Efficacy and safety of 18 anti-osteoporotic drugs in the treatment of patients with osteoporosis caused by glucocorticoid: A network meta-analysis of randomized controlled trials

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Abstract

Background
Glucocorticoids are widely used in a variety of diseases, especially autoimmune diseases and inflammatory diseases, so the incidence of glucocorticoid-induced osteoporosis is high all over the world.

Objectives
The purpose of this paper is to use the method of network meta-analysis (NMA) to compare the efficacy of anti-osteoporosis drugs directly and indirectly, and to explore the advantages of various anti-osteoporosis drugs based on the current evidence.

Methods
We searched PubMed, Embase and Cochrane Library for randomized controlled trials (RCTs), of glucocorticoid-induced osteoporosis (GIOP) and compared the efficacy and safety of these drugs by NMA. The risk ratio (RR) and its 95% confidence interval (CI) are used as the influence index of discontinuous data, and the standardized mean difference (SMD) and its 95% CI are used as the influence index of continuous data. The statistical heterogeneity was evaluated by the calculated estimated variance ($\tau^2$), and the efficacy and safety of drugs were ranked by the surface under the cumulative ranking curve (SUCRA). The main outcome of this study was the incidence of vertebral fracture after taking several different types of drugs, and the secondary results were the incidence of non-vertebral fracture and adverse events, mean percentage change of lumbar spine (LS) and total hip (TH) bone mineral density (BMD) from baseline to at least 12 months.
Results

Among the different types of anti-GIOP, teriparatide (SUCRA 95.9%) has the lowest incidence of vertebral fracture; ibandronate (SUCRA 75.2%) has the lowest incidence of non-vertebral fracture; raloxifene (SUCRA 98.5%) has the best effect in increasing LS BMD; denosumab (SUCRA 99.7%) is the best in increasing TH BMD; calcitonin (SUCRA 92.4%) has the lowest incidence of serious adverse events.

Conclusions

Teriparatide and ibandronate are effective drugs to reduce the risk of vertebral and non-vertebral fractures in patients with GIOP. In addition, long-term use of raloxifene and denosumab can increase the BMD of LS and TH.

Introduction

Glucocorticoids are widely used in a variety of diseases, especially autoimmune diseases and inflammatory diseases, such as rheumatoid arthritis, nephrotic syndrome, systemic lupus erythematosus, inflammatory bowel disease and severe infection and shock. Nearly 1–2% of the world’s people take GCs for a long time, and up to 30–40% of them may have a history of fragile fractures [1], especially the TH, LS and femoral neck fractures [2]. The duration and dose of glucocorticoids can have a serious impact on the risk of fracture. Among the patients who used GCs for a long time, the incidence of fracture (5%) was twice as high as that of those who used GCs for a short time (2.5%) [3]. In addition, the higher the dose, the higher the incidence of fracture. Taking 2.5 mg of prednisone per day will increase the risk of fracture. If the dose is more than 7.5 mg, the risk of fracture will increase as much as 5 times [4].

There are mainly three kinds of anti-osteoporosis drugs: (1) Anti-bone resorption drugs include bisphosphonates (such as alendronate, zoledronic acid, risedronate, ibandronate, etidronate and clodronate, etc.), calcitonin (such as elcatonin and salcatonin), selective estrogen receptor modulators (SERMs) (such as raloxifene) and cathepsin K inhibitors. (2) Drugs that promote bone formation include parathyroid hormone analogue (PTHa) (such as teriparatide), active vitamin D and its analogues (such as alfalcacidol and calcitriol); (3) double-acting drugs including strontium salts (such as strontium ranelate) and receptor activator of nuclear factor kappaB ligand (RANKL) inhibitors (such as denosumab). This study will systematically compare the effectiveness and safety of the above-mentioned drugs.

Bisphosphonate is currently the most widely used anti-osteoporosis drug. As an analog of pyrophosphate, it has a strong affinity for hydroxyapatite and can be selectively absorbed and adhered to the mineral surface of bones, resulting in osteoclasts apoptosis, thus exerting an anti-bone resorption effect [5].

Calcitonin drugs mainly reduce bone resorption by inhibiting the number and secretion activity of osteoclasts. Its efficacy is 40–50 times that of human calcitonin, and it can take effect quickly within 2 hours [6].

SERMs play different roles in different tissues. For example, raloxifene can play an estrogen-like effect after binding to the receptor in bone tissue: inhibit bone resorption, increase bone density, and reduce fracture incidence. In the uterus or breast tissue, it presents an estrogen antagonistic effect: inhibits the proliferation of breast and endometrium.

As a PTHa that promotes bone formation, teriparatide can enhance osteoblast activity, promote bone formation, increase bone mineral density, improve bone quality, and reduce the risk of vertebral and non-vertebral fractures [7].
Representative drugs of active vitamin D and its analogues are 1α-hydroxyvitamin D₃ (alfacalcidol) and 1,25 (OH)₂ -VD₃ (calcitriol). They are more suitable for the elderly, patients with osteoporosis complicated with renal insufficiency and with 1α hydroxylase deficiency or reduction, which can increase bone density, reduce falls, and the incidence of fractures [8].

As an inhibitor of nuclear factor kappa-B receptor activating factor ligand (RANKL), denosumab can inhibit the binding of RANKL to its receptor and reduce the formation, function and survival of osteoclasts, thus reducing bone resorption, increasing bone mass and improving the strength of cortical or cancellous bone [9].

The above-mentioned different types of drugs have different mechanisms of action. Generally speaking, they can be summarized as anti-bone resorption and promoting bone formation. However, there are few studies that can comprehensively compare these drugs. This article compares their efficacy and safety through a NMA, which provides more valuable suggestions for clinical medication.

**Materials and methods**

This study is reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (see S1 File) and AMSTAR (Assessing the methodological quality of systematic reviews) (see S2 File).

**Search strategy and selection criteria**

We searched randomized controlled trials published by PubMed, Embase and Cochrane Library until March 2020. The keywords are "Glucocorticoid(s)" or"corticoid(s)" or"corticosteroid(s)" or"methylprednisolone" or"prednisone" or"prednisolone" or"hydrocortisone" or"triamcinolone" or"dexamethasone" and "osteoporosis".

The inclusion criteria are as follows: (1)Patients were at least 18 years old; (2) Patients had taken prednisone or its equivalent at a dosage of ≥5 mg/day for ≥3 months prior to screening; (3) Patients were required to have a LS or TH BMD T score of ≤−2.0 or ≤−1.0 plus at least one fragility fracture while taking glucocorticoids; (4) Language was English; (5) Studies were RCTs.

The exclusion criteria are as follows: (1) Primary osteoporosis (including postmenopausal osteoporosis, senile osteoporosis and idiopathic osteoporosis) and other secondary osteoporosis caused by non-glucocorticoid; (2) The type of articles was review, meta-analysis, and other non-RCT; (3) The content and outcome are not the incidence of vertebral fracture and the change of BMD.

**Data extraction and quality assessment**

The main outcome that this study focuses on were the incidence of vertebral and non-vertebral fracture, and the secondary outcome were mean percent changes from baseline to at least 12 months in BMD of the FN and TH, and the incidence of serious adverse events.

In this paper, two persons independently conducted literature search, screening, data extraction and heterogeneity analysis. If there is any objection, they will reach an agreement after discussion, complete the preliminary search according to the established search strategy, and read the abstract and full text to exclude studies that do not meet the inclusion criteria.

**Data synthesis and analysis**

All values are expressed as mean ± SD. We use the risk ratio (RR) and its 95% confidence interval (CI) as the effect index for discontinuous data, and the standardized mean difference (SMD) and its 95% confidence interval (CI) as the effect index of continuous data. We use the
calculated estimated variance ($\tau^2$) to evaluate the statistical heterogeneity, use the surface under the cumulative ranking curve (SUCRA) to rank the efficacy and safety of these drugs. The larger the value, the higher the ranking. The loop-specific heterogeneity test is used to evaluate the inconsistency between direct comparison and inter-comparison. If $p<0.05$, it means that there is a statistically significant inconsistency. A funnel chart is drawn to detect publication bias. All data are analyzed by stata16 MP.

Results

Search results and characteristics of included studies

We searched the PubMed, Embase and Cochrane Library for studies on the treatment of GIOP. Initially, there were 307 articles, 72 of which were excluded due to non-RCTs, including 20 reviews, 30 meta-analysis, and 22 other types of non-RCTs. We screened the remaining 235 full-text studies, and excluded 184, including 85 duplicate studies. The content and outcome of 89 studies are not the incidence of vertebral fracture and the change of BMD, and 10 studies failed due to insufficient recruitment and cessation of intervention (Fig 1).

Our study included 51 randomized controlled trials [10–60], a total of 6803 subjects, a total of 18 drugs were analyzed and compared, they are alendronate, alfalcaldiol, calcium, teriparatide, denosumab, calcitonin, pamidronate, zoledronic acid, risedronate, cladronate, etidronate, parathyroid hormone, raloxifene, sodium fluoride (NaF), eldecalcitol, monofluorophosphate, minodronate, ibandronate, Vitamin D$_3$.

Table 1 shows the basic characteristics of these studies, including the first author and published year; the dose and duration of patients taking glucocorticoids; the patient’s age, gender, BMD or T-score of LS; and the number and proportion of menopausal women among them.

Incidence of vertebral fractures

There were 24 studies involving vertebral fractures, with a total of 4796 patients. The network relationship is shown in Fig 2a, and the included studies do not form a closed loop. It can be seen from the funnel chart that the study is uniformly distributed in the middle and upper part of the funnel, and no research falls outside the funnel diagram, so it can be considered that the risk of small sample effect or publication bias is very small (Fig 4a). In terms of reducing the incidence of vertebral fractures, teriparatide (SUCRA 95.9%) has the best effect, followed by pamidronate (SUCRA 84.3%) and raloxifene (SUCRA 78.7%), while the worst effect is minodronate (SUCRA 8.0%), the specific ranking is shown in Fig 5a and Table 2. In addition, the incidence of vertebral fractures was lower in teriparatide (RR0.06, 95%CI 0.010.27) and etidronate (RR0.29, 95%CI 0.160.51) than placebo.

Incidence of non-vertebral fractures

There were 13 studies on non-vertebral fractures, with a total of 3455 patients. The network relationship is shown in Fig 2b, and the included studies do not form a closed loop. From the funnel chart, we can see that the included research is not very balanced, basically distributed at the top of the funnel, and no research falls outside the funnel chart. The risk of small sample effect or publication bias is relatively high (Fig 4b). In reducing the incidence of non-vertebral fracture, ibandronate (SUCRA 75.2%) is the best, followed by alendronate (SUCRA 70.2%) and etidronate (SUCRA 67.2%), while the worst effect is denosumab (SUCRA 19.6%). The specific ranking is shown in Fig 5b and Table 2.
Mean percentage change of BMD of LS from baseline

There were 51 articles studying the changes of BMD of LS, involving a total of 6803 subjects. The network relationship is shown in Fig 2c, the consistency test is shown in Fig 3a, and the
Table 1. Characteristics of the included studies*a.

| Comparison | n  | GC dose(mg/d)b | GC Duration(m) | Age(y) | Sex (M/F) | postmenopausal n (%) | LS BMD (gm/cm²) or T-score |
|------------|----|----------------|---------------|--------|-----------|----------------------|---------------------------|
| Ron N.J. de Nijs 2007 | | | | | | | |
| Alendronate | 99 | 23±20 | >6 | 60±14 | 40/59 | 52(52.5) | 0.99±0.17 |
| Alfacalcidol | 101 | 22±18 | >6 | 62±15 | 36/65 | 55(54.5) | 1.02±0.16 |
| Seiji Takeda 2008 | | | | | | | |
| Alendronate | 17 | 12.1±6.6 | >6 | 49.2±14.6 | 0/17 | 11(64.7) | 0.838±0.153 |
| Alfacalcidol | 16 | 11.5±10.5 | >6 | 45.0±13.2 | 0/16 | 7(43.8) | 0.893±0.132 |
| S. Kitazai 2008c | | | | | | | |
| Alendronate | 16 | 9.7±9.7 | 110.4±108 | 41.2±12.8 | 10/6 | NM | 0.926±0.098 |
| Alfacalcidol | 20 | 10.9±6.5 | 67.2±73.2 | 38.1±15.5 | 12/8 | NM | 0.906±0.125 |
| S. Aubrey-Stoch 2009 | | | | | | | |
| Alendronate | 114 | 16.5±11.6 | 54.6±72.0 | 51.9±14.4 | 44/70 | 29(25.4) | -0.33±1.37 |
| Placebo | 59 | 15.6±12.0 | 44.8±63.0 | 54.6±14.8 | 28/31 | 17(28.8) | 0.38±1.11 |
| Philip N Sambrook 2002 | | | | | | | |
| Alendronate | 64 | 12.0±9.9 | >6 | 62.4±13.5 | 20/44 | NM | 1.02±0.20 |
| Calcitriol | 67 | 15.8±15.4 | >6 | 57.9±13.0 | 21/46 | NM | 1.07±0.24 |
| Johannes W.G. Jacobs 2007 | | | | | | | |
| Alendronate | 99 | 23±20 | >6 | 60±14 | 40/59 | 52(52.5) | 1.06±0.21 |
| Alfacalcidol | 101 | 22±18 | >6 | 62±15 | 36/65 | 55(54.5) | 1.09±0.21 |
| Ken Iseri 2018 | | | | | | | |
| Denosumab | 14 | 5.0 | 6.9 | 66.5 | 6/8 | 5(35.7) | 0.895 |
| Alendronate | 14 | 5.0 | 9.0 | 65.5 | 6/8 | 4(28.6) | 0.875 |
| Funda Tascioglu 2004 | | | | | | | |
| Alendronate | 22 | 8.00±1.77 | 48.00±21.12 | 55.67±6.67 | 0/22 | 22(100.0) | 0.69±0.07 |
| Calcitonin | 24 | 7.58±2.04 | 54.48±27.36 | 58.13±6.51 | 0/24 | 24(100.0) | 0.68±0.07 |
| Shegeki Yamada 2007 | | | | | | | |
| Risedronate | 6 | 3.5±1.7 | 33.3±5.7 | 69.2±6.0 | 0/6 | 6(100) | 0.64±0.10 |
| Alfacalcidol | 6 | 3.8±2.8 | 25.6±12.3 | 72.0±8.7 | 0/6 | 6(100) | 0.64±0.10 |
| Jese S. Siffledeen 2005 | | | | | | | |
| Etidronate | 72 | NM | 5.6±1.9 | 40.0±12.1 | 38/34 | NM | 0.94±0.10 |
| Placebo | 71 | NM | 5.4±1.6 | 40.1±14.1 | 34/37 | NM | 0.91±0.11 |
| Kenneth G. Saag 2007 | | | | | | | |
| Alendronate | 214 | 7.8 | 14.4 | 57.3±14.0 | 41/173 | 143(82.7) | 0.85±0.13 |
| Teriparatide | 214 | 7.5 | 18 | 56.1±13.4 | 42/172 | 134(77.9) | 0.85±0.13 |
| Benito R. Losada 2008 | | | | | | | |
| Alendronate | 32 | 7.5±1.7 | 5.3±2.9 | 54.9±4.5 | 5/27 | NM | 0.8±0.05 |
| Teriparatide | 29 | 8.8±1.9 | 2.7±3.2 | 52.5±5.0 | 5/24 | NM | 0.8±0.05 |
| Alan L. Burshell 2009 | | | | | | | |
| Alendronate | 77 | 8.0 | 16.8 | 60.6±2.5 | 17/60 | 50(64.9) | -2.7±0.1 |
| Teriparatide | 80 | 7.5 | 14.4 | 56.1±2.6 | 13/67 | 41(51.3) | -2.5±0.1 |
| Jean-Pierre 2009 | | | | | | | |
| Alendronate | 192 | 10.1±0.7 | 5.1±0.5 | 57.1±1.0 | NM | NM | 0.85±0.01 |
| Teriparatide | 195 | 9.4±0.4 | 5.2±0.6 | 55.8±1.0 | NM | NM | 0.85±0.01 |
| B. L. Langdahl 2009 | | | | | | | |
| Alendronate | 143 | 7.3 | 26.4 | 62.1±1.2 | 0/143 | 143(100) | -2.7±0.1 |
| Premenopausal | 30 | 10.0 | 10.8 | 35.8±2.1 | 0/30 | 0 | -2.6±0.2 |
| Men | 41 | 10.0 | 25.2 | 59.7±1.9 | 41/0 | 0 | -2.3±0.2 |

(Continued)
| Comparison      | n  | GC dose (mg/d) | GC Duration (m) | Age (y) | Sex (M/F) | postmenopausal n (%) | LS BMD (gm/cm²) or T-score |
|-----------------|----|----------------|-----------------|---------|-----------|----------------------|-----------------------------|
| teriparatide    |    |                |                 |         |           |                      |                             |
| Postmenopausal  | 134| 7              | 31.2            | 61.9±1.2| 0/134     | 134 (100)            | −2.7±0.1                    |
| Premenopausal   | 37 | 8              | 21.6            | 40.0±1.9| 0/37      | 0                    | −2.4±0.2                    |
| Men             | 42 | 10             | 27.6            | 55.5±1.9| 42/0      | 0                    | −2.3±0.2                    |
| Kenneth G. Saag 2009 | | | | | | | |
| alendronate     | 214| ≥5             | 24              | 57.3±14.0| 41/173    | 143 (66.8)           | 0.86±0.014                  |
| teriparatide    | 214| ≥5             | 27.6            | 56.1±13.4| 42/172    | 134 (62.6)           | 0.86±0.014                  |
| Kenneth G Saag 2016 | | | | | | | |
| alendronate     | 214| 7.5            | 48              | 57.1±14  | 41/173    | NM                   | −2.5±0.1                    |
| teriparatide    | 214| 7.5            | 27.6            | 56±13    | 42/172    | NM                   | −2.4±0.1                    |
| Kenneth G Saag 1998 | | | | | | | |
| placebo         | 159| 10             | NM              | 54±15    | 52/107    | 67 (42.1)            | 0.95±0.16                   |
| alendronate     | 157| 10             | NM              | 55±15    | 44/113    | 83 (52.9)            | 0.93±0.16                   |
| S. Aubrey. Stoch 2009 | | | | | | | |
| Alendronate     | 114| 16.5±11.6      | 54.6±72.0       | 51.9±14.4| 44/70      | 29 (25.4)            | −0.33±1.37                  |
| Placebo         | 59 | 15.6±12.0      | 44.8±63.0       | 54.6±14.8| 28/31      | 17 (28.8)            | 0.38±1.11                   |
| Jonathan D. Adachi 2000 | | | | | | | |
| Placebo         | 61 | 20.4±20.7      | >3              | 54±15    | 19/42     | 25 (41.0)            | 0.93±0.15                   |
| Alendronate     | 55 | 17.4±18.0      | >3              | 53±15    | 15/40     | 26 (47.3)            | 0.93±0.15                   |
| Chi Chiu Mok 2010 | | | | | | | |
|Raloxifene       | 57 | 7.2±6.2        | 58.1            | 55.4±7.8| 0/57      | 57 (100)             | 0.86±0.136                  |
| Placebo         | 57 | 6.5±5.5        | 67.8            | 55.2±7.6| 0/57      | 57 (100)             | 0.848±0.147                 |
| David M Reid 2009 | | | | | | | |
| Zoledronic acid | 272| 10             | >12             | 53.2±14.0| 87/185    | 118 (43.4)           | −1.34±1.34                  |
| Risedronate     | 273| 10             | >12             | 52.7±13.7| 90/183    | 117 (42.9)           | −1.40±1.28                  |
| Philip N Sambrook 2011 | | | | | | | |
| Zoledronic acid | 75 | 15.3±13.11     | >3              | 57.2±14.73| 75/0       | 0                   | 0.929±0.152                 |
| Risedronate     | 77 | 15.5±12.12     | >3              | 55.7±13.95| 77/0       | 0                   | 0.920±0.139                 |
| Claus-C. Güer 2012 | | | | | | | |
| Teriparatide    | 45 | 8.8            | 85.2            | 57.5±12.8| NM        | NM                  | −2.48                       |
| Risedronate     | 47 | 8.8            | 58.8            | 55.1±15.5| NM        | NM                  | −2.33                       |
| Kenneth G. Saag 2019 | | | | | | | |
| Risedronate     | 252| 11.1±7.69      | >3              | 61.3±11.1| 67/185    | 157 (62.3)           | −1.96±1.38                  |
| Denosumab       | 253| 12.3±8.09      | >3              | 61.5±11.6| 68/185    | 159 (62.8)           | −1.92±1.38                  |
| R. Eastell 1999 | | | | | | | |
| Placebo         | 40 | 812±286        | 199.2           | 65.0±6.3 | 0/40      | 40 (100)             | 0.76±0.13                   |
| Risedronate     | 40 | 810±298        | 162             | 64.5±7.2 | 0/40      | 40 (100)             | 0.80±0.13                   |
| David M. Reid 1999 | | | | | | | |
| Placebo         | 96 | 15±13          | 62±72           | 59±12    | 36/60     | 53±55.2              | −1.7±1.5                    |
| Risedronate     | 100| 15±12          | 57±58           | 58±12    | 36/64     | 55±55.0              | −1.7±1.6                    |
| Sonsoles Guadalix 2011 | | | | | | | |
| Risedronate     | 45 | 3931.2±2129.4  | 12              | 57.9±6.5 | 32/13     | 13 (28.9)            | 0.792±0.104                 |
| Placebo         | 44 | 4584.0±2638.6  | 12              | 54.6±8.8 | 38/6      | 4 (9.1)              | 0.844±0.089                 |
| Naohiko Fujii 2006 | | | | | | | |
| Placebo         | 37 | 10.6±5.1       | 6.5±8.1         | 42.2±16.5| 16/21     | 6 (16.2)             | 1.09±0.119                  |
| Risedronate     | 40 | 9.9±5.0        | 5.2±6.3         | 40.0±16.3| 15/25     | 6 (15.0)             | 1.054±0.137                 |

A Rmando T Orres 2004

(Continued)
Table 1. (Continued)

| Comparison     | n   | GC dose(mg/d) | GC Duration(m) | Age(y) | Sex (M/F) | postmenopausal n (%) | LS BMD (gm/cm²) or T-score |
|----------------|-----|---------------|----------------|--------|-----------|----------------------|-----------------------------|
| Calcitriol     | 45  | 10            | 12             | 46.7±12.2 | 37/8       | 3(6.7)               | 1.02 ± 0.12                 |
| Placebo        | 41  | 10            | 12             | 51.1±11.9 | 30/11      | 7(17.1)              | 0.98 ± 0.12                 |
| Toshio Matsumoto 2020 | |   | | | | |
| Eldecalcitol   | 178 | 10.3±9.0      | >3             | 58.5±15.7 | 59/123     | 75(61.0)             | -0.70±1.39                 |
| Alfacalcidol   | 182 | 9.5±7.7       | >3             | 58.4±15.7 | 62/116     | 72(62.1)             | -0.54±1.39                 |
| J. D. Ringe 1999 | |   | | | | |
| Alfacalcidol   | 43  | 9.7           | 70.8           | 60.6    | 15/28      | NM                   | -3.28                       |
| vitamin D      | 101 | 7.5           | 36             | 60.3±9.9 | 36/65      | NM                   | 3.25±0.39                  |
| Satoshi Soen 2019 | |   | | | | |
| Minodronate    | 40  | 7.53±6.57     | 44.0±48.3      | 62.0±13.5 | 17/23      | NM                   | 93.1±16.0                  |
| Placebo        | 42  | 7.62±5.74     | 41.5±42.5      | 61.3±9.6 | 23/19      | NM                   | 93.1±16.0                  |
| P. Pitt 1997   |     |               |                |         |            |                      |                            |
| placebo        | 58  | ≥7.5          | ≥12            | 59.0±13.6 | 20/38      | 30(51.7)             | 0.92±0.12                  |
| etidronate     | 59  | ≥7.5          | ≥12            | 58.5±13.9 | 22/37      | 27(45.8)             | 0.89±0.15                  |
| Jacques P. Brown 2001 | |   | | | | |
| placebo        | 61  | 22.7±21.7     | ≥52            | 60±17   | 24/37      | 29(47.5)             | NM                         |
| etidronate     | 53  | 20.5±22.2     | ≥52            | 64±13   | 17/36      | 29(54.7)             | NM                         |
| I. García-Delgado 1996 | |   | | | | |
| Calcitonin     | 13  | NM            | NM             | 55.9±1.63 | 13/0       | NM                   | 0.85±0.069                 |
| Etidronate     | 14  | NM            | NM             | 52.7±1.82 | 14/0       | NM                   | 0.87±0.091                 |
| Y. Boutsen 1997 | |   | | | | |
| Pamidronate    | 14  | 31.2±23.8     | NM             | 60±16   | 3/11       | 3(21.4)              | 0.857±0.118                |
| Calcium        | 13  | 28.1±23.8     | NM             | 61±12   | 2/11       | 2(15.4)              | 0.960±0.161                |
| Y. Boutsen 2000 | |   | | | | |
| Pamidronate    | 9   | ≥10           | ≥3             | 59±21   | 4/5        | 4(44.4)              | 0.965±0.161                |
| Calcium        | 9   | ≥10           | ≥3             | 57±18   | 4/5        | 4(44.4)              | 0.963±0.173                |
| T. Bianda 2000 | |   | | | | |
| Calcitonin     | 12  | 14800±1200    | 12             | 54.5±1.0 | 11/1       | NM                   | 0.97±0.04                  |
| Pamidronate    | 14  | 13800±1700    | 12             | 51.1±3.0 | 13/1       | NM                   | 1.01±0.03                  |
| Se Hwa Kim 2003 | |   | | | | |
| Placebo        | 20  | NM            | NM             | 48±18   | 9/11       | 7(35.0)              | 0.897±0.193                |
| Pamidronate    | 25  | NM            | NM             | 49±15   | 14/11      | 7(28.0)              | 0.864±0.185                |
| A Nzeusseu Toukap 2005 | |   | | | | |
| Pamidronate    | 16  | ≥7.5          | ≥12            | 30.5±7.4 | NM         | NM                   | 0.954±0.108                |
| Placebo        | 14  | ≥7.5          | ≥12            | 25.3±9.2 | NM         | NM                   | 0.974±0.147                |
| B. Frediani 2003 | |   | | | | |
| Clodronate     | 84  | 8.4±3.2       | NM             | 61.1±12.2 | 0/84       | 63(75.0)             | 0.99±0.18                  |
| Placebo        | 79  | 8.9±4.1       | NM             | 62.4±13.4 | 0/79       | 61(77.2)             | 0.98±0.16                  |
| Vered Abitbol 2007 | |   | | | | |
| Clodronate     | 33  | 15.0          | 12             | 30      | 16/17      | NM                   | -1.3±1.10                  |
| Placebo        | 34  | 14.0          | 12             | 30      | 14/20      | NM                   | -1.2±1.33                  |

(Continued)
Funnel chart is shown in Fig 4c, which shows that the included studies are more symmetrical, most of the studies are at the top, but very few studies are in the lower part of the funnel and outside. Therefore, the risk of small sample effect or publication bias is small. Among various types of anti-osteoporosis drugs, raloxifene (SUCRA 98.5%) is the best in increasing LS BMD, followed by pamidronate (SUCRA 86.2%) and denosumab (SUCRA 78.9%). On the contrary, the worst effect is Vitamin D$_3$ (SUCRA 15.6%), the specific ranking is shown in Fig 5c and Table 2. Moreover, compared with placebo, raloxifene (SMD 12.56, 95%CI 6.33–18.78) and pamidronate (SMD 6.84, 95%CI 2.26–11.42) significantly increased LS BMD.

Mean percentage change of BMD of TH from baseline

There were 26 studies involving changes in TH BMD, with a total of 3946 patients. The network relationship is shown in Fig 2d, and the consistency test is shown in Fig 3b. It can be seen from the funnel chart that most of the studies are at the top, but there are 4 studies outside the funnel chart, so the risk of small sample effects or publication bias is not excluded (Fig 4d). Among various types of anti-osteoporosis drugs, denosumab (SUCRA 99.7%) is the best in
increasing total hip bone density, followed by pamidronate (SUCRA 87.9%) and raloxifene (SUCRA 68.5%), and the worst effect is NaF (sodium fluoride) (SUCRA 19.1%), the specific ranking is shown in Fig 5d and Table 2. Compared with placebo, denosumab (SMD 12.63, 95% CI 6.51–18.75 and pamidronate (SMD 5.14, 95% CI 3.15–8.94) increased the BMD of the TH.

Serious adverse events

There were 35 studies on adverse reactions, with a total of 6028 patients. The network relationship is shown in Fig 2e, and the consistency test is shown in Fig 3c. As can be seen from the funnel chart, the included studies are not very balanced, most of them are distributed at the top of the funnel, and one study falls outside the funnel chart, which does not rule out the risk of small sample effect or publication bias (Fig 4e). In terms of the incidence of adverse reactions, calcitonin (SUCRA 92.4%) is the best, followed by alfacalcidol (SUCRA 81.5%) and Vitamin D3 (SUCRA 79.3%), while the worst effect is ibandronate (SUCRA 15.5%). The specific ranking is shown in Fig 5e and Table 2.

Discussion

We conducted a NMA of different types of anti-osteoporosis drugs and reached the following conclusions: Among the different types of anti-osteoporosis drugs, teriparatide (SUCRA 95.9%)

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Fig 2. Network meta-analysis plots. (2a) Incidence of vertebral fractures, (2b) Incidence of non-vertebral fractures, (2c) Mean percentage change of BMD of LS from baseline, (2d) Mean percentage change of BMD of TH from baseline, (2e) Serious adverse events. The size of each node is positively correlated with the number of direct comparative studies of different anti-osteoporotic drugs, and the line thickness is positively correlated with the sample size included in the study.

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has the best effect in reducing the incidence of vertebral fractures; ibandronate (SUCRA 75.2%) has the best effect in reducing the incidence of non-vertebral fractures; raloxifene (SUCRA 98.5%) has the best effect in increasing LS BMD; denosumab (SUCRA 99.7%) is the best in increasing TH BMD; calcitonin (SUCRA 92.4%) has the lowest incidence of adverse events.

We obtained the following results through NMA of different kinds of anti-osteoporotic drugs. Compared with placebo, the incidence of vertebral fracture was very low in teriparatide (RR 0.06, 95%CI 0.01–0.27) and etidronate (RR 0.29, 95%CI 0.16–0.51); raloxifene (SMD 12.56, 95%CI 6.33–18.78) and pamidronate (SMD 6.84, 95%CI 2.26–11.42) significantly increased LS BMD; denosumab (SMD 12.63, 95%CI 6.51–18.75) and pamidronate (SMD 5.14, 95%CI 3.15–8.94) increased BMD of the TH. There were no significant differences in the incidence of non-vertebral fractures or adverse effects of the other drugs compared with placebo.

Previous NMA showed that teriparatide was the most effective anti-osteoporotic drug for vertebral fractures [61–66] and the lowest incidence of ibandronate for non-vertebral fractures [61,63]. These two conclusions are consistent with this study. For the increase of LS BMD, the results of, M. A. Amiche et al. [61] show that ibandronate is the best, while this paper found that raloxifene is the best, we should be cautious about the differences in these results.

In addition, our analysis shows that vitamin D analogues (such as calcitriol) and active metabolites (such as alfacalcidol) may be more effective in preventing fractures than vitamin D alone. This provides an evidence-based medicine basis for clinical drug use in the future. Vitamin D should not be used only, but its analogues and active metabolites should be used in combination.

Although the efficacy of the above anti-osteoporotic drugs is significant, their adverse reactions cannot be ignored at the same time. As one of the representative drugs of bisphosphate, the main adverse events of ibandronate are gastrointestinal reactions, including epigastric pain, acid regurgitation, inflammation of the esophagus and stomach and so on. Other adverse reactions include affecting renal function, so patients with GFR less than 35 mL/min should disable ibandronate. In addition, the lower incidence of adverse events included osteonecrosis of the jaw and atypical femur fracture [67]. A randomized controlled trial showed that adverse events to teriparatide included nausea (18%), headaches (13%) and leg cramps (3%) [7].
main adverse reactions of denosumab are infections, such as urinary tract infection, sinusitis, pharyngitis, bronchitis and cellulitis. Others include joint pain and hypocalcemia [68]. Raloxifene is well tolerated, the side effects are limited to hot flashes and vaginal dryness, and the risk of thromboembolism is slightly increased [69]. Intranasal calcitonin can cause rhinitis, nosebleeds and allergic reactions, especially in people with a history of salmon allergy [70].

This article has the following advantages. First, this article is to study the most complete mesh meta-analysis of anti-osteoporosis drugs. Second, this article is an earlier study of an NMA of anti-osteoporosis drugs on the BMD of the LS and TH. Third, this article first includes several drugs that have not been studied in previous NMA, including calcitonin,
clodronate, sodium fluoride, eldecalcitol, monofluorophosphate, and mineralronate. However, there are some shortcomings in our research. First, the menopause of female subjects may affect the efficacy of the drug. Second, the patients included in this study were given long-term calcium and vitamin D supplementation, which also had an impact on the efficacy of the drug. Third, the research time of the articles included in this paper varies greatly, from 12 months to 36 months, or even longer. Fourth, the number of randomized controlled trials for direct comparison of some drugs included in this paper is relatively small, which leads to the fact that the results of indirect comparison may not be very persuasive and should be treated with caution. Last, this paper includes the original research of different countries and

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Fig 4. Funnel chart. (4a) Incidence of vertebral fractures, (4b) Incidence of non-vertebral fractures, (4c) Mean percentage change of BMD of LS from baseline, (4d) Mean percentage change of BMD of TH from baseline, (4e) Serious adverse events.
regions, which is also one of the limitations of this paper. Therefore, more experiments are needed to verify or correct the results of this paper.

**Conclusion**

In terms of the incidence of vertebral and non-vertebral fractures, teriparatide and ibandronate are the most effective drugs. Raloxifene and denosumab have the most significant effect on increasing BMD of LS and TH. There was no significant difference in the incidence of adverse events among different drugs.

Table 2. SUCRA ranking.

| Rank or Outcomes | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| LS BMD           | RAL | PAM | DEN | CLO | MFP | NaF | TPTD | Ca  | CT  | MIN | ALE | ELD | IBA | ALF | ZOL | ETI | RIS | PLA | VD3 |
| TH BMD           | DEN | PAM | RAL | Ca  | TPTD | ALE | IBA  | RIS | CT  | ZOL | ETI | ELD | MIN | PLA | ALE | NaF |     |     |
| VF               | TPTD | PAM | RAL | ETI | VD3 | CT  | ALE  | CLO | DEN | RIS | ELR | NaF | ZOL | PLA | ALF | MFP | MIN |     |
| non-VF           | IBA | ALE | ETI | ALF | TPTD | ELD | PLA  | VD3 | RIS | DEN |     |     |     |     |     |     |     |     |
| AE               | CT  | ALF | VD3 | MIN | ELD | ALE  | TPTD | ETI | CLO | ZOL | RAL | Ca  | DEN | MFP | PLA | RIS | PAM | IBA |

SUCRA = the surface under the cumulative ranking curve; LS = lumbar spine; TH = total hip; BMD = bone mineral density; RAL = raloxifene; PAM = pamidronate; DEN = denosumab; CLO = clodronate; MFP = monofluorophosphate; NaF = sodium fluoride; TPTD = teriparatide; Ca = calcium; CT = calcitonin; MIN = minodronate; ALE = alendronate; ELR = etidronate; IBA = ibandronate; ALF = alfacalcidol; ZOL = zoledronic acid; ETI = etidronate; RIS = risedronate; PLA = placebo; VD3 = Vitamin D3; VF = vertebral fractures; non-VF = non-vertebral fractures; AE = adverse events.

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Supporting information

S1 Table. Characteristics of the included studies.
(DOCX)

S2 Table. SUCRA ranking.
(DOCX)

S1 File. The PRISMA network meta-analysis checklist.
(DOCX)

S2 File. Risk of bias summary: Review authors’ judgements about each risk of bias item for each included study.
(PNG)

S3 File. Risk of bias graph: Review authors’ judgements about each risk of bias item presented as percentages across all included studies.
(PNG)

S4 File. Search strategy.
(DOCX)

S5 File. Risk of bias summary.
(DOCX)

S6 File. Minimal data set.
(XLSX)

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