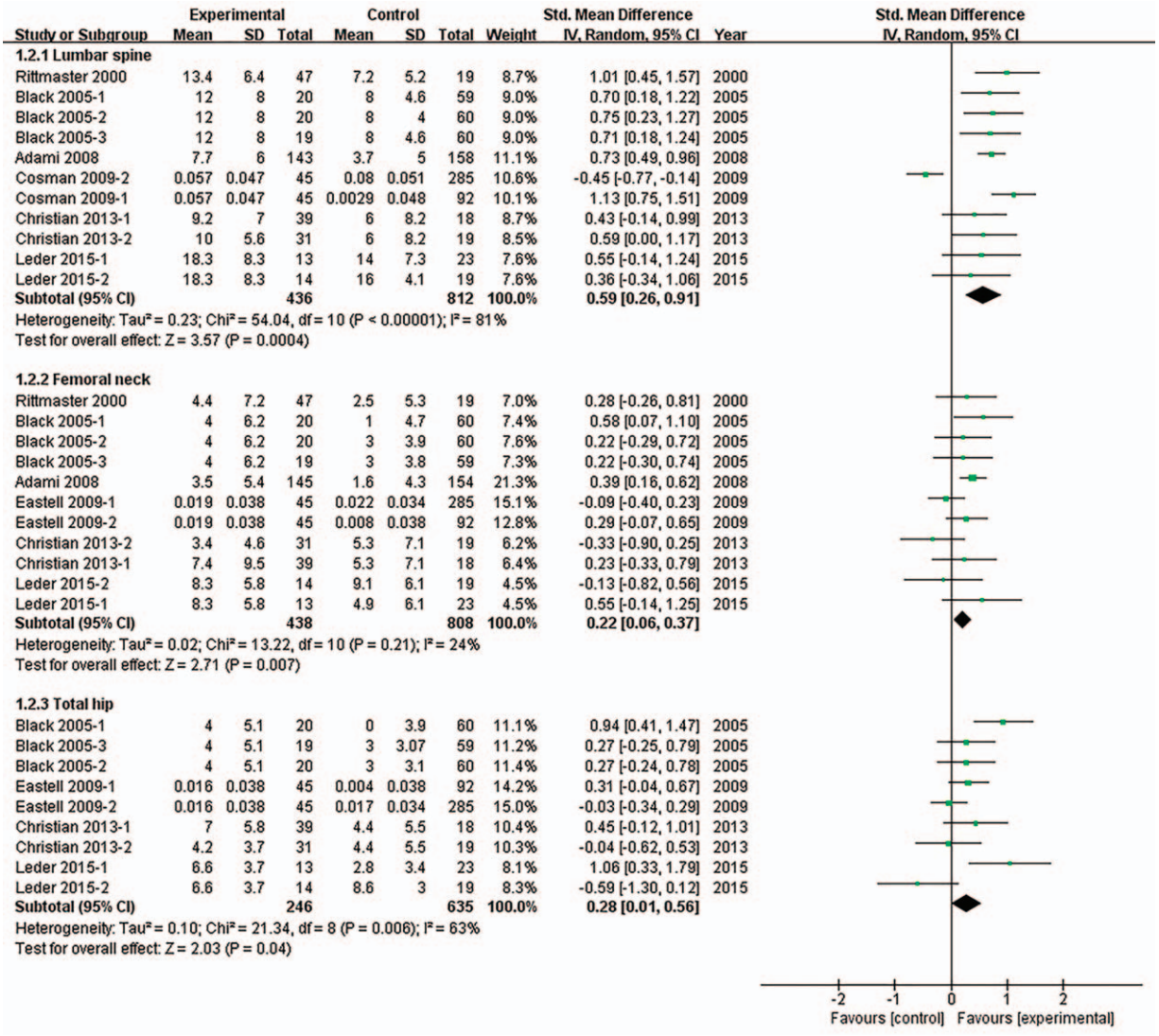

Figure 6. Forest plot for the change in BMD from baseline.

switch from anabolic drugs to placebo. At the lumbar spine, compared with monotherapy of antiresorptive drugs, the sequential therapy significantly increased BMD (SMD, 0.63; 95% CI, 0.26–1.00) and was mostly equal to the therapy of anabolic drugs (SMD, 0.15; 95% CI, −0.60 to 0.90). At the lumbar spine, no statistical differences were found compared with monotherapy of antiresorptive drugs (SMD, 0.24; 95% CI, −0.12 to 0.60) or monotherapy of anabolic drugs (SMD, 0.05; 95% CI, −0.20 to 0.30). Moreover, the sequential therapy from single drug to single drug had more advantages compared with the sequential therapy from combined drugs to single drug at the lumbar spine (SMD, 0.53; 95% CI, 0.22–0.84) and was almost equal at the total hip (SMD, −0.13; 95% CI, −0.92 to 0.66). Finally, it is interesting that the effect of sequential therapy might be affected by the order of anabolic and antiresorptive drugs, and switching treatment from anabolic to antiresorptive drugs seemed more effective at the lumbar spine (SMD, 0.54; 95% CI, −0.03 to 1.11) and total hip (SMD, 1.05; 95% CI, 0.45–1.64), although the differences were not significant at the lumbar spine ($P = 0.06$).

3.6. GRADE profile evidence and publication bias

GRADE evidence profiles for each outcome are shown in Table 2. The available evidence of each outcome is moderate to low. All the included trials are RCTs and have no serious risk of bias, indirectness, or imprecision. Inconsistency exists in each outcome, and the most common causes for the decreased level of evidence are the significant heterogeneity and the various methods of sequential therapy.

Publication bias of the primary outcomes was assessed through visual inspection of funnel plots (Fig. 8).

4. Discussion

4.1. Summary of evidence

We systematically reviewed the available literatures with regard to the sequential therapy of postmenopausal osteoporosis and found that after switching treatment, the alternative drugs maintained the BMD and further increased the change in BMD. Moreover, the increases in BMD after the sequential therapy were

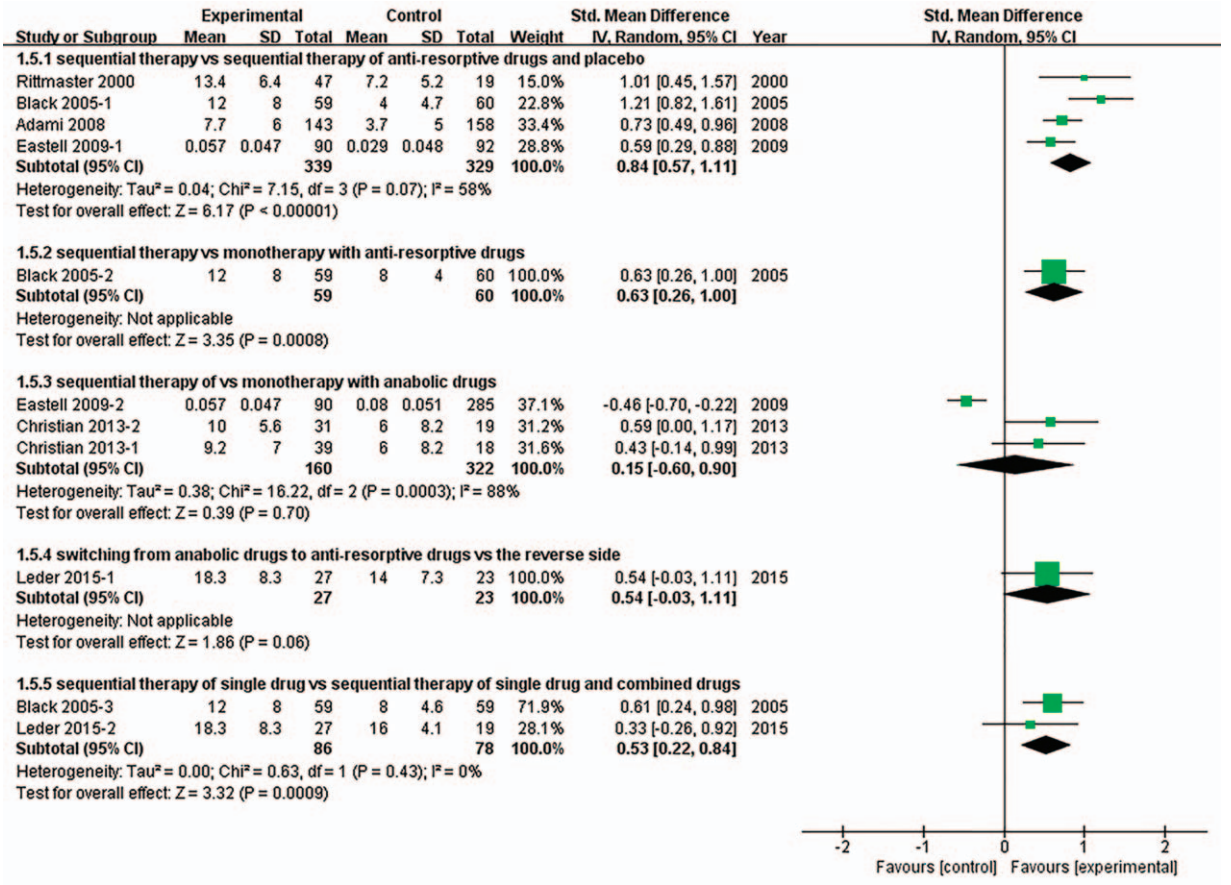

Figure 7. Subgroup analysis for the lumbar spine BMD change from baseline.

larger when compared with antiresorptive drugs under the same treatment duration and were mostly equal to those noted with anabolic drugs. Our findings were strengthened by the comprehensive search and only RCTs were included. However, the available evidence of each outcome was only moderate to low. The included RCTs were considered high quality evidence but might be rated down by the following limitations. The eligible trials in our analysis had methodological limitations, including lack of blindness of patients and unclear allocation concealment in some trials. Results were sometimes inconsistent across trials. Concerns about publication bias arose from the limited number of trials,[43] although we did not rate down the evidence for publication bias. The strength of inference was therefore limited.

Fracture prevention is the primary treatment goal for osteoporotic patients.[44] BMD is a key risk factor for fractures.[45] Epidemiological evidence demonstrates a strong relationship between decreases in BMD and increases in fracture risk.[46] The variation in BMD is an important parameter to evaluate the curative effect of antiosteoporotic drugs.[47–49] There is also a robust relationship between treatment-induced BMD changes and fracture risk reduction.[50–53] Anabolic drugs including teriparatide and recombinant PTH are generally reserved for patients with severe osteoporosis and patients with acquired intolerance to antiresorptive drugs. Additionally, the duration of anabolic drugs for osteoporosis treatment is limited to 24 months, and discontinuation of teriparatide is associated with rapid and significant bone loss.[22,40] The limited application of anabolic drugs has brought some clinically important questions. Teriparatide and PTH, anabolic drugs, are usually used for treatment-experienced patients previously treated with antiresorptive drugs, but could parathyroid hormone be used successfully after antiresorptive therapy? In clinical practice, there are several types of antiresorptive drugs, but could these drugs for BMD maintenance be used after the discontinuation of parathyroid hormone?

Analysis of the primary outcomes shows that antiresorptive drugs, including raloxifene, bisphosphonates, and denosumab that are commonly used in clinical practice, could maintain or further increase BMD after withdrawal of anabolic drugs. Moreover, anabolic therapy after antiresorptive treatment still has a strong anabolic effect, which is consistent with other studies.[39,54] Analysis of the secondary outcome shows that the BMD increase after the sequential therapy is more significant compared with any antiresorptive drug under the same treatment period and is mostly equal to that noted with anabolic drugs.

In addition, anabolic drugs are expensive and depend on daily subcutaneous injection, which would be a burden to patients. These results indicate a sequential therapy provides beneficial effects on BMD and shortens the application time of anabolic drugs; thus, the sequential therapy might relieve the burden on patients and outperform the monotherapy in terms of both economy and effects.

Results have some heterogeneity at the lumbar spine and total hip, but not at the femoral neck. However, any set of studies is

Table 2

The GRADE evidence quality for each outcome.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential therapy	Control	Relative (95% CI)	Absolute	Quality	Importance
BMD changes from switching—lumbar spine (follow-up 9 to 24 mo; better indicated by higher values)												
6	Randomized trials	No serious risk of bias	Very serious[*,†]	No serious indirectness	No serious imprecision	None	473	458	—	MD 3.59 higher (2.26–4.93 higher)	⊕⊕OO Low	Critical
BMD changes from switching—femoral neck (follow-up 9 to 24 mo; better indicated by higher values)												
6	Randomized trials	No serious risk of bias	Serious[†]	No serious indirectness	No serious imprecision	None	475	454	—	MD 1.44 higher (0.6–2.27 higher)	⊕⊕⊕O Moderate	Critical
BMD changes from switching—total hip (follow-up 9 to 24 mo; better indicated by higher values)												
5	Randomised trials	No serious risk of bias	Very serious[†,‡]	No serious indirectness	No serious imprecision	None	330	300	—	MD 1.24 higher (−0.12 lower to 2.60 higher)	⊕⊕OO Low	Critical
BMD changes from baseline—lumbar spine (follow-up 12 to 48 mo; better indicated by higher values)												
6	Randomised trials	No serious risk of bias	Very serious[†,§]	No serious indirectness	No serious imprecision	None	436	812	—	SMD 0.59 higher (0.26–0.91 higher)	⊕⊕OO Low	Important
BMD changes from baseline—femoral neck (follow-up 12–48 mo; better indicated by higher values)												
6	Randomised trials	No serious risk of bias	Serious[†]	No serious indirectness	No serious imprecision	None	438	808	—	SMD 0.22 higher (0.06–0.37 higher)	⊕⊕⊕O Moderate	Important
BMD changes from baseline—total hip (follow-up 12–48 mo; better indicated by higher values)												
4	Randomised trials	No serious risk of bias	Very serious[‖]	No serious indirectness	No serious imprecision	None	246	635	—	SMD 0.28 higher (0.01–0.56 higher)	⊕⊕OO Low	Important

BMD = bone mineral density.

[*] I^2 = 73%.

[†] There were several methods of sequential therapy.

[‡] I^2 = 74%.

[§] I^2 = 88%.

[‖] I^2 = 75%.

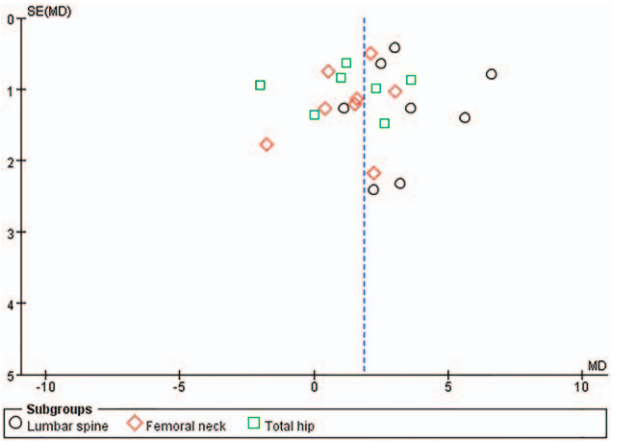

Figure 8. Funnel plot for publication bias.

inevitably clinically heterogeneous. The heterogeneity could partly be explored by the following reasons. On one hand, the effect of anabolic drugs was different at the lumbar spine and total hip. Anabolic drugs could rapidly increase BMD at the lumbar spine in the first year of therapy; while anabolic therapy does not appreciably increase hip BMD in the first year, but does so in the second year of therapy, which were demonstrated in the included trials[31,33,37] and prior clinical trials.[6,55–57]

On the other hand, various applications of sequential methods were included in this meta-analysis, although these trials meeting our inclusion criteria have strong homogeneity, and the diverse settings might considerably improve the generalizability and usefulness of our meta-analysis.[58] Because of the advantage of the diverse settings, we could further perform subgroup analyses based on the different methods of sequential therapy. We found that the effect of sequential therapy might be affected by the sequence of antiresorptive and anabolic drugs; the sequential therapy with the primary administration of anabolic drugs seems more effective than the one with primary use of antiresorptive drugs. It might also be affected by the strength of antiresorptive drugs; anabolic drugs followed by potent antiosteoporosis drugs (bisphosphonates or denosumab) were preferred than anabolic drugs followed by weak antiosteoporosis drugs (raloxifene). Nevertheless, the sequential therapy of 2 agents still needs to be confirmed with further research.

4.2. Limitations

Although our study was performed in compliance with the PRISMA guidelines and Cochrane Collaboration recommendations, this meta-analysis still has several limitations. First, the included trials were conducted with various applications of sequential methods, which might mainly account for the significant heterogeneity of outcomes. Although our meta-analysis involves several types of interventions, these trials meeting our inclusion criteria have strong homogeneity, and the diverse settings might considerably improve the generalizability and usefulness of our meta-analysis.[58] In addition, the results were further confirmed by sensitivity analyses and subgroup analyses. Second, the number of included trials is limited for a quantitative analysis of publication bias. We could perform tests for funnel plot asymmetry, however, when fewer than 10 studies were included, the power of the tests is too low to distinguish chance from real asymmetry. Finally, no direct assessment of antifracture efficacy was performed, though BMD has been proven to be a reliable predictor of antifracture efficacy in patients treated with osteoporosis drugs.[50–53]

5. Conclusions

Meta-analysis of 8 studies involving 1509 patients shows that sequential therapy maintains and further increases BMD, and the BMD increase after the sequential therapy is more significant compared with antiresorptive drugs under the same treatment duration and is mostly equal to that noted with anabolic drugs. Thus, sequential therapy may be recommended as an effective treatment for osteoporotic women. Nevertheless, more RCTs are needed to determine the best order and most appropriate drugs of the sequential therapy.

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