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SYSTEMATIC REVIEW

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Effectiveness and safety of traditional Chinese medicine for bone loss associated with endocrine therapy in patients with breast cancer: a systematic review and meta-analysis

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Abstract

The incidence rate of breast cancer is high, and endocrine therapy for breast cancer frequently causes bone loss. We conducted a systematic review and meta-analysis to review the effect of TCM on bone loss associated with endocrine therapy in patients with breast cancer. Medline (Ovid), EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), VIP full-text Database, Wanfang Database, Chinese Biomedical Literature data (CBM), relevant Chinese and foreign periodicals, conference papers, degree papers, and supplemented by literature tracing were searched. Data from randomized controlled trials (RCTs) on the effects of TCM on bone loss associated with endocrine therapy in patients with breast cancer were collected according to the inclusion and exclusion criteria from the establishment of each database to May 2022. Twenty-two clinical controlled studies were eventually selected. The results of the meta-analysis showed effectiveness (RR (Risk Ratio): 1.22, 95% CI (confidence interval): 1.10–1.36, I^2 = 0%), improvement of lumbar bone mineral density (BMD) (WMD (weighted mean difference): 0.07, 95% CI: 0.06–0.08, I^2 = 23%), improvement of BMD T value (WMD: 0.37, 95% CI: 0.28–0.46, I^2 = 66%), and improvement of BMD in the femoral neck (WMD: 0.07, 95% CI: 0.05–0.09, I^2 = 33%). The funnel chart suggested that a publication bias was observed in the literature, which may be explained by the heterogeneity in the study data and the limited number of included examples. Sensitivity analysis was conducted to confirm that the differences among the studies were acceptable. No study reported adverse effects. Our results indicated that TCM is helpful for bone loss associated with endocrine therapy in patients with breast cancer based on the effectiveness, lumbar BMD, BMD T value, and BMD of the femoral neck. The use of TCM is thus safe.

Keywords

Traditional Chinese medicine; Bone loss; Endocrine therapy; Breast cancer; Meta-analysis

1. Introduction

The incidence rate of breast cancer has increased in recent times. It has surpassed that of lung cancer to become the malignant tumor with the highest incidence rate among women. The mortality rate of breast cancer is also the highest and become the malignant tumor for women. Hormone receptor-positive breast cancer accounts for 80% of breast cancer cases. At present, the treatment of breast cancer involves surgery, radiotherapy, chemotherapy, endocrine therapy, and molecular targeted therapy [1]. Endocrine therapy for breast cancer can effectively inhibit the aromatase activity by approximately 95% to 98%, thereby significantly reducing the level of estradiol and exerting an anti-tumor effect [2].

Endocrine therapy is the primary treatment method for hormone receptor-positive breast cancer [3]. At present, as the first-line treatment plan for endocrine therapy for hormone receptor-positive breast cancer, tamoxifen is the first choice for premenopausal patients, whereas third-generation aromatase inhibitors, including anastrozole, letrozole, and exemestane, are primarily used for postmenopausal patients [4].

Endocrine therapy may significantly reduce the recurrence rate of breast cancer and improve the disease-free survival rate of patients, bringing new gospel to patients. Estrogen can inhibit bone absorption and promote calcitonin secretion. Most patients with breast cancer are perimenopausal or menopausal women, and their estrogen levels have usually reduced to varying degrees. They may experience bone loss or a decline

in bone density. After endocrine therapy, estrogen loses its activity, which causes further bone loss [5]. The reduction or absence of estrogen may increase the risk of fracture in women. Therefore, endocrine therapy is bound to further reduce the estrogen level in postmenopausal women. This can lead to bone loss and other serious clinical symptoms, which affects the quality of life of patients. Concurrently, owing to the lack of estrogen in the body, the activity of osteoblasts in patients is reduced, whereas that of osteoclasts is increased. This eventually leads to a decline in bone density [6]. The long-term application can increase the risk of osteoarthritis, bone pain, and fracture, thus reducing the compliance and quality of life of patients. To improve the quality of life of patients with breast cancer undergoing endocrine therapy, the value of active prevention and treatment of bone loss should be widely valued [7]. Guidelines recommend that patients who take aromatase inhibitors orally for a long time should assess the risk factors of fracture, take vitamin D and calcium supplements, and use bisphosphonate preparations, especially in cases of medium or high risk [8].

The measures taken in modern medicine to prevent and treat bone loss after endocrine therapy for breast cancer primarily include calcium supplements and vitamin D. Bisphosphonates can increase the bone density of patients but provide no obvious relief of the clinical symptoms of bone loss. In addition, the drug cost is high, which increases the economic burden on patients. An increasing number of reports have been published on the treatment of bone loss with traditional Chinese medicine (TCM), which also has good efficacy and safety [9]. TCM can alleviate bone and joint symptoms related to endocrine therapy of breast cancer, especially soreness and pain in the lower back [10]. Therefore, to explore the law of medical treatment, in this study, we investigate and summarize traditional Chinese medicine prescriptions for bone loss after endocrine treatment of breast cancer and provide reference for future clinical treatments of bone loss after the endocrine treatment of breast cancer.

2. Research contents and methods

2.1 The sources and retrieval methods of documents

Medline (Ovid), EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), VIP full-text Database, Wanfang Database, Chinese Biomedical Literature data (CBM) as well as relevant Chinese and foreign periodicals, conference papers, degree papers, and supplemented by literature tracing were searched. Data from randomized controlled trials (RCTs) on the effects of TCM on bone loss associated with endocrine therapy for breast cancer were retrieved according to the inclusion and exclusion criteria. The duration of data extraction was from the establishment of the database to May 2022. The following items were used as keywords in the retrieval strategy.

#1 exp Medicine, Chinese Traditional/
#2 (medicine adj5 chinese adj5 traditional).tw.
#3 (chung adj5 i adj5 hsueh).tw.
#4 zhong yi xue.tw.
#5 exp Plants, Medicinal/
#6 (plant$ adj5 medicinal).tw.
#7 (pharmaceutical adj5 plant$).tw.
#8 (healing adj5 plant$).tw.
#9 or/1-8
#10 exp bone loss/
#11 exp endocrine therapy/
#12 endocrine therapy.mp.
#13 or/11-12
#14 exp breast cancer/
#15 early breast cancer.mp.
#16 early breast carcinoma.mp.
#17 early breast tumor.mp.
#18 early breast tumour.mp.
#19 early breast neoplasm.mp.
#20 locally advanced breast cancer.mp.
#21 locally advanced breast carcinoma.mp.
#22 locally advanced breast neoplasm.mp.
#23 locally advanced tumor.mp.
#24 locally advanced tumour.mp.
#25 or/14-24
#26 #9 and #10 and #13 and #25

2.2 Literature inclusion and exclusion criteria

2.2.1 Literature inclusion criteria

(1) The type of study: All RCTs on the effects of TCM on bone loss associated with endocrine therapy of breast cancer.

(2) Participant: all patients met the diagnostic criteria for breast cancer and exhibited bone loss associated with endocrine therapy. The gender, age, and race of the participants were not limited.

(3) Intervention: the control group was only treated with routine drugs, and in the experimental group, TCM was used based on routine drugs. The routine drugs including.

(4) The primary outcome was the clinical effect.

(5) The secondary outcome included changes in the bone mineral density (BMD) or the condition of the patients.

2.2.2 Literature exclusion criteria

(1) No case-control or cohort study was conducted; (2) an incomplete data report, such that the data could not be adopted; (3) the research content was repeated; (4) the evaluation of the efficacy of the study was not suitable; (5) review of related literature; (6) clinical cases.

2.3 Quality evaluation and data extraction

The Cochrane System Review Manual 5.3 bias risk assessment tool was used to evaluate the bias risk in the included studies.

2.4 Data extraction

Two researchers independently conducted literature screening and data extraction. The third author participated in the discussion in the occurrence of a disagreement. Extracting the data, evaluating the quality, and cross-checking were done by the whole team. Endnote 9.3 (Clarivate Analytics, Philadelphia, PA, United States). was used to manage and extract research

data as the document management software, and Excel office software 2021 (Microsoft Corporation, Redmond, WA, United States) was also used.

For additional information or potential gaps in the literature, the author of the article was contacted. The data that were extracted included: (1) basic information: writer, publication time, number of cases; (2) intervention: plan, course of treatment; (3) outcome indicators: joint symptoms: clinical effect, any changes in the BMD or conditions of patients.

2.5 Statistical analysis

RevMan5.4 software (Cochrane Collaboration, London, UK) was used for conducting meta-analysis. In the counting efficiency, we adopted the relative risk (RR). For continuous data, we used the mean difference (MD). Forest plots were used to display the individual and pooled results. Heterogeneity was evaluated using the I-squared (I^2) statistic. When the statistic was considered notable ($I^2 > 50\%$), the random-effects model was selected. It is appropriate to select the fixed effect models in the absence of heterogeneity. A funnel plot was used to assess the publication bias. The Eggers's test was applied to the inverted funnel chart to determine the publication bias in the literature. The data may have heterogeneity, which can be analyzed by subgroup analysis and sensitivity analysis.

3. Results and analysis

In all, 1251 articles were retrieved by searching Medline (Ovid), EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), VIP full-text Database, Wanfang Database, and Chinese Biomedical Literature data (CBM) as well as relevant Chinese and foreign periodicals, conference papers, degree papers, and supplemented by literature tracing. Six hundred and thirty-two articles were collected after excluding duplicates. Based on a preliminary reading of article titles and abstracts, 33 articles were selected, excluding irrelevant studies, reviews, case reports, and uncontrolled studies. After carefully reading the full text, 22 articles were excluded owing to incomplete data and the absence of primary outcome indicators. Twenty-two clinical controlled studies were eventually used for the meta-analysis. Fig. 1 shows the diagram used for literature screening, and Table 1 shows the basic characteristics of the literature found (Fig. 1; Table 1).

4. Result of meta-analysis

4.1 Bias of risks of the methodology adopted in the literature

Twenty-two studies were considered for conducting the bias of risks assessment. Three studies used random sequence generation with high risks. Four studies had unclear allocation concealment. None of the studies mentioned the blinding of participants and personnel or the blinding of outcome assessment. One study may have had selective reporting, and four studies may have other biases. No study reported incomplete outcomes (Fig. 2).

4.2 Effectiveness

Five clinical RCT studies with 311 samples were included in this study. A meta-analysis was conducted to assess the effectiveness of TCM for bone loss associated with endocrine therapy in breast cancer. The results showed the following: RR: 1.22, 95% CI: 1.10–1.36, $I^2 = 0\%$. The heterogeneity test results indicated the absence of heterogeneity. The fixed effect model analysis showed that TCM was effective in the experimental group ($p < 0.05$) (Fig. 3).

4.3 Improvement of lumbar BMD

Thirteen studies reported an improvement in the lumbar BMD. A meta-analysis was conducted, and the result showed the following: WMD: 0.07, 95% CI: 0.06–0.08, $I^2 = 23\%$. The heterogeneity test results indicated limited heterogeneity. The random effect model analysis was used to avoid the diversity of clinical outcomes. As per the results, TCM treatment could improve lumbar BMD ($p < 0.05$). The funnel plot showed that the left and right sides are asymmetric, and there could have been some publication bias. The sensitivity analysis was conducted to confirm that the differences among studies were acceptable (Fig. 4).

4.4 Improvement of BMD T value

Twelve studies reported the BMD T value. A meta-analysis was conducted, and the results were the following: WMD: 0.37, 95% CI: 0.28–0.46, $I^2 = 66\%$. The heterogeneity test results indicated the absence of heterogeneity. The random effect model analysis was used to avoid the diversity of clinical outcomes. The results showed that TCM treatment can improve the BMD T value ($p < 0.05$). Subgroup analysis was conducted according to the age and treatment term. However, these factors did not affect the heterogeneity. Therefore, we used a funnel plot and sensitivity analysis. The funnel plot showed that the left and right sides are asymmetric, and there may have been publication bias. Sensitivity analysis was conducted to confirm whether the differences among studies were acceptable (Fig. 5).

4.5 Improvement of BMD of the femoral neck

Eight studies reported the BMD of the femoral neck. A meta-analysis was conducted, and the result showed the following: WMD: 0.07, 95% CI: 0.05–0.09, $I^2 = 33\%$. The random effect model analysis was used. The result showed that TCM treatment could improve the BMD of the femoral neck ($p < 0.05$). A funnel plot and sensitivity analyses were used to confirm that the differences among the studies were acceptable (Fig. 6).

4.6 Adverse events

No studies reported adverse events as a result of TCM treatment for bone loss associated with endocrine therapy in patients with breast cancer.

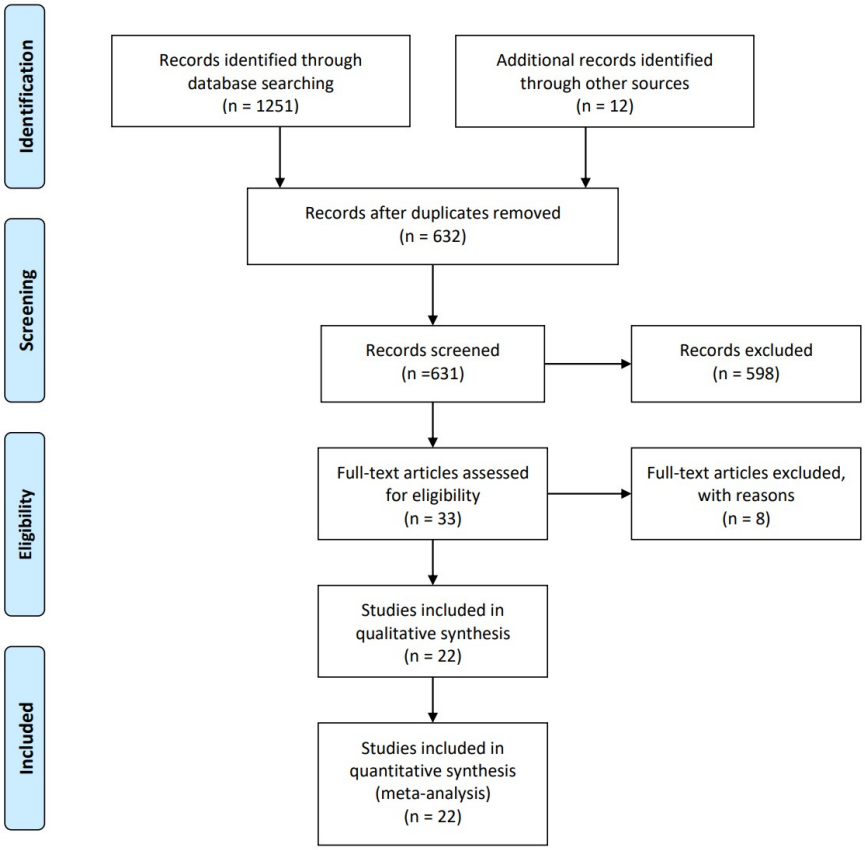

FIGURE 1. Literature retrieval flow diagram.

TABLE 1. Basic characteristics of included studies.

Studies	Period of treatment (mon)	Numbers	Exp. Interventions	Con. Interventions	Jadad score	Outcomes
Chen [11] 2013	6	28/28	TCM	N/A	2	2, 3
Lv [12] 2014	12	39/35	TCM + Caltrate D	Caltrate D	3	3
Xu [13] 2014	12	32/40	TCM + Caltrate D	Caltrate D	2	2
Li [14] 2014	6	21/17	TCM + Caltrate D	Caltrate D	3	2, 4
Mo [15] 2015	12	34/34	TCM + Caltrate D	Caltrate D	4	1, 2, 4
Jiang [16] 2015	3	21/20	TCM + Caltrate D	Caltrate D	4	1
Yuan [17] 2016	6	35/35	TCM + Caltrate D	Caltrate D	2	3
Huang [18] 2016	6	30/30	TCM + Caltrate D	Caltrate D	3	3
Zhang [19] 2016	3	42/41	TCM + Caltrate D	Caltrate D	2	3
Bai [20] 2017	6	45/45	TCM + Caltrate D	Caltrate D	3	1, 2, 4
Li [21] 2017	3	42/41	TCM + Caltrate D	Caltrate D	2	3
Shi [22] 2017	6	23/17	TCM + Caltrate D	Caltrate D	4	2, 3, 4
Zhu [23] 2017	6	46/46	TCM + Caltrate D	Caltrate D	3	2
Yuan [24] 2018	12	28/29	TCM + Caltrate D	Caltrate D		2, 3
Yin [25] 2018	6	58/58	TCM + Caltrate D + Vitamin D	Caltrate D + Vitamin D	2	2
Zhao 2018	3	26/21	TCM	N/A	3	1, 2, 4
Zou [26] 2018	3	33/32	TCM + Caltrate D	Caltrate D	4	2
Liang 2019	6	35/35	TCM + Caltrate D	Caltrate D	3	2, 4
Liu [27] 2019	3	32/32	TCM + Caltrate D	Caltrate D	2	1
Qu [28] 2019	18	62/64	TCM + Caltrate D	Caltrate D	4	3
Huang [29] 2020	3	30/28	TCM + Caltrate D	Caltrate D	2	3
He [30] 2021	3	24/24	TCM + Caltrate D	Caltrate D	3	2

Note: 1: Effectiveness; 2: Improvement of lumbar bone mineral density; 3: Improvement of lumbar bone mineral density; 4: Improvement of bone mineral density T value. TCM: traditional Chinese medicine; N/A: not applicable.

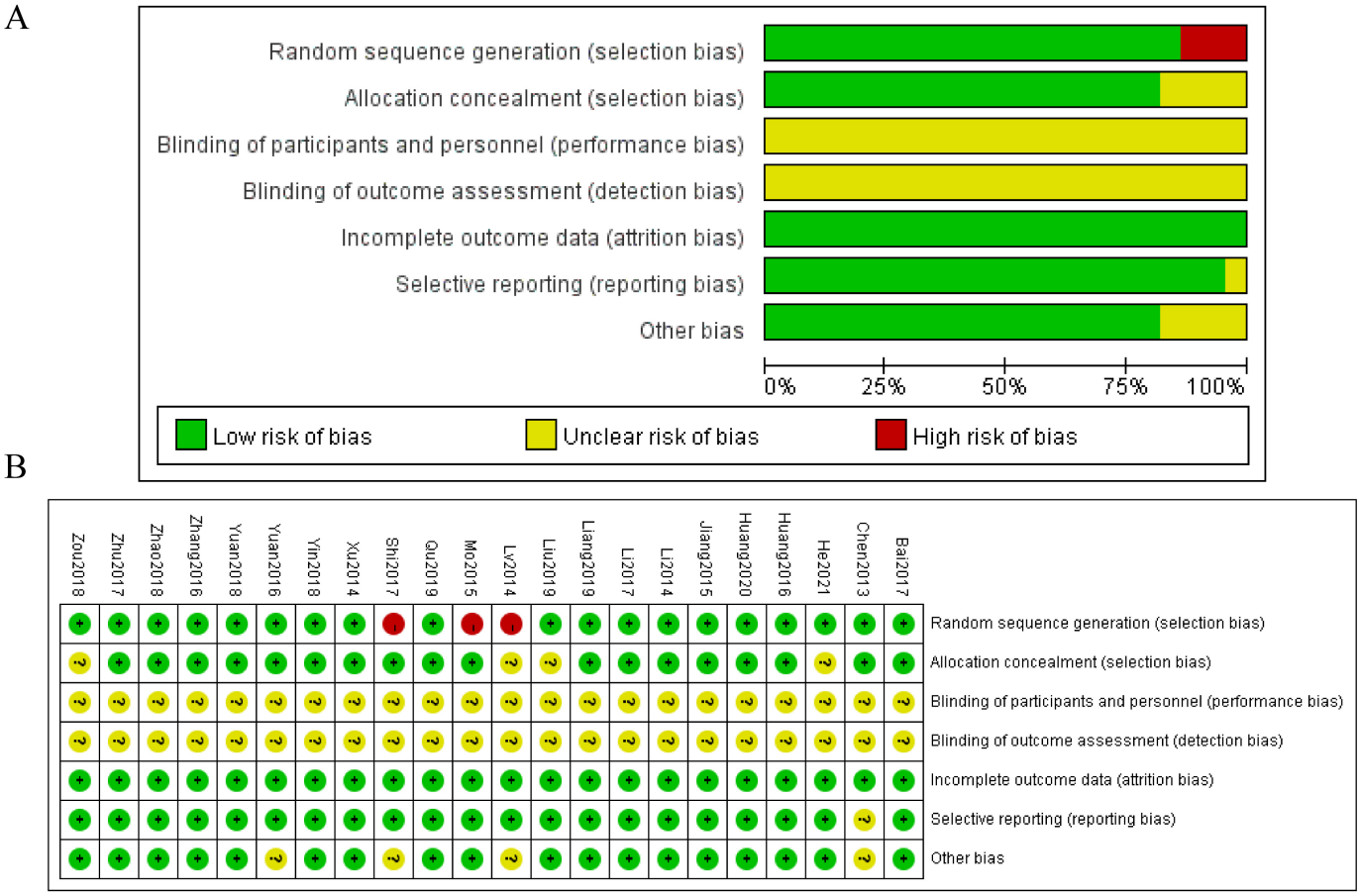

FIGURE 2. Bias of risks in the included literature.

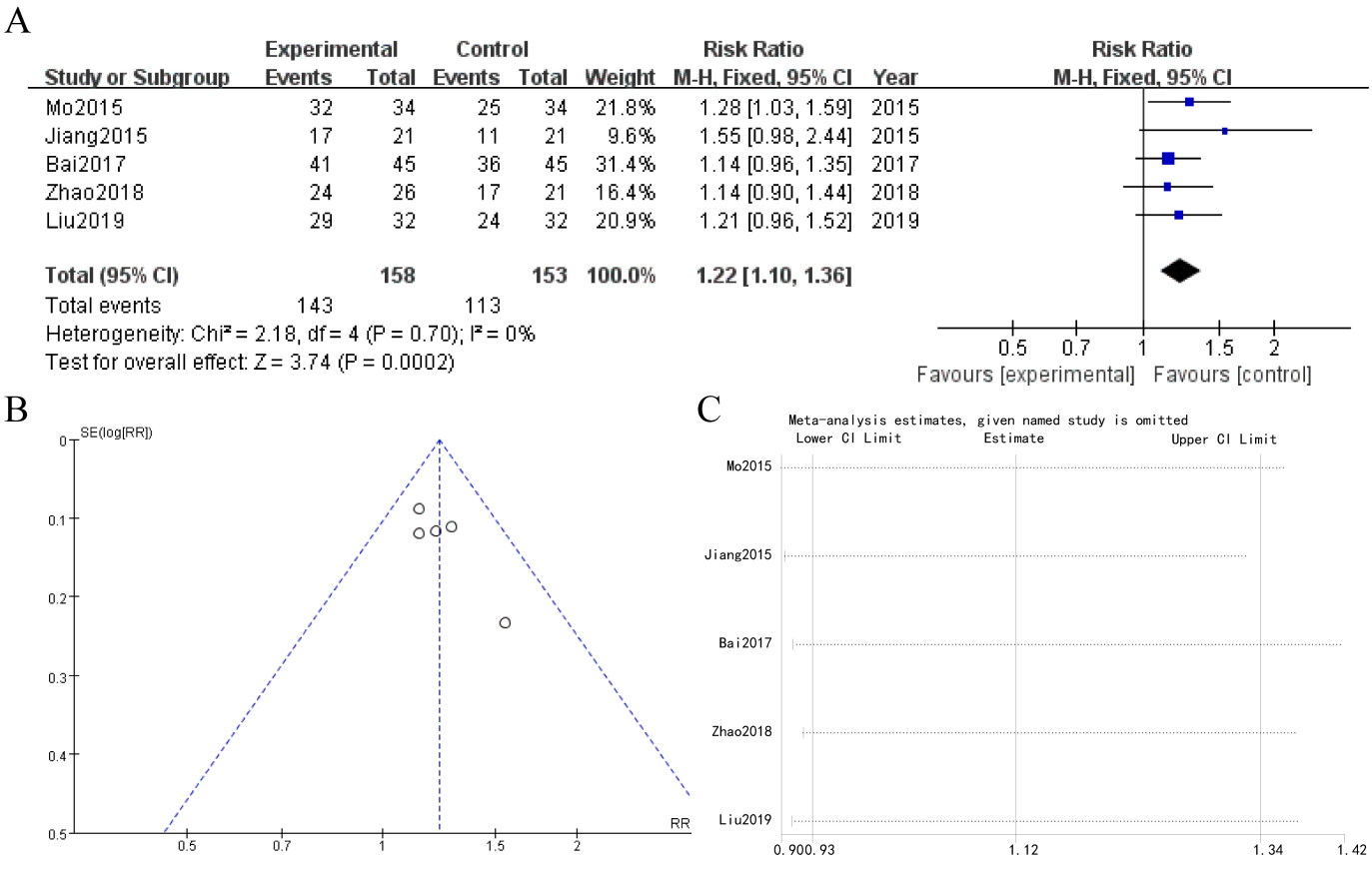

FIGURE 3. Effectiveness.

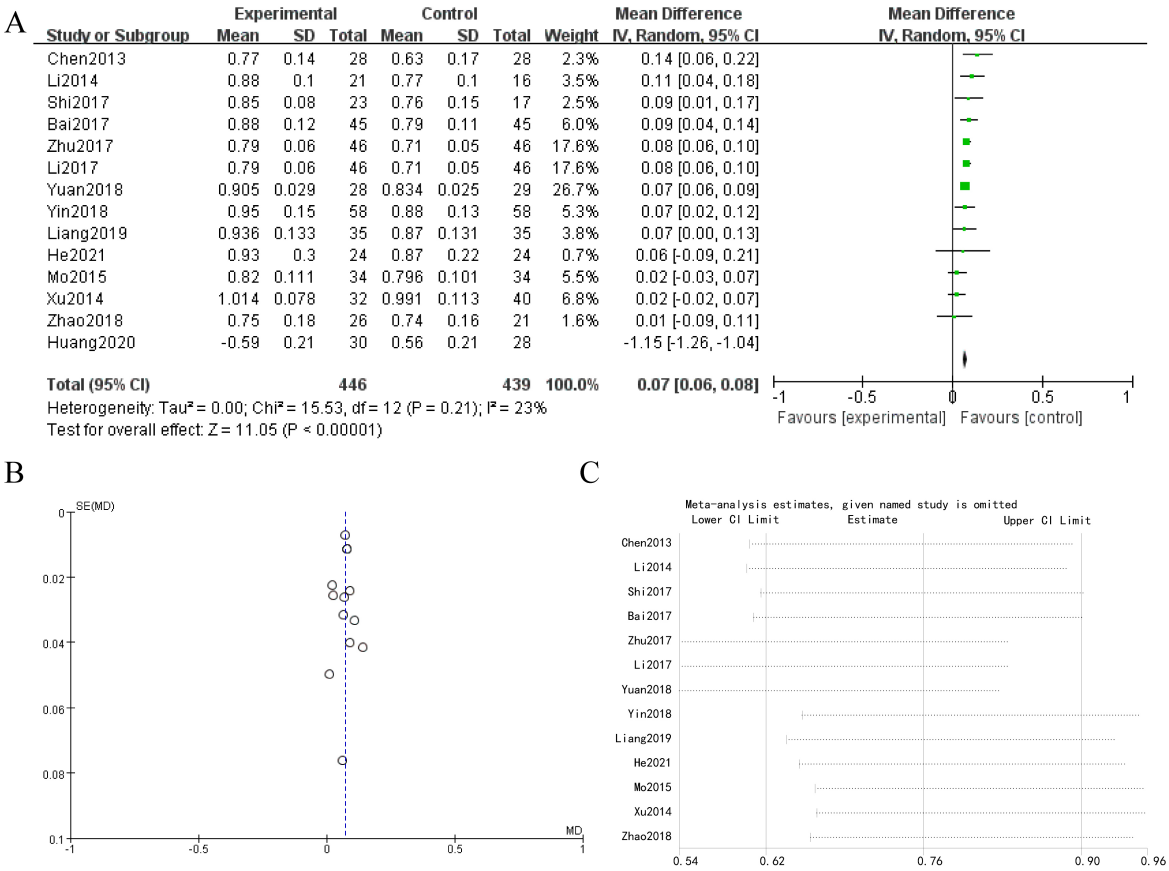

FIGURE 4. Improvement of the lumbar bone mineral density.

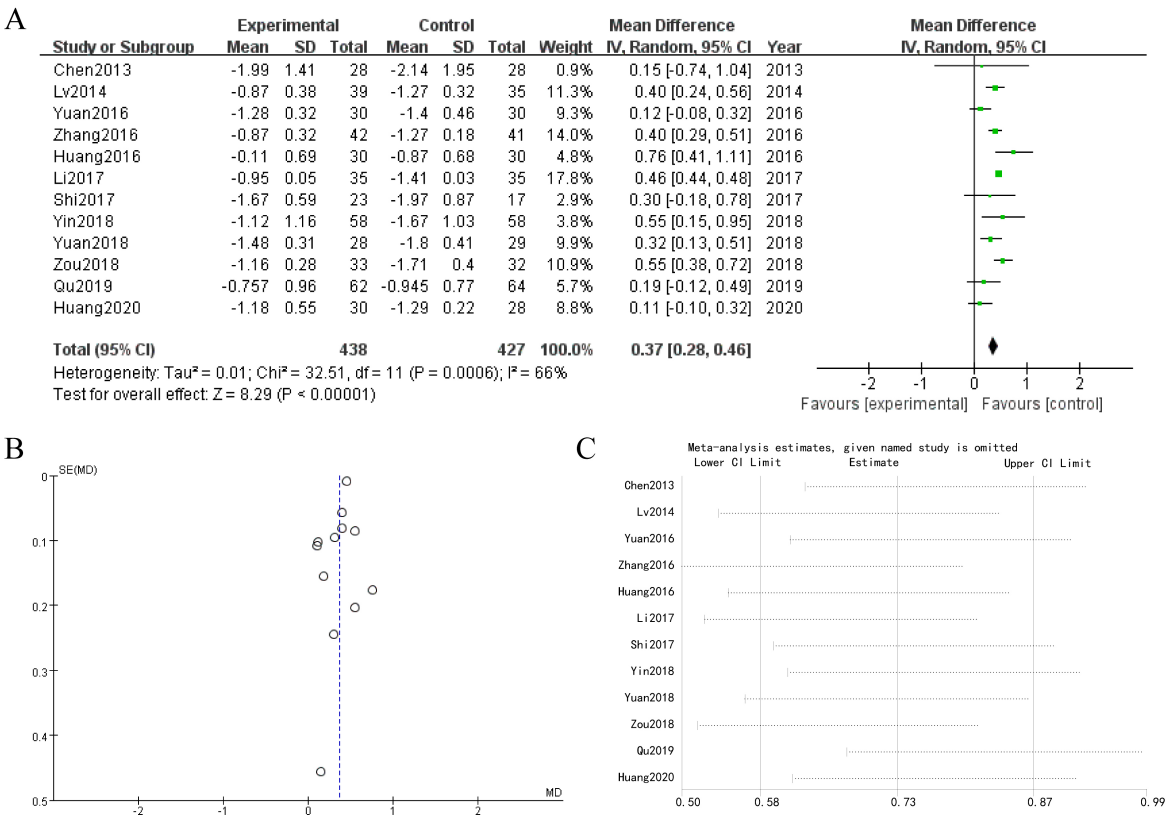

FIGURE 5. Bone mineral density T value. SD: standard deviation.

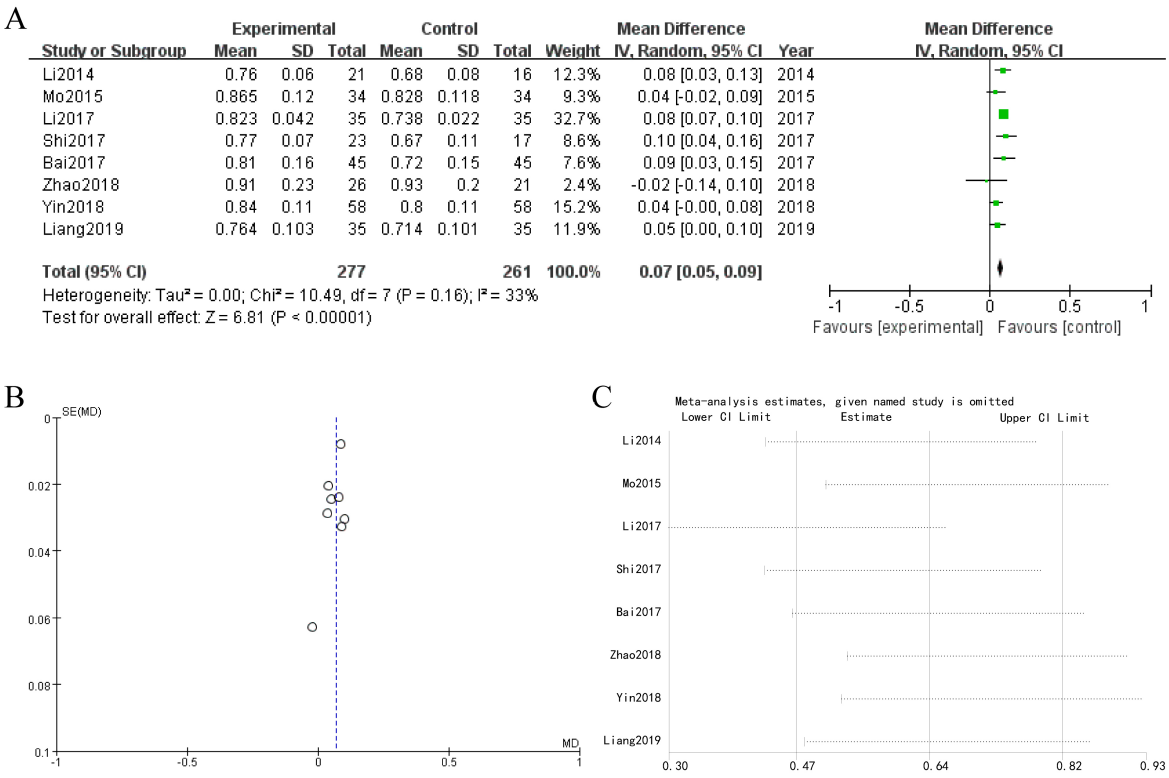

FIGURE 6. Bone mineral density of the femoral neck.

5. Discussion

The fact that patients with hormone receptor-positive breast cancer suffer from bone loss after endocrine therapy, which leads to fracture, is a problem worthy of clinical attention and prevention [31, 32]. Bone loss is more likely to lead to osteoporosis, which may lead to fracture [33]. The treatment of bone loss with TCM is promising to help patients with breast cancer relieve pain [34]. Twenty-two clinical controlled studies were eventually included in this meta-analysis to assess the effectiveness and safety of TCM for endocrine therapy for bone loss in patients with breast cancer. Three studies used random sequence generation with high risks. Four studies had unclear allocation concealment. None of the studies mentioned the blinding of participants and personnel or the blinding of outcome assessment. One study may have had selective reporting, and four studies may have had other biases. The results of the meta-analysis showed effectiveness (RR: 1.22, 95% CI: 1.10–1.36, I^2 = 0%), improvement of lumbar BMD (WMD: 0.07, 95% CI: 0.06–0.08, I^2 = 23%), improvement of BMD T value (WMD: 0.37, 95% CI: 0.28–0.46, I^2 = 66%), and improvement of BMD of the femoral neck (WMD: 0.07, 95% CI: 0.05–0.09, I^2 = 33%). The funnel chart suggested that a publication bias was observed in the literature, which may be explained by the heterogeneity of the study and the limited number of examples included. Sensitivity analysis was conducted to confirm that the differences among the studies were acceptable. No study reported adverse effects [35].

The meta-analysis of the literature included in this study showed that TCM exerts clinical effects on bone loss caused by endocrine therapy for breast cancer, especially in improving the lumbar bone density, bone density T value, and the femoral and tibial bone density of patients.

This study had the following limitations: (1) the risk of bias may have decreased the quality of evidence; (2) only 22 articles were included, and most of them were small-sample studies; (3) Different treatment courses, basic drugs, and doses were adopted in the included studies. This may have led to an increase in the heterogeneity; (4) The funnel plot showed potential publication bias; (5) In terms of safety evaluation, none of the studies included mentioned adverse events. (6) Sub-analyses are unable to perform due to all the studies used different herbs. We add it in the discussion part.

The reliability of conclusions remains low owing to the lack of unified treatment of the literature included in this study and insufficient evidence strength. The clinical efficacy of TCM for the treatment of bone loss caused by endocrine therapy in breast cancer still requires validation in high-quality, standardized, rigorous, multi center, double-blind RCTs.

6. Conclusion

Our results indicated that TCM is helpful for bone loss associated with endocrine therapy in patients with breast cancer according to effectiveness, lumbar BMD, BMD T value, and BMD of the femoral neck. The use of TCM may thus be considered safe.

ABBREVIATIONS

BMD, bone mineral density; CBM, Chinese Biomedical Literature data; CNKI, China National Knowledge Infrastructure; TCM, randomized controlled trial; RCT, randomized controlled trial.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

WL—was responsible for the study design, implementation, and quality control, wrote the manuscript draft. DHF—independently performed the literature search, data extraction, and quality assessment. QW—was responsible for the data analysis. YCS, YMM and YWL—reviewed the language. All authors have read and approved the final version of the manuscript for submission.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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