INPLASY PROTOCOL

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None declared.

Comparison of the efficacy and safety of different treatments on postmenopausal osteoporosis: A protocol for a systematic review and network meta-analysis

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Review question / Objective: **(1) Participations: The subjects were postmenopausal women who were previously untreated and objectively diagnosed with osteoporosis by dual-energy X-ray densitometry (DXA). However, participants will not be included in the study if they meet one of the following conditions: 1) men; 2) secondary osteoporosis caused by certain medical conditions or treatments, such as metastasis, Paget's disease, hypercalcemia, or glucocorticoid-induced osteoporosis; 3) previous postmenopausal osteoporosis treatment with continuous medication. (2) Intervention: All treatments for patients with postmenopausal osteoporosis, Including different drug combinations, different routes of administration. (3) Comparator: Different types of treatments for postmenopausal osteoporosis. (4) Outcomes: Primary outcomes included percentage change in bone mineral density (BMD) from baseline at lumbar spine (LS), total hip (TH), or distal radius (RU) after postmenopausal osteoporosis treatments and the incidence of fracture (vertebral [VF], nonvertebral [NVF], and wrist). The secondary result was the incidence of adverse events including cancer, cardiovascular disease (CVD), hip fracture, death, and osteonecrosis of the jaw. (5) Study designRandomized controlled trials (RCTs) that compared the efficacy and safety among different treatments in postmenopausal osteoporosis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 September 2021 and was last updated on 21 September 2021 (registration number INPLASY202190067).

INTRODUCTION

Review question / Objective: **(1) Participations: The subjects were postmenopausal women who were previously untreated and objectively diagnosed with osteoporosis by dual-energy X-ray densitometry (DXA). However, participants will not be included in the study if they meet one of the following conditions: 1) men; 2) secondary osteoporosis caused by certain medical conditions or treatments, such as metastasis, Paget's disease,**

hypercalcemia, or glucocorticoid-induced osteoporosis; 3) previous postmenopausal osteoporosis treatment with continuous medication. (2) Intervention: All treatments for patients with postmenopausal osteoporosis, Including different drug combinations, different routes of administration. (3) Comparator: Different types of treatments for postmenopausal osteoporosis. (4) Outcomes: Primary outcomes included percentage change in bone mineral density (BMD) from baseline at lumbar spine (LS), total hip (TH), or distal radius (RU) after postmenopausal osteoporosis treatments and the incidence of fracture (vertebral [VF], nonvertebral [NVF], and wrist). The secondary result was the incidence of adverse events including cancer, cardiovascular disease (CVD), hip fracture, death, and osteonecrosis of the jaw. (5) Study designRandomized controlled trials (RCTs) that compared the efficacy and safety among different treatments in postmenopausal osteoporosis.

Rationale: To date, one study compared the efficacy and safety of different drugs for postmenopausal osteoporosis, one study compared the efficacy and safety of monoclonal antibodies with conventional drugs for postmenopausal osteoporosis, several studies have compared the efficacy and safety of Chinese Herbal Medicine with conventional drugs for postmenopausal osteoporosis , There have been studies comparing the efficacy and safety of exercise, different drug delivery routes, and acupuncture in the treatment of postmenopausal osteoporosis , but there have been no studies comparing all these interventions. Therefore, this study will provide some reference for clinical work. Our study was according to Cochrane Handbook and meta-analysis (PRISMA) extension statement for NMAs . This study evaluated the efficacy and safety of postmenopausal osteoporosis by directly and indirectly comparing various treatments, and generate a treatment ranking based on these outcomes. The current protocol is designed in accordance with PRISMA guidelines, and its scientific nature and operability are remarkable.

Condition being studied: Osteoporosis has become one of the most serious health crises in our society in an aging population. Fractures constitute the most important clinical complication of osteoporosis, and the 1-year cumulative mortality rate after osteoporotic hip fracture varies between 20% and 40%. In the absence of effective preventive measures, approximately one half of older Americans face a high risk of fracture due to osteoporosis by 2020. The direct medical cost due to osteoporotic fractures in the United States is projected to exceed $25 billion by 2025, and the cumulative cost of incident fractures is projected to reach $228 billion over the 10-year period from 2016 to 2025 . The cost of osteoporosis, including pharmacological intervention in the EU in 2010, was estimated at 37 billion . The disease burden is even greater in China, which is the largest developing country in the world, constituting one-fifth global population and even higher percentage of elderly population but limited medical resources. Given these realities, it is imperative to identify therapeutic measures that can effectively prevent fragility fractures resulting from osteoporosis, particularly in postmenopausal women. The drugs and measures currently used to treat postmenopausal osteoporosis are: (1) Anti-bone resorption drugs; (2) Drugs that promote bone formation; (3) Double-acting drugs, they can be used alone or in combination to treat postmenopausal osteoporosis, and the way and dose of administration will also affect its efficacy and safety. They are highly effective but are also often associated with many side effects, such as increased cancer risk with long-term estrogen and salmon calcitonin use, the use of selective estrogen receptor modulators (SERMs) is associated with adverse cardiovascular and thromboembolic events, and two unusual side effects emerged with the long-term use of antiresorptive drugs—atypical fractures of the femoral shaft and osteonecrosis of the jaw. Meanwhile, many Chinese herbs, acupuncture, exercise therapies have also been used in the treatment of postmenopausal osteoporosis, and many evidence-based

evidences have proved its effectiveness in the treatment of postmenopausal osteoporosis. Although there have been many systematic reviews and network meta-analyses comparing the efficacy and safety of different drugs for the treatment of postmenopausal osteoporosis, they have not included other treatment measures together, so the conclusions that they draw remain imperfect. Given the adequate comparison of various therapeutic measures for the treatment of postmenopausal osteoporosis and analyzing their relative safety and efficacy may benefit clinicians seeking individualized treatment. This prompted us to systematically and comprehensively search the databases, include various RCTs that met the inclusion criteria and conduct a network meta-analysis to determine which osteoporosis treatment measures show the best efficacy for postmenopausal women at high risk of fragility fracture.

METHODS

Search strategy: Search Name: 骨质疏松检索式，cochrane. Last Saved: 14/09/2021 11:34:43 - ID Search #1 MeSH descriptor: [Osteoporosis] explode all trees | #2 (Osteoporoses):ti,ab,kw OR (Osteoporosis, Post-Traumatic):ti,ab,kw OR (Osteoporosis, Post Traumatic):ti,ab,kw OR (Post-Traumatic Osteoporoses):ti,ab,kw OR (Post-Traumatic Osteoporosis):ti,ab,kw (Word variations have been searched) | #3 (Osteoporosis, Senile):ti,ab,kw OR (Osteoporoses, Senile):ti,ab,kw OR (Senile Osteoporoses):ti,ab,kw OR (Osteoporosis, Involutional):ti,ab,kw OR (Senile Osteoporosis):ti,ab,kw (Word variations have been searched) | #4 (Osteoporosis, Age-Related):ti,ab,kw OR (Osteoporosis, Age Related):ti,ab,kw OR (Bone Loss, Age-Related):ti,ab,kw OR (Age-Related Bone Loss):ti,ab,kw OR (Age-Related Bone Losses):ti,ab,kw (Word variations have been searched) | #5 (Bone Loss, Age Related):ti,ab,kw OR (Bone Losses, Age-Related):ti,ab,kw OR (Age-Related Osteoporosis):ti,ab,kw OR (Age Related Osteoporosis):ti,ab,kw OR (Age-Related Osteoporoses):ti,ab,kw (Word variations have been searched) | #6 (Osteoporoses, Age-Related):ti,ab,kw (Word variations have been searched) | #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 | #8 MeSH descriptor: [Osteoporosis, Postmenopausal] explode all trees | #9 (Post-Menopausal Osteoporosis):ti,ab,kw OR (Bone Losses, Perimenopausal):ti,ab,kw OR (Postmenopausal Bone Loss):ti,ab,kw OR (Osteoporosis, Post Menopausal):ti,ab,kw OR (Postmenopausal Osteoporoses):ti,ab,kw (Word variations have been searched) | #10 (Osteoporoses, Postmenopausal):ti,ab,kw OR (Postmenopausal Osteoporosis):ti,ab,kw OR (Osteoporoses, Post-Menopausal):ti,ab,kw OR (Osteoporosis, Post-Menopausal):ti,ab,kw OR (Bone Loss, Perimenopausal):ti,ab,kw (Word variations have been searched) | #11 (Postmenopausal Bone Losses):ti,ab,kw OR (Bone Loss, Postmenopausal):ti,ab,kw OR (Post-Menopausal Osteoporoses):ti,ab,kw OR (Perimenopausal Bone Losses):ti,ab,kw OR (Bone Losses, Postmenopausal):ti,ab,kw (Word variations have been searched) | #12 (Perimenopausal Bone Loss):ti,ab,kw (Word variations have been searched) | #13 #8 OR #9 OR #10 OR #11 OR #12 | #14 #7 OR #13 | #15 ("randomised controlled trials"):pt OR ('controlled trial, randomized'):ti,ab,kw OR ('randomised controlled study'):ti,ab,kw OR ('randomised controlled trial'):ti,ab,kw OR ('randomized controlled study'):ti,ab,kw (Word variations have been searched) | #16 ('trial, randomized controlled'):ti,ab,kw (Word variations have been searched) | #17 #15 OR #16 | #18 #14 AND #17.

Participant or population: Participations: The subjects were postmenopausal women who were previously untreated and objectively diagnosed with osteoporosis by dual-energy X-ray densitometry (DXA). However, participants will not be included in the study if they meet one of the following conditions: 1) men; 2) secondary osteoporosis caused by certain medical conditions or treatments, such as metastasis, Paget's disease, hypercalcemia, or glucocorticoid-induced osteoporosis; 3) previous postmenopausal

osteoporosis treatment with continuous medication.

Intervention: All treatments for patients with postmenopausal osteoporosis, Including different drug combinations, different routes of administration.

Comparator: Different types of treatments for postmenopausal osteoporosis.

Study designs to be included: This study will conduct an overview of systematic reviews the efficacy of different treatments on postmenopausal osteoporosis and a network meta-analysis will be performed on the included RCTs. Because this is a literature-based study, ethical approval is not required. This study will follow the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement for reporting our overview.

Eligibility criteria: (1) Participations: The subjects were postmenopausal women who were previously untreated and objectively diagnosed with osteoporosis by dual-energy X-ray densitometry (DXA). However, participants will not be included in the study if they meet one of the following conditions: (1) men; (2) secondary osteoporosis caused by certain medical conditions or treatments, such as metastasis, Paget's disease, hypercalcemia, or glucocorticoid-induced osteoporosis; (3) previous postmenopausal osteoporosis treatment with continuous medication. (2) Intervention: All treatments for patients with postmenopausal osteoporosis, Including different drug combinations, different routes of administration.(3) Comparator: Different types of treatments for postmenopausal osteoporosis.(4) Outcomes: Primary outcomes included percentage change in bone mineral density (BMD) from baseline at lumbar spine (LS), total hip (TH), or distal radius (RU) after postmenopausal osteoporosis treatments and the incidence of fracture (vertebral [VF], nonvertebral [NVF], and wrist). The secondary result was the incidence of adverse events including cancer, cardiovascular disease (CVD), hip fracture, death, and osteonecrosis of the jaw.(5) Articles published in Chinese or English.(6) Randomized controlled trials (RCTs) that compared the efficacy and safety among different treatments in postmenopausal osteoporosis.

Information sources: PubMed, EMBASE, MEDLINE, and the Cochrane library were searched up to 1 September 2021 for randomized controlled trials of postmenopausal osteoporosis treatments using defined terms.

Main outcome(s): Primary outcomes included percentage change in bone mineral density (BMD) from baseline at lumbar spine (LS), total hip (TH), or distal radius (RU) after postmenopausal osteoporosis treatments and the incidence of fracture (vertebral [VF], nonvertebral [NVF], and wrist). The secondary result was the incidence of adverse events including cancer, cardiovascular disease (CVD), hip fracture, death, and osteonecrosis of the jaw.

Additional outcome(s): The secondary result was the incidence of adverse events including cancer, cardiovascular disease (CVD), hip fracture, death, and osteonecrosis of the jaw.

Data management: All the searched literatures were imported into Endnote X7 software. We identified 14823 records through database searching, preliminarily excluded 5048 duplicate records, and the remaining literatures were still being read the titles and abstracts. All the screening process was completed by 2 reviewers independently. The difference will be determined after discussion with the third reviewer. Finally, the included RCTs were used for direct meta-analysis and indirect network meta-analysis. The process of literature screening will be shown in Figure 1.

Quality assessment / Risk of bias analysis: We used the Cochrane risk of bias tool to assess the risk bias of the included studies. The Cochrane risk of bias tool consists of 7 domains: random sequence generation,

allocation concealment, blinding of participants and experimenters, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The Grades of Recommendations Assessment Development and Evaluation (GRADE) guidance will be used to assess the quality of evidence. We will allocate the quality of the evidence as high, moderate, low, or very low according to the GRADE guidance. Two authors independently assess the quality of evidence and the risk of bias in randomized clinical trials included randomized clinical trials included. Also, a third reviewer will be available to resolve any disagreement.

Strategy of data synthesis: 2.6.3. Direct meta-analysis (DMA) The statistical analyses were carried out using Stata software version 14.0 (Stata Corporation, College Station, TX). The risk ratio (RR) and the standardized mean difference (SMD) along with the 95% confidence interval (CI) were estimated for dichotomous and continuous outcomes, respectively. The point estimate of the RR value was considered statistically significant at $P < 0.05$. The point estimate of the SMD value was considered statistically significant at $P < 0.05$. They were then pooled across studies using a random effects model if heterogeneity was present (Cochrane's Q Test $P \leq 0.05$ or $I2 \geq 25\%$). If $I2 \geq 50\%$, we believe that the heterogeneity was large, and sensitivity analysis was performed accordingly. If sensitivity analysis did not reveal a source of heterogeneity, we manually excluded the included studies one by one to observe changes in heterogeneity. We did not use a funnel plot to identify possible publication bias because the number of included studies in one comparison was not larger than 10. 2.6.4. Network meta-analysis (NMA) All statistical analyses were conducted using the R Software Version 3.4.1(R Foundation for Statistical Computing. Vienna, Austria), plots depicting the network geometry were generated using Stata version 14.0. Bayesian NMA and the random-effects model were adopted throughout our analysis, due to the large heterogeneity of clinical trials. Dichotomous results were expressed as risk ratio (RR) with 95% confidence interval (CI), as for continuous outcomes, the standardized mean difference (SMD) was used to evaluate the treatment effects. Furthermore, each therapy at each endpoint was ranked according to their surface under the cumulative ranking curve (SUCRA), which indicated the performance of each treatment.

Subgroup analysis: According to the problems encountered in the analysis process, we will analyze different subgroups such as quality of articles, degree of disease, etc. If possible, we will do some additional subgroup analyses based on the results of heterogeneity and inconsistency.

Sensitivity analysis: If the heterogeneity is large ($I2 \geq 50$), we will conduct a sensitivity analysis to exclude those important data missing, low quality or small studies, and high risk of bias trials to ensure the stability of the results.

Language: Articles published in Chinese or English.

Country(ies) involved: China.

Keywords: Network meta-analysis, Postmenopausal osteoporosis, Bone morphogenetic protein (BMP), Randomized controlled trial (RCTs).

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