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Pharmacological Interventions for Glucocorticoid-Induced Osteoporosis: An Umbrella Review

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ABSTRACT

There is still a lack of high-quality evidence-based studies on the efficacy of drug treatment for glucocorticoid-induced osteoporosis (GIOP). The purpose of this umbrella review is to comprehensively evaluate the existing evidence to determine the efficacy and safety of pharmacological interventions for GIOP. We searched PubMed, Embase, and the Cochrane Library for systematic reviews and/or meta-analyses (SRs) of randomized controlled trials (RCTs) aimed at evaluating drug therapy for GIOP. Both the methodological quality and the strength of recommendation of the endpoints included in the SRs were evaluated by using the AMSTAR-2 tool and GRADE system, respectively. Six SRs involving 7225 GIOP patients in 59 RCTs were included in this umbrella review. The results of the methodological quality evaluation showed that 2 high-quality, 2 low-quality and 2 critically low-quality SRs were included. The GRADE evaluation results showed that the quality of evidence and the strength of recommendation of 46 outcome indicators were evaluated in the umbrella review; there were 3 with high-level evidence, 20 with moderate-level evidence, 15 with low-level evidence, and 8 with very low-level evidence. Moderate- to high-level evidence suggests that teriparatide, bisphosphonates, and denosumab can improve the bone mineral density in patients with GIOP. The findings of this umbrella review can enable patients and clinical healthcare professionals to choose the best drug prescription.

Introduction

Glucocorticoids (GCs) are widely used in clinical work due to their effectiveness in achieving immunosuppression, an anti-inflammatory response, and other pharmacological effects [1, 2]; in fact, GCs are used to treat many types of diseases. However, long-term use of GCs can induce osteoblast regulation, increase osteoclast activation, and reduce calcium absorption by the digestive system [1–3]. Glucocorticoid-induced osteoporosis (GIOP), a metabolic bone disease caused by endogenous or exogenous GCs, is the most common type of secondary osteoporosis [4]. Studies have shown that

approximately 1 % of the population in the United States requires the long-term use of GCs [5]. The incidence of osteoporotic fractures in patients with long-term use of GCs at doses beyond the physiological levels will reach 30–50 %, and the risk of refracture after the initial fracture will increase significantly [6]. Existing epidemiological data show that continuous oral administration of GCs for 3–6 months (or longer), high-dose inhaled GCs or intermittent use of oral GCs can lead to decreased bone density and an increased fracture risk [7, 8]. The incidence rate of GIOP is high, making it the third most common form of osteoporosis, and this incidence is second only to that of postmenopausal osteoporosis and senile osteoporosis [9]. Therefore, treatment for GIOP requires the attention of patients and medical professionals.

At present, the most commonly used therapeutic drugs for GIOP are calcium (Ca) and vitamin D (Vit D); bisphosphonates (BPs), teriparatide, and other drugs are also used to treat GIOP [10, 11]. However, there is a lack of advanced evidence-based studies on GIOP drugs, and this deficiency is not conducive to the application of clinical drugs. According to the American College of Rheumatology (ACR), the prevention and treatment guidelines for GIOP show that evidence on existing drugs used to treat GIOP is limited; therefore, the application of anti-GIOP drugs has specific usage conditions [12]. In recent years, clinical randomized controlled trials (RCTs) and systematic reviews and/or meta-analyses (SRs) of drug treatment for GIOP have been studied and disclosed, thus confirming that there are high-level evidence-based studies on drug treatment for GIOP. Umbrella reviews, also known as systematic reviews of systematic reviews, systematic reviews of meta-analyses, and overviews of reviews [13], provide healthcare decision-makers with current comprehensive evidence on specific issues by systematically retrieving SRs and extracting, analyzing, and summarizing the results of the existing evidence [14]. In this context, we reviewed published SRs of RCTs for inclusion in this umbrella review to further evaluate the efficacy of pharmacological interventions for GIOP. Another objective of this study is to provide guidance for improving the clinical study design, a reference for the clinical application of drug therapy for GIOP and a plan for clinical guidelines.

Materials and Methods

Inclusion and exclusion criteria

The following are the inclusion criteria of this umbrella review: 1) the included studies were SRs of RCTs; 2) the cases included in the SR were osteoporosis secondary to taking GCs, and there was no restriction on the duration of the primary disease or the dose of GC; 3) the experimental group (EG) was treated with any drug, combined with other drugs on the basis of the control group, or evaluated for a certain class of drugs (such as BPs); 4) the control group was a placebo, blank group, positive drug or basic drug treatment (such as Ca and a vitamin); and 5) the main outcome measures were the bone mineral density (BMD) change rate. Secondary outcome measures were risk of infection, adverse events (AEs), risk of a new nontraumatic fracture (NTF), incidence of vertebral (VF) or nonvertebral fractures (NVF), N-terminal propeptide of type I collagen (PINP), and C-telopeptide of type I collagen (CTX).

The exclusion criteria were as follows: 1) narrative reviews, 2) network meta-analyses, 3) animal experiments, 4) repeated published literature, and 5) literature published in a language other than English.

Retrieval strategy

We searched PubMed, Embase, and the Cochrane Library for SRs of drug therapy for GIOP. We searched for literature published from database inception to November 2022. In addition, we manually searched the references of the included studies to supplement SRs that might meet the inclusion criteria. The literature was searched by using a combination of subject words and free words, and the retrieval strategy was adjusted according to the retrieval characteristics of each database. The key words included glucocorticoids, osteoporosis, glucocorticosteroids, glucocorticoid-induced osteoporosis, meta-analysis and systematic review. The retrieval formulas of the above three databases are shown in **Supplementary Material 1**.

Literature screening and data extraction

Two researchers (HL and JZ) independently read the titles and abstracts as well as the full text of the literature to determine whether the publications met the inclusion criteria. If there was any disagreement, it was resolved through consultation with the third researcher (TT). The data that were collected included the author, the year of publication, the number of included studies, the number of samples, the intervention measures, the quality evaluation methods of the included studies, and the outcome indicators. If there were multiple SRs focused on the same subject or drug therapy, one systematic review was reserved for subsequent analysis according to the principle of the highest quality of SR methodology and the largest number of RCTs included.

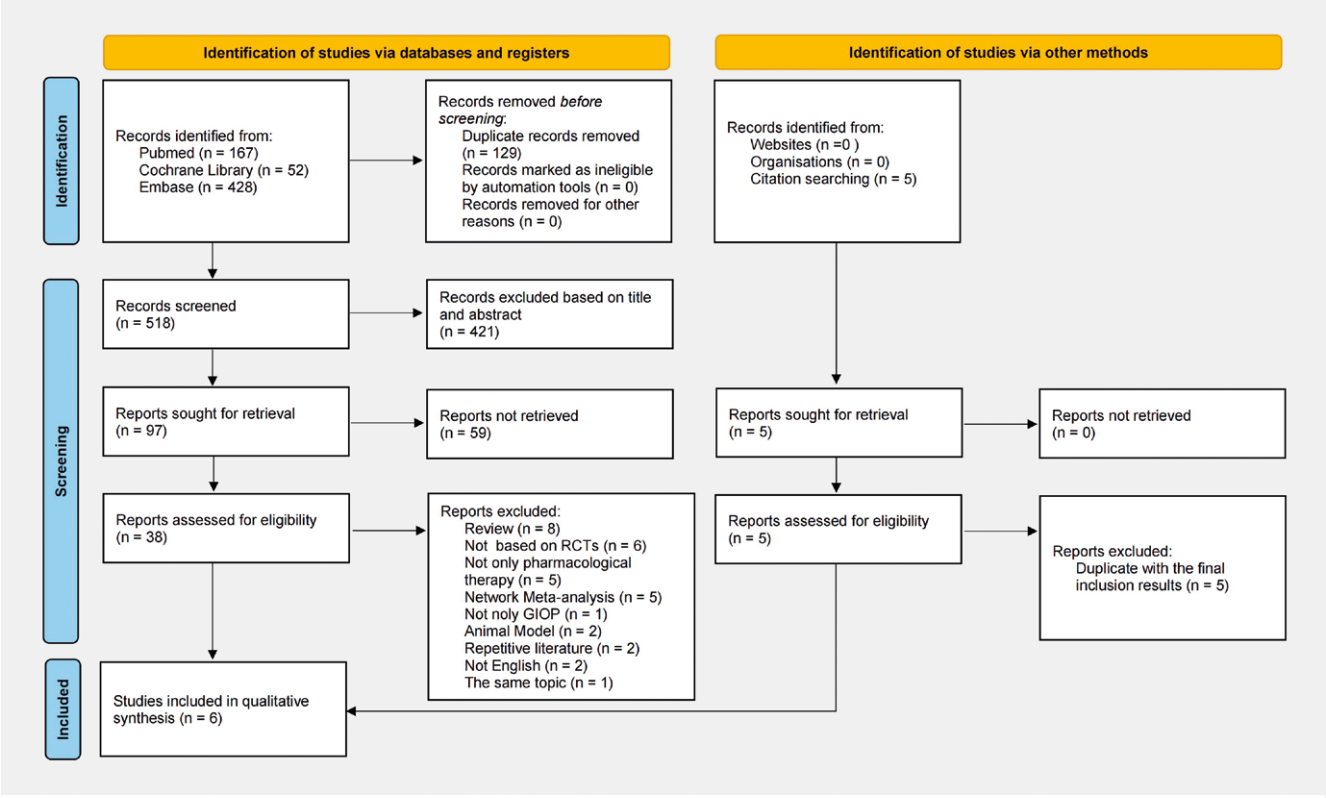
Methodology and evidence quality evaluation

We used A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) to evaluate the methodological quality of the included SRs [15]. The AMSTAR-2 includes 16 items (**Supplementary Material 2**), of which items 2, 4, 7, 9, 11, 13, and 15 are key items and the remaining items are non-key items [15]. According to the AMSTAR-2 evaluation standard, the methodological quality of each SR can be evaluated as high, moderate, low and critically low quality.

The GRADE (Grades of Recommendations Assessment, Development and Evaluation) grading system was used to evaluate the quality of evidence for the outcome indicators in the SR [16]. The factors that reduce the level of evidence are divided into five dimensions: limitation, inconsistency, indirection, accuracy and publication bias. According to the degree of compliance with the degradation factors, the evidence level of the outcome indicators can be rated as high, moderate, low and very low. To help readers understand our research conclusions, we generated an evidence map according to the comparative results of the combined effect values and GRADE score.

Statistical method

We conducted a descriptive analysis to summarize the evidence results of the included SRs. Based on the primary and secondary



▶ **Fig. 1** Flow diagram of the umbrella review.

outcome measures, the efficacy and safety outcomes of pharmacological interventions for GIOP were re-evaluated.

Results

Retrieval results of literature

After double checking and reading the title and abstract of the results, we included 38 SRs for full-text reading. After excluding a narrative review, a network meta-analysis, and animal experiments, 6 SRs [17–22] of pharmacological interventions for GIOP were ultimately included. The list of excluded documents and reasons are shown in **Supplementary Material 3**. The literature screening process and results are shown in ▶ **Fig. 1**.

Basic characteristics of the included SRs

Six SRs [17–22] involving 59 RCTs with 7225 patients exhibiting GIOP were included in this umbrella review. All the included patients were diagnosed with GIOP. SRs published between 2010 and 2022 were included. The drug therapies covered in this umbrella review included BPs, Ca + Vit D, alendronate, denosumab and teriparatide. The specific characteristics of the included SRs are shown in ▶ **Table 1**.

Methodological quality evaluation

According to the evaluation results of the AMSTAR-2 tool, the 6 SRs included in this review included 2 high-quality [17, 18], 2 low-quality [20, 21], and 2 critically low-quality SRs [19, 22]. The specific details of the methodological quality evaluation are shown in ▶ **Table 2**.

Results of evidence quality evaluation of outcome indicators

In this umbrella review, we evaluated 46 quality studies of 11 outcome indicators (▶ **Table 3** and ▶ **Table 4**), among which the outcome indicators mainly included the BMD, fracture incidence, bone turnover markers and AEs. According to the GRADE evaluation criteria, this review included 3 high-level studies, 20 moderate-level studies, 15 low-level studies, and 8 very low-level studies. The evidence map of pharmacological interventions for GIOP is shown in ▶ **Fig. 2**.

Effects of pharmacological treatments for GIOP

Primary outcome

BMD of the lumbar spine (LSBMD)

LSBMD was reported in six SRs [17–22]. Compared with low-dose BPs, standard-dose BPs improved the LSBMD (MD: 0.95 %, 95 % CI: 0.37 % to 1.53 %, $p < 0.001$). The doses of different classes of BPs are shown in **Supplementary Material 4**. Compared with alendronate, teriparatide had better efficacy in increasing LSBMD, and its evidence level is high. Compared with Vit D alone, BPs, risedronate and alendronate also showed better effects. There was no significant difference between ibandronate and Vit D in increasing LSBMD (MD: 3.77 %, 95 % CI: 0.05 % to 7.49 %, $p = 0.05$). Compared with Vit D alone, the combined application of BPs was more effective in increasing LSBMD. Compared with Ca (or placebo), Ca + Vit D was

▶ **Table 1** Characteristics of the systematic reviews and meta-analyses included in the umbrella review.

Study	No. of RCTs (Sample size)	Participants	Descriptions of Interventions		Methodological quality evaluation tool	GRADE evaluation	Outcomes assessed
			EG	CG			
CS Allen 2016 [17]	27 (3075)	Adults taking a mean steroid dose of 5.0 mg/day or more	Standard-dose BPs	Low-dose BPs	ROB	Yes	Percent change in BMD
J Homik 2010 [18]	5 (274)	Patients (older than age of 18) taking systemic corticosteroids	Ca and Vit D	Ca alone or placebo	Jadad scores	No	Percent change in BMD, fracture incidence
ZM Liu 2022 [19]	5 (1460)	Patients were at least 21 years old	Alendronate	Teriparatide	ROB	No	Percent change in BMD, fracture incidence, AE, changes in turnover markers
YK Wang 2018 [20]	10 (1002)	Adult patients with GIOP taking alendronate for at least 6 months.	Alendronate plus EG	Ca and Vit D	Jadad scores	No	Percent change in BMD, fracture incidence, AE
J Wang 2019 [21]	9 (545)	Eastern Asians	BPs Alone	Vit D Alone or a Combination	ROB	No	Percent change in BMD and turnover markers
ZA Yanbeiy 2019 [22]	3 (869)	Subjects taking systemic glucocorticoid therapy	Denosumab	BPs	No	No	Percent change in BMD, fracture incidence, infection

RCTs: Randomized controlled trials; EG: Experimental Group; CG: Control Group; BPs: Bisphosphonates; Ca: Calcium; Vit D: Vitamin D; ROB: Cochrane Risk of Bias Tool; BMD: Bone Mineral Density; AE: Adverse Events.

more effective in increasing LSBMD. Compared with BPs, denosumab had better clinical efficacy for increasing LSBMD (MD: 2.32 %, 95 % CI: 1.72 % to 2.91 %, p < 0.001) (▶ **Table 3** and ▶ **Fig. 2**).

BMD of the femoral neck (FNBMD)

In terms of increasing FNBMD, risedronate was more effective in increasing FNBMD than Vit D alone (MD: 2.20 %, 95 % CI: 0.56 % to 3.84 %, p = 0.008). Compared with alendronate, teriparatide had better efficacy in increasing FNBMD. Vit D had better efficacy than BPs in increasing FNBMD. Compared with the combined application of BPs, Vit D alone was more effective in increasing the efficacy of FNBMD (MD: 36.20 %, 95 % CI: 26.87 % to 45.52 %, p < 0.001). Compared with Vit D alone, risedronate was more effective in increasing FNBMD.

BMD of total hip (THBMD)

THBMD was reported in a total of 2 SRs [19, 22]. The existing evidence indicates that teriparatide has better efficacy in increasing THBMD than alendronate (SMD: 0.17 %, 95 % CI: 0.05 % to 0.28 %, p = 0.004). Denosumab was more effective in increasing THBMD than BPs (MD: 1.52 %, 95 % CI: 1.10 % to 1.94 %), and the difference was statistically significant (p < 0.001).

BMD of the distal radius (DRBMD)

One SR showed changes in DRBMD [18]. Compared with Ca (or placebo), Ca + Vit D significantly increased DRBMD (MD: 2.49 %, 95 % CI: 0.62 % to 4.36 %), and the difference was statistically significant (p = 0.0092).

Secondary outcome

Risk of infection

Compared with BPs, denosumab in GIOP patients did not increase the risk of infection (RR: 2.16, 95 % CI: 0.38 to 12.34), and the difference was not statistically significant (p = 0.39) (▶ **Table 4** and ▶ **Fig. 2**).

AEs

AEs were reported in two SRs [19, 20]. The existing evidence indicates that the combination of alendronate with Ca + Vit D does not significantly increase the incidence of AE compared with Ca + Vit D treatment alone (OR: 1.04, 95 % CI: 0.72 to 1.51, p = 0.84). There was no significant difference in the incidence of AE between teriparatide and alendronate (RR: 1.02, 95 % CI: 0.89 to 1.18, p = 0.76).

▶ **Table 2** AMSTAR scoring results of the included systematic reviews and meta-analysis.

Study	Q1	Q2*	Q3	Q4*	Q5	Q6	Q7*	Q8	Q9*	Q10	Q11*	Q12	Q13*	Q14	Q15*	Q16	Ranking of quality
CS Allen 2016 [17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
J Homik 2010 [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High
ZM Liu 2022 [19]	Y	N	Y	Y	Y	Y	PY	PY	Y	N	Y	PY	N	N	N	Y	Critically Low
YK Wang 2018 [20]	Y	N	Y	Y	Y	Y	PY	Y	PY	N	Y	Y	PY	PY	PY	Y	Low
J Wang 2019 [21]	Y	N	Y	Y	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	PY	Y	Low
ZA Yanbeiy 2019 [22]	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	N	N	N	Y	Critically Low

* Key entry; PY: Partial yes; Y: Yes; N: No. The specific contents of 16 items are shown in **Supplementary Material 2**.

NTFs

There was no significant difference in the incidence of new NTFs between denosumab and BPs (RR: 1.16, 95 % CI: 0.68 to 1.98, p = 0.59). Compared with Ca (or placebo), Ca + Vit D did not significantly increase or decrease the incidence of new NTFs (OR: 0.55, 95 % CI: 0.12 to 2.44, p = 0.43).

Incidence of VFs

In terms of reducing the incidence of VFs, teriparatide significantly reduced the risk of fracture compared with alendronate (RR: 0.13, 95 % CI: 0.05 to 0.34), and the difference was statistically significant (p < 0.001). There was no significant difference in the application of alendronate whether combined or not with Ca + Vit D (OR: 0.46, 95 % CI: 0.21 to 1.02, p = 0.06).

Incidence of NVFs

There was no significant difference in the incidence of NVFs between teriparatide and alendronate (RR: 1.28, 95, 95 % CI: 0.81 to 2.02, p = 0.29). There was no significant difference between Ca + Vit D and alendronate + Ca + Vit D (OR: 1.48, 95 % CI: 0.50 to 4.37, p = 0.47).

PINP

After 1 (SMD: 3.51 %, 95 % CI: 3.15 % to 3.87 %), 6 (SMD: 5.02 %, 95 % CI: 3.35 % to 6.69 %), and 18 (SMD: 4.97 %, 95 % CI: 4.48 % to 5.46 %) months of follow-up, teriparatide was more effective in increasing PINP levels than alendronate, and the difference was statistically significant (p < 0.001).

CTX

In terms of the influence on CTX, teriparatide was more effective in increasing the content in serum than alendronate, and the difference was statistically significant. Compared with Vit D, BPs reduced the level of CTX in serum (MD: −72.27 % 95 % CI: −85.19 % to −59.34 %), and the difference was statistically significant (p < 0.001).

Discussion

In this umbrella review, we evaluated 6 SRs of pharmacological interventions for GIOP, including calcium, Vit D, BPs, denosumab, teriparatide and their combined applications, which provided a stronger evidence-based foundation for us to further understand the efficacy of drug therapy for GIOP. In combination with the GIOP treatment guidelines published by the ACR [12], we found that due to the lack of a sufficient evidence-based study, the recommendation strength of many drug applications was low, or the application of drugs was restricted by certain conditions. In this study, we have summarized the latest SRs on drug therapy for GIOP, which can provide the latest and best evidence-based recommendation for patients and medical personnel to select drugs for GIOP. The findings of this study are the latest supporting reference and can be used to help revise the guidelines. In addition, due to the limitation of the level of clinical evidence, we recommend that users carefully consider low-level and very low-level evidence in this umbrella review or select appropriate drug prescriptions according to the comorbidities, advantages and disadvantages of GIOP patients.

▶ **Table 3** GRADE quality of evidence score for outcomes reported in the systematic reviews included in the umbrella review of pharmacological interventions for GIOP (primary outcomes).

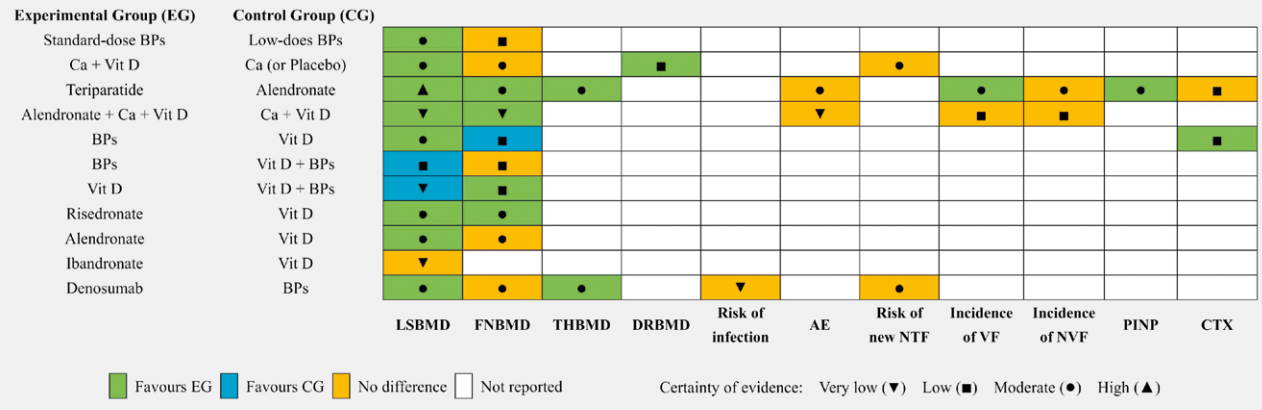
Out-come	Intervention and comparator	Follow-up	Effect Size (95% CI)	I^2 (%)	p	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Publica-tion bias	GRADE quality
LSBMD	Standard-dose vs. Low-does BPs	12 months	MD: 0.95% (0.37% to 1.53%)	0	0.0014	No	No	No	No	Serious	Moderate
	Ca + Vit D vs. Ca (or Placebo)	12 months	MD: 2.63% (0.74% to 4.53%)	0	0.0065	No	No	No	No	Serious	Moderate
	Teriparatide vs. Alendronate	6 months	SMD: 0.30% (0.19% to 0.42%)	0	<0.001	No	No	No	No	No	High
		12 months	SMD: 0.48% (0.36% to 0.60%)	45	<0.001	No	No	No	No	No	High
		18 months	SMD: 0.53% (0.42% to 0.64%)	48	<0.001	No	No	No	No	No	High
	Alendronate + Ca + Vit D vs. Ca + Vit D	6 months	SMD: 0.67% (–0.02% to 1.36%)	81	0.06	Serious	Serious	No	No	Serious	Very Low
		12 months	SMD: 0.83% (0.58% to 1.08%)	54	<0.001	Serious	Serious	No	No	Serious	Very Low
		24 months	SMD: 0.80% (0.49% to 1.10%)	38	<0.001	Serious	No	No	No	Serious	Low
	BPs vs. Vit D	Unspecified	MD: 4.11% (3.11% to 5.11%)	34	<0.001	No	No	No	No	Serious	Moderate
	BPs vs. Vit D + BPs	Unspecified	MD: –2.09% (–3.72% to –0.46%)	54	0.01	No	Serious	No	No	Serious	Low
	Vit D vs. Vit D + BPs	Unspecified	MD: –6.83% (–8.63% to –5.03%)	53	<0.001	No	Serious	No	Serious	Serious	Very Low
	Risedronate vs. Vit D	Unspecified	MD: 4.00% (2.79% to 5.22%)	0	<0.001	No	No	No	No	Serious	Moderate
	Alendronate vs. Vit D	Unspecified	MD: 4.49% (2.91% to 6.06%)	0	<0.001	No	No	No	No	Serious	Moderate
	Ibandronate vs. Vit D	Unspecified	MD: 3.77% (0.05% to 7.49%)	88	0.05	No	Serious	No	Serious	Serious	Very Low
	Denosumab vs. BPs	Unspecified	MD: 2.32% (1.72% to 2.91%)	0	<0.001	No	No	No	No	Serious	Moderate
FNBMD	Standard-dose vs. Low-does BPs	12 months	MD: 0.74% (–-0.42% to 1.90%)	54	0.21	No	Serious	No	No	Serious	Low
	Ca + Vit D vs. Ca (or Placebo)	12 months	MD: 0.37% (–1.09% to 1.83%)	0	0.62	No	No	No	No	Serious	Moderate
	Teriparatide vs. Alendronate	18 months	SMD: 0.17% (0.05% to 0.29%)	0	0.006	No	No	No	No	Serious	Moderate
	Alendronate + Ca + Vit D vs. Ca + Vit D	6 months	SMD: 0.94% (0.64% to 1.24%)	0	<0.001	Serious	No	No	No	Serious	Low
		12 months	SMD: 0.29% (–0.28% to 0.87%)	92	0.32	Serious	Serious	No	No	Serious	Very Low
		24 months	SMD: 0.60% (0.06% to 1.13%)	80	0.03	Serious	Serious	No	No	Serious	Very Low
	BPs vs. Vit D	Unspecified	MD: –28.53% (–34.56% to –22.50%)	0	<0.001	No	No	No	Serious	Serious	Low
	BPs vs. Vit D + BPs	Unspecified	MD: 1.96% (–6.26% to 10.18%)	0	0.64	No	No	No	Serious	Serious	Low
	Vit D vs. Vit D + BPs	Unspecified	MD: 36.20% (26.87% to 45.52%)	0	<0.001	No	No	No	Serious	Serious	Low
	Risedronate vs. Vit D	Unspecified	MD: 2.20% (0.56% to 3.84%)	2	0.008	No	No	No	No	Serious	Moderate
	Alendronate vs. Vit D	Unspecified	MD: 1.19% (–0.56% to 2.95%)	0	0.18	No	No	No	No	Serious	Moderate
	Denosumab vs. BPs	Unspecified	MD: 1.35% (–1.59% to 4.30%)	46	0.37	No	No	No	No	Serious	Moderate
THBMD	Teriparatide vs. Alendronate	18 months	SMD: 0.17% (0.05% to 0.28%)	0	0.004	No	No	No	No	Serious	Moderate
	Denosumab vs. BPs	Unspecified	MD: 1.52% (1.10% to 1.94%)	0	<0.001	No	No	No	No	Serious	Moderate
DRBMD	Ca + Vit D vs. Ca (or Placebo)	12 months	MD: 2.49% (0.62% to 4.36%)	54	0.0092	No	Serious	No	No	Serious	Low

BPs: Bisphosphonates; Ca: Calcium; Vit D: Vitamin D; BMD: Bone mineral density; LSBMD: BMD of lumbar spine; FNBMD: BMD of femoral neck; THBMD: BMD of total Hip; DRBMD: BMD of distal radius; MD: Weighted mean difference; SMD: Standard mean difference; CI: Confidence intervals.

▶ **Table 4** GRADE quality of evidence score for outcomes reported in the systematic reviews included in the umbrella review of pharmacological interventions for GIOP (secondary outcomes).

Outcome	Intervention and comparator	Follow-up	Effect Size (95 % CI)	I^2 (%)	p	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE quality
Risk of infection	Denosumab vs. BPs	Unspecified	RR: 2.16 (0.38 to 12.34)	66	0.39	No	Serious	No	Serious	Serious	Very Low
AE	Alendronate + Ca + Vit D vs. Ca + Vit D	Unspecified	OR: 1.04 (0.72 to 1.51)	0	0.84	Serious	No	No	No	Serious	Low
	Teriparatide vs. Alendronate	Unspecified	RR: 1.02 (0.89 to 1.18)	0	0.76	No	No	No	No	Serious	Moderate
Risk of new non-traumatic fracture	Ca + Vit D vs. Ca (or Placebo)	Unspecified	OR: 0.55 (0.12 to 2.44)	0	0.43	No	No	No	No	Serious	Moderate
	Denosumab vs. BPs	Unspecified	RR: 1.16 (0.68 to 1.98)	0	0.59	No	No	No	No	Serious	Moderate
Incidence of VF	Teriparatide vs. Alendronate	Unspecified	RR: 0.13 (0.05 to 0.34)	0	< 0.001	No	No	No	No	Serious	Moderate
	Alendronate + Ca + Vit D vs. Ca + Vit D	Unspecified	OR: 0.46 (0.21 to 1.02)	0	0.06	Serious	No	No	No	Serious	Low
Incidence of NVF	Teriparatide vs. Alendronate	Unspecified	RR: 1.28 (0.81 to 2.02)	0	0.29	No	No	No	No	Serious	Moderate
	Alendronate + Ca + Vit D vs. Ca + Vit D	Unspecified	OR: 1.48 (0.50 to 4.37)	0	0.47	Serious	No	No	No	Serious	Low
PINP	Teriparatide vs. Alendronate	1 months	SMD: 3.51 % (3.15 % to 3.87 %)	0	< 0.001	No	No	No	No	Serious	Moderate
		6 months	SMD: 5.02 % (3.35 % to 6.69 %)	91	< 0.001	No	Serious	No	No	Serious	Low
		18 months	SMD: 4.97 % (4.48 % to 5.46 %)	0	< 0.001	No	No	No	No	Serious	Moderate
CTX	Teriparatide vs. Alendronate	1 months	SMD: 4.83 % (2.87 % to 6.79 %)	96	< 0.001	No	Serious	No	No	Serious	Low
		6 months	SMD: 5.77 % (2.19 % to 9.34 %)	97	0.002	No	Serious	No	Serious	Serious	Very Low
		18 months	SMD: 5.33 % (4.23 % to 6.43 %)	80	< 0.001	No	Serious	No	No	Serious	Low
	BPs vs. Vit D	Unspecified	MD: −72.27 % (−85.19 % to −59.34 %)	0	< 0.001	No	No	No	Serious	Serious	Low

BPs: Bisphosphonates; Ca: Calcium; Vit D: Vitamin D; NTF: Non-traumatic fracture; AE: Adverse events; VF: Vertebral fractures; NVF: Non-vertebral fractures; PINP: N-terminal propeptide of type I collagen; CTX: C-telopeptide of type I collagen; MD: Weighted mean difference; SMD: Standard mean difference; OR: Odds ratio; RR: Risk ratio; CI: Confidence intervals.



▶ **Fig. 2** Heat map of pharmacological Interventions on GIOP. BPs: Bisphosphonates; Ca: Calcium; Vit D: Vitamin D; BMD: Bone Mineral Density; AE: Adverse Events; LSBMD: BMD of Lumbar Spine; FNBMD: BMD of femoral neck; THBMD: BMD of total hip; DRBMD: BMD of distal radius; NTF: Nontraumatic fracture; VF: Vertebral fractures; NVF: Nonvertebral fractures; PINP: N-terminal propeptide of type I collagen; CTX: C-telopeptide of type I collagen.

In this umbrella review, we found that many drug treatments, such as standard-dose BPs, Ca + Vit D, teriparatide, alendronate + Ca + Vit D, BPs, Vit D + BPs, risedronate, alendronate, and denosumab, showed better efficacy for increasing LSBMD compared with that in the control group. Notably, since the control groups included in this umbrella review were all positive drug controls, users need to choose the best drug prescription according to the corresponding reference drug and the patient's tolerance to the drug when selecting the above single-drug or combination therapies. In terms of dose application of BPs, our study showed that low-dose BPs were not more effective in increasing BMD than standard-dose BPs [17]. However, there was no significant difference in the increase in FNBMD between the two doses. We believe that these findings may be due to the different responses achieved with different doses at different anatomical sites and to the fact that each site has a different blood supply [23, 24]. Drug metabolism may be affected because the blood flow in the lumbar spine is rich and the blood flow in the total hip joint and the femoral neck is poor [23, 24]. Therefore, the effects of higher doses of BPs on BMD of the total hip and femoral neck deserve further study, but the effects of higher doses of BPs on metabolic organ function should also be observed. A clinical study with a follow-up time of 16 weeks showed that alendronate combined with Vit D could significantly improve osteoporosis without obvious side effects [25]. We found that compared with the application of Vit D or BPs alone, Vit D + BPs had better efficacy in increasing LSBMD, which suggests that the combination of Vit D and BPs is an obvious option for the treatment of lumbar osteoporosis in GIOP patients, rather than the application of Vit D or BPs alone. However, the patient's tolerance to the combination should also be considered.

In terms of improving FNBMD, teriparatide, alendronate + Ca + Vit D, Vit D and risedronate all have better effects on increasing BMD. We found that the application of teriparatide has a better impact on increasing FNBMD than alendronate by synthesizing the existing evidence. In addition, we believe that the combined application of teriparatide and alendronate is not recommended because bone formation markers such as osteocalcin can be significantly decreased after the application of alendronate, which will reduce the role of teriparatide in promoting bone formation [26]. Therefore, while considering the severity of osteoporosis in the femoral neck of GIOP patients, if the patients have good tolerance to teriparatide and alendronate, there is moderate evidence that supports the recommendation that teriparatide be selected preferentially. Valenti et al. found that risedronate can affect bone metabolism by upregulating the expression of cyclooxygenase-2 (COX-2) [27], and the inhibition of COX is associated with reduced bone formation and delayed fracture healing in vivo. In this review, moderate-strength evidence indicates that risedronate has a better effect on increasing FNBMD than Vit D, which provides an option for GIOP patients who cannot tolerate Vit D.

In addition, we also reviewed the evidence of adverse reactions, fracture risk, and infection risk of different drug therapies. We found that most of the included drug therapies had no difference in the above indicators, which indicates that there was no significant difference in the increase or decrease in AEs between the existing commonly used drugs. Notably, compared with alendronate, teriparatide can reduce the incidence of VF, which suggests that teriparatide is an optimal choice for GIOP patients with a high risk of VF and no drug contraindications. The study by Bouxein et al. [28] showed that compared to placebo, teriparatide reduced the rates of new VFs, adjacent VFs, and nonadjacent VFs in patients with vertebral fractures and osteoporosis by 72 %, 75 %, and 70 %, respectively, which indicates that teriparatide has a significant advantage in reducing vertebral fractures.

Although there are still other drugs used in the treatment of GIOP, there is still a lack of high-level evidence-based recommendations, and more pharmaceutical researchers are needed to design and implement higher quality RCTs or SRs to evaluate the efficacy and safety of these drugs in the treatment of GIOP. In this umbrella review, it is encouraging that we found some moderate- to high-intensity evidence that teriparatide, BPs and denosumab have better clinical efficacy in increasing the BMD of patients with GIOP.

In addition to the above findings, this umbrella review also has the following shortcomings. First, since this study did not include SRs involving non-RCTs, there may be a lack of new drug therapies in this umbrella review. Second, the control group was not limited

to blank controls or placebo in the included SR, which is not conducive to our horizontal comparison of the efficacy of different drug treatments in the same outcome index. Third, although our research findings suggest that teriparatide, BPs, and denosumab are drug choices for improving BMD in GIOP patients, there is still a lack of high-level evidence to compare the efficacy differences between these drugs.

Conclusions

In this umbrella review, we have summarized and compared the SRs of drug therapy for GIOP, and the existing evidence indicates that teriparatide, BPs, and denosumab have better clinical efficacy in increasing the BMD of patients with GIOP. These findings can be used to provide evidence-based care to patients and to assist clinical medical personnel in selecting the best drug prescription.

Authors' Contributions

HD Liang: participation in study design, execution, analysis, article drafting and critical discussion; JL Zhao: participation in study design, critical discussion; TZ Tian: participation in study design, article drafting and critical discussion. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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