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REVIEW ARTICLE

Acupuncture for Osteoporosis: a Review of Its Clinical and Preclinical Studies

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Acupuncture has gained growing attention in the management of osteoporosis (OP). However, a comprehensive review has not yet been conducted on the efficacy and challenges of acupuncture in preliminary research and clinical trials. Therefore, an extensive literature search was conducted using electronic databases, including PubMed (www.ncbi.nlm.nih.gov/pubmed), CNKI (www.cnki.net), and Web of Science, for studies published from the beginning of 2000 to the end of May 2022. Combinations of synonyms for OP, acupuncture, traditional Chinese medicine, clinical trial, preclinical study, and animal experiments were searched. A total of 290 papers were consulted, including 115 reviews, 109 clinical observations, and 66 preclinical studies. There is accumulating evidence to support the beneficial role of acupuncture in preserving bone quality and relieving clinical symptoms based on clinical and preclinical investigations. The top ten most commonly used acupoints are BL23, ST36, BL20, BL11, CV4, GV4, SP 6, KI3, BL18, and GB39. The underlying mechanisms behind the benefits of acupuncture may be linked with the regulation of the hypothalamic-pituitary-gonadal (adrenal) axis and activation of the Wnt/β-catenin and OPG/RANKL/RANK signaling pathways. In summary, strong evidence may still come from prospective and well-designed clinical trials to shed light on the potential role of acupuncture in preserving bone loss. Future investigations are needed to explore the potential underlying mechanisms, long-term clinical efficacy, and compliance of acupuncture in OP management.

Keywords: Osteoporosis, Acupuncture, Clinical trial, Preclinical study, Clinical investigations

INTRODUCTION

Osteoporosis (OP) is one kind of chronic metabolic disease characterized by a reduction in bone mineral density (BMD) and a deterioration in bone microstructure leading to a decline in bone strength and an increase in bone fragility and fracture risk [1,2]. The main etiology of OP is attributed to the faster rate of osteoclastic bone resorption than that of osteoblastic bone formation [3]. Many risk factors could trigger the development of OP, such as gonadal steroid deficiency, anorexia nervosa, calcium and vitamin D deficiency, medication intervention, inactive lifestyle, cigarette smoking, excessive alcohol consumption, aging, diabetes, hyperparathyroidism, and renal failure [4,5]. OP is usually classified as either primary OP (POP, including postmenopausal OP, senile OP, and idiopathic OP) or secondary OP (caused by certain medical conditions). Among these, primary OP occupies the leading incidence of compromised bone strength and mainly affects people over 50, especially postmenopausal women. With the accelerated aging of the world population, the incidence of OP is escalating. Given the high morbidity and mortality and the heavy social and economic burdens, OP has become one of the most important social health issues [6]. The current drug therapies are limited in their clinical use for managing OP because of the potential side effects [7]. Therefore, the unmet medical needs require new solutions for OP management [8]. Recently, acupuncture has gained increasing attention in protection against OP for its effectiveness, relatively low cost, and low risk of side effects [9].

As a non-drug therapy option, acupuncture has been used for OP management in traditional Chinese medicine (TCM) clinics for more than 2000 years [1,10]. According to TCM theory, acupuncture improves circulation and distribution of Qi, blood, and body fluid and preserves organ functions via stimulation of meridian acupoints [11]. In addition, the etiology of OP has been attributed to Qi deficiency and blood stasis, which may be related to the dysfunctions of the liver, kidney, and spleen [12]. Appropriate mechanical stimulation and loading are beneficial to maintain bone reconstruction and repair minor bone injuries and could avoid the accumulation of minor injuries and fractures [13]. Emerging lines of evidence from preclinical and clinical studies have demonstrated the beneficial role of acupuncture in preserving bone quality and reducing osteoporotic syndromes [14]. Indeed, most TCM practitioners in China and other countries have employed acupuncture to treat patients with OP [15,16]. Although studies on acupuncture for OP management have increased in the past few decades, an update-to-date comprehensive review has not yet been conducted. Here, we summarize the recent advances in acupuncture therapy for OP in TCM clinical trials and preclinical studies, attempting to provide scientific evidence for future studies and clinical practices of this non-drug treatment.

DATA AND METHODS

1. Literature source

The following databases were used for retrieving information on OP and acupuncture: PubMed (www.pubmed.com), China National Knowledge Infrastructure (CNKI; www.cnki.net), and Web of Science (apps.webofknowledge.com). The following words and phrases in various combinations were used to retrieve the references: OP, acupuncture, TCM, clinical trial, preclinical study, and animal experiments. The studies examined were published from the beginning of 2000 to the end of May 2022.

2. Inclusion criteria

Studies on OP research, clinical observations where the intervention group was treated with acupuncture or moxibustion or other related methods, and clinical trials where the prescription is clear and the treatment is effective were included in this review.

3. Exclusion criteria

Studies where no acupuncture-related treatment was used, acupuncture was used to treat other complications, repeated publications, and instances where complete articles could not be obtained were excluded in this review (Fig. 1).

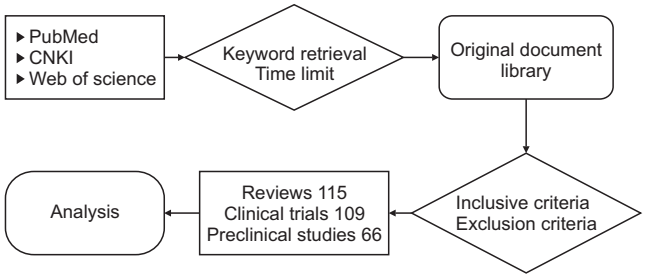

Fig. 1. Flow chart of the literature analysis.

RESULTS AND DISCUSSION

1. Clinical advances in using acupuncture for OP management

Based on the retrievals from the databases mentioned above, around 353 papers were published focused on the effects of acupuncture for OP management in the past 22 years. After removing the duplicates, 290 eligible papers were analyzed. Of these, 115 reviews, 109 clinical trials, and 66 preclinical studies underwent further analysis. Table 1 [17-125] briefly summarizes the main achievements of the 109 clinical trials, including the study design, type of OP, number of patients, treatment duration, acupoint selection, and key results.

Most of the clinical trials were randomized, and only eight single-blind, three double-blind, and two triple-blind trials were conducted. In a randomized-controlled trial, the blind design was mainly implemented with sham acupuncture (i.e., shallow acupuncture at non-acupoints and no sense of Qi), to eliminate the differences in pain perception during acupuncture. In addition, the examiners were strictly blinded to the patients, which is very important for improving the quality of randomized trials [126]. In future clinical trial design, randomized-controlled trials with double-blind or even triple-blind methods are desired.

Of the 109 clinical trials, 37 were focused on primary OP, 34 on postmenopausal OP, 15 on senile OP, 2 on OP in males, 1 on secondary OP. Other trials did not clearly identify the types of OP studied.

Among these trials, the top ten commonly used acupoints were BL23, ST36, BL20, BL11, CV4, GV4, SP6, KI3, BL18, and GB39. The clinical application frequency of these acupoints were 89.9%, 65.1%, 49.5%, 45.9%, 44.0%, 42.2%, 41.3%, 31.2%, 30.3%, and 26.6%, respectively (Table 2). These results indicate that acupoint selection may follow the principles of tonifying the kidney and spleen, which is consistent with the etiology of OP in TCM [127,128]. Moreover, Ashi points were always acupunctured to relieve the pain [129].

In addition, matching acupoints were always treated to improve clinical efficacy according to the principle of

Table 1. The Clinical Studies for Acupuncture on Osteoporosis (OP) management

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Not identified.	SOP, 28, 10 times per course, 3-6 courses with 3 months follow-up.	The main acupoints: GV 20, GV14, GV9, GV3, GV4. The matching acupoints:CV4, CV6, BL23, BL20, GB39, KI3, ST36, SP6, BL31, BL32, co-treatment with mild moxibustion.	Effective rate: 78.6%; BMD increased.	[17]
Randomized.	PMOP, 40, 85 days.	The main acupoints: BL11, GV14, GV4. The matching acupoints: GB39, BL17, ST36, co-treatment with mild moxibustion.	Lumbar BMD increased.	[18]
Randomized.	PMOP, 30, 180 days.	BL11, GV4, GB39, ST36, co-treatment with mild moxibustion.	ICS reduced; lumbar and femoral neck BMD increased.	[19]
Randomized.	PMOP, 42, 6 months.	BL23, CV4, KI3.	lumbar BMD increased.	[20]
Randomized. Single-blind trial.	POP, 45, 6 months.	CV4, ST36, SP6, BL23, KI3, BL20.	Lumbar vertebrae and femur BMD increased.	[21]
Not identified.	OP, 43, 7 days per course, 5 courses.	BL11, BL17, BL18, BL23, BL20, GV4, ST36, GB39, GB34, KI3, CV4. Needle warming moxibustion.	Effective rate: 97.67%.	[22]
Randomized.	PMOP, 45, 8 weeks.	CV4, ST36, bilateral, EX-B2, bilateral and BL 40, bilateral. EA.	Clinical symptoms and signs improved; BMD, E2, ALP and blood Ca increased; IL-6, P and urine Ca/Cr decreased.	[23]
Randomized.	PMOP, 45, 2 months.	CV4, ST36, bilateral, EX-B2, bilateral and BL 40, bilateral. EA.	BMD increased.	[24]
Not randomized.	SOP, 1, 15 times is a course, 3-5 courses	The main acupoints: GV1, GV2, GV4, GV6, GV9, GV12, GV14, GV20. The matching acupoints: GB30, BL23, BL20, ST36, BL40, SP6, EX-B2, EX-B6, co-treatment with mild moxibustion.	BMD increased.	[25]
Randomized.	PMOP, 56, 6 months.	BL23. Embedding thread.	Effective rate: 100%; Osteodynia scores reduced.	[26]
Randomized.	POP, 89, 3 months.	CV8, CV4, CV6, GV4, BL23 and BL 20, and acupoint sticking.	Effective rate: 88.64%; Cumulative osteodynia scores relieved; BMD increased.	[27]
Randomized.	OP, 64, 2 weeks.	BL40, EX-B2. EA.	Effective rate: 85.7%; VAS scoring decreased	[28]
Randomized. Single-blind trial.	PMOP, 42, 12 weeks.	Bilateral BL20 and BL23 Embedding thread.	E2 increased; VAS decreased.	[29]
Randomized. Single-blind trial.	POP, 40, 6 months.	Bilateral BL20, and BL23. Embedding thread.	BMD increased; VAS decreased.	[30]
Randomized.	POP, 48, 3 months.	GB39, bilateral BL23 and GV4.	Clinical symptoms improved; blood Ca and BMD increased; P decreased.	[31]
Randomized.	POP, 90, 6 days per course, 12 courses with 2-month follow-up.	Bilateral EX-B2, T11, L1, L3, L5, S2 in Jiaji points group. BL20, BL23, KI3, SP3, LR3, SP6 and SP10. Acupoint-injection.	Effective rate: 93.3%; Osteodynia scores reduced; BMD improved.	[32]

Table 1. Continued

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Randomized.	POP, 90, 6 days per course, 12 courses with 2 months follow-up.	Bilateral EX-B2, T11, L1, L3, L5, S2 (odd weeks); T10, T12, L2, L4, S1 (even weeks). Bilateral BL20, BL23, ST36, SP6 and SP10. Acupoint-injection.	Effective rate: 93.3%; BMD, ALP and blood Ca increased; Osteodynia scores, P, urine Ca and Ca/Cr decreased.	[33]
Randomized. Double-blind trial.	POP, 186, 3 months.	GB39, bilateral, BL23, bilateral, GV4.	Effective rate: 91.40%; pain scores, VAS and P decreased; blood Ca and BMD increased.	[34]
Randomized.	PMOP, 40, 8 weeks.	Bilateral ST36, BL23, BL20, KI3 and Ashi points. Matching acupoints: If shoulder pain, LI15 was punctured; If elbow pain, LI11 and SJ5 were punctured; If leg pain, BL40 was punctured.	Effective rate: 70%; ICS reduced; BMD improved.	[35]
Randomized.	PMOP, 40, 3 months.	BL11, BL18, BL23, ST36, GB34, GB 39, SP6, and CV4. In addition, warm needle moxibustion was used to treat BL11, BL23, ST36 and GB39 acupoints, CV4 only use moxibustion.	BMD and E2 increased; BGP and urine Ca/Cr decreased; clinical symptoms improved.	[36]
Not randomized.	POP, 60, 3 months.	GV16, BL11, BL23, ST36. If kidney deficiency, GV4, KI3 and KI7 were punctured; If spleen deficiency, SP9, SP6 and BL20 were punctured. If blood stasis, BL17 and SP6 were punctured. Co-treatment with cupping (through the first lateral line, GV14, BL23 to Ashi points).	QOL improved.	[37]
Randomized.	POP, 60, 3 months.	BL23, ST36, GB39, BL11, warm needling. CV4, moxibustion. BL18, SP6, GB34.	Effective rate: 93.3%; Osteodynia score reduced; Testosterone and calcitriol increased.	[38]
Randomized.	POP, 40, 3 months.	BL23, ST36, GB39, BL11, warm needling. CV4, moxibustion. BL18, SP6, GB34).	NO, BGP and aging integral decreased; BMD and SOD increased.	[39]
Randomized.	PMOP, 112, 3 months.	BL23, GV4, CV4, BL15, BL18, BL20 and SP6. Co-treatment with TDP.	Effective rate: 94.6%; BMC, BMC/BW, E2 increased; FSH, LH and endometrial thickness decreased.	[40]
Randomized.	PMOP, 65, 3 months.	SP6, BL23 and CV4. If liver-kidney Yin deficiency, BL18 was included. If spleen-kidney Yang deficiency, ST36 and BL20) were included. Except for CV4 which is applied every time, all other acupoints were alternatively treated. All acupoints were implanted with Catgut.	Effective rate: 93.9%; BGP, CT, PTH, ALP and MDA decreased; E2 and SOD increased.	[41]
Randomized.	POP, 70, 6 months.	BL23. Embedding thread.	BMD increased; Bone fracture risk decreased.	[42]
Randomized. Single-blind trial.	OP, 64, 3 months.	BL40, bilateral, KI3, bilateral. Acupuncture combined with Tuina.	Lumbar CR improved; BGP increased; P, DPD and VAS decreased.	[43]
Randomized.	PMOP, 65, 3 months.	Bilateral BL23, SP6, CV4. If liver-kidney Yin deficiency, BL18, bilateral was punctured. If spleen-kidney Yang deficiency, Bilateral ST36, and BL20 were punctured. Except CV4 was applied every time, all other acupoints were alternatively treated.	Effective rate: 93.9%; E2, T, QOL scores (except for RP and SF) increased; FSH, LH, BGP, CT, PTH, ALP decreased.	[44]

Table 1. Continued

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Randomized.	Male OP, 55, 6 months.	Group A: BL20, BL23 and GV4. Group B: CV8, ST36 and SP6. The acupoints of the two groups were treated alternately. Acupuncture and moxibustion.	ICS decreased; BMD increased.	[45]
Randomized.	Male OP, 55, 6 months.	Group A: BL20, BL23 and GV4. Group B: CV8, ST36 and SP6. The acupoints of the two groups were treated alternately. Acupuncture and moxibustion.	ICS, ALP, BGP, PTH, PYD/Cr decreased.	[46]
Randomized.	POP, 60, 10 times per course, 9 courses.	ST36, BL20, BL23, GV4. Heat-sensitive point moxibustion.	Effective rate: 86.7%; BMD improved; S-ALP, U-Ca/Cr reduced.	[47]
Randomized.	POP, 63, every other day for 45 times.	BL11, BL18, BL23, ST36, GB34, SP6, GB39, CV4.	BMD increased; BGP, osteodynia scores, aging score decreased.	[48]
Randomized.	PMOP, 105, 6 months.	At acute stage, BL23, BL18, EX-B2, BL40. At remission stage, BL23, BL18, SP6, BL20, ST36, SP9, EX-B2 and BL40. Acupoint catgut embedding.	Effective rate: 91.4%; VAS reduced; BMD and E2 increased.	[49]
Randomized.	OP, 60, 7 times.	BL23, BL25, BL 40, ST36, GB39, KI3, Ashi points; Bilateral.	Effective rate: 83.3%; VAS and ICS decreased.	[50]
Randomized.	SOP, 64, 30 times.	BL40, KI3, bilateral and Tuina on lumbar region.	P and DPD decreased; BGP increased.	[51]
Randomized.	PMOP, 87, 3 months.	The main acupoints: BL20, BL21, BL23. The matching acupoints: GV4, GV3, GV9, co-treatment with mild moxibustion.	Effective rate: 86.2%; BMD, BGP, BALP increased; VAS, TRACP-5b, OPG decreased.	[52]
Randomized.	SOP, 86, 10 times per course, 3-6 courses.	The main acupoints: GV20, GV9, GV 14, GV3, GV4. The matching acupoints: CV4, BL23, CV6, GB39, BL20, ST36, KI3, SP6, BL31, and BL32, co-treatment with mild moxibustion.	Effective rate: 97.67%.	[53]
Randomized.	SOP, 64, 30 times.	BL40, bilateral, KI3, bilateral and Tuina on lumbar area.	Lumbar lordosis index and sacral inclination angle increased.	[54]
Randomized.	PMOP, 471, 6 months.	Day 1: GV20, LI11, LI4, CV12, ST25, CV4, ST36, SP6, LR3. Cupping ST25, Daimai. Day 2: GV14, BL17, BL20, BL23, GB20, and GV12. Cupping the Bladder Meridian of Foot-Taiyang.	Effective rate: 79.6%.	[55]
Randomized.	POP, 186, 30 days per course, 3 courses.	GB39, BL23, GV4.	Effective rate: 91.4%; VAS decreased.	[56]
Randomized.	POP, 48, 1 month.	The main acupoints: GV4, GV9, GV3, GV20, GV14. The matching acupoints: SP6, ST36, BL31, BL32, BL23, BL 18, BL20, CV6, CV4, and KI3.	Effective rate: 91.0%; VAS reduced; BMD increased.	[57]
Randomized.	OP, 100, 10-day per course, 2 courses.	Group 1: CV12, CV11, CV6, CV4, SP10, ST36, SP6, SP9. Group 2: GV8, GV6, GV4, GV3, BL23, BL25, ST34, and GB34. The two groups of acupoints were treated alternately. Moxibustion is a plus.	Effective rate: 100%.	[58]

Table 1. Continued

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Randomized.	OP, 80, 28 days.	BL13, BL25, BL20, GV4.	VAS decreased; BMD increased.	[59]
Randomized.	PMOP, 90, 30 days.	BL11, BL23, GB39. Warm acupuncture, EA.	VAS, IL-6 and TNF-α decreased; IGF-1 increased.	[60]
Randomized.	POP, 108, 6-time per course, 3 courses.	GV14, BL11, ST36, BL20, BL23, GV4, CV8, CV12, CV4, KI3, and Ashi points, co-treatment with moxibustion and cupping.	Effective rate: 94.4%; VAS decreased; emotional scale improved.	[61]
Not randomized. Open trial.	Secondary OP, 40, 3 months	Option 1: GV14, GV4, BL11, bilateral BL23, BL20, and BL21. Option 2: ST36, bilateral SP6, KI3, and GB34. Option 1 and option 2 alternatively treated, during acupuncture treatment, moxibustion is applied at CV8.	TNF-α and IgM decreased; BMD increased.	[62]
Randomized.	POP, 60, once a week, 12 weeks.	GV14 to GV2. Spreading moxibustion.	Effective rate: 86.67%; VAS score and TCM symptoms scores reduced. BMD increased;	[63]
Not identified.	POP, 86, 10 days per course, 6 courses.	The main acupoints: GV3, GV4, GV14, GV20. The matching acupoints: CV6, CV4, BL23, BL25, BL20, SP6, ST36, KI3, Ashi points.	VAS reduced; BMD increased.	[64]
Not identified.	OP, 80, 10 days per course, 2 courses.	Group 1: CV12, CV6, CV4, ST36, SP10, ST34, and SP6. Moxibustion at CV8. Group 2: EX-B2, bilateral BL23, BL25, and BL32. EA was applied to the two groups of acupoints alternately.	Effective rate: 100%.	[65]
Randomized.	PMOP, 36, 6 months.	BL18, BL23, GB34, ST36, BL11, SP6, GB39, CV4. Warm moxibustion.	BMD increased; Effective rate: 88.9%.	[66]
Randomized.	SOP, 68, 6 months.	BL11, BL23, BL52, EX-B7, BL25, BL40, KI3, co-treatment with Tuina.	BMD increased; VAS reduced; lumbar biomechanical index improved.	[67]
Randomized.	PMOP, 85, 30 days per course, given an interval of 60 days between each course, 4 courses.	BL11, BL23, GB39. Warm needling.	BMD, S-BGP and Hyp/Cr increased.	[68]
Randomized.	POP, 147, 3 months.	BL23, BL18, GB21, ST36, LU5, LU7, PC6, warm needling. GV9, BL40, Beishu points, GV3, co-treatment with Tuina.	Effective rate: 95.45%; BMD and Barthel index increased; VAS reduced.	[69]
Randomized.	POP, 60, 3 months.	BL23, BL18, GB21, ST36, LU5, LU7, PC6, warm needling. GV9, BL40, Beishu points, and GV3, co-treatment with Tuina.	Effective rate: 86.7%.	[70]
Randomized.	POP, 50, 15 days per course, 6 courses.	ST36, BL23, GB39, BL20, KI3, BL11, CV4, SP6, BL18, and GB34.	Effective rate: 93%; Osteodynia scores decreased; Testosterone and calcitriol increased;	[71]
Randomized. Single-blind trial.	PMOP, 61, 6 months.	BL11, BL23, ST36. EA.	Effective rate was 86.7%; ICS decreased.	[72]
Randomized.	PMOP, 90, 2 months.	BL23, ST36. Acupoint injection of salmon calcitonin.	NBAP and lumbar BMD increased; ICS, CTX and urine Ca/Cr decreased.	[73]

Table 1. Continued

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Randomized.	POP, 80, 15 days per course, 5 courses.	BL23, ST36, GB39, BL11, warm needling. BL18, SP6, GB34, CV4, moxibustion.	Effective rate: 92.5%; Osteodynia scores decreased; Testosterone and calcitriol increased.	[74]
Randomized. Single-blind trial.	OP, 53, 5 weeks.	BL23, BL25, BL40, Kunlun (BL 60), GB34, KI3, GV20, and Ashi points.	Pain relieved; scores improved.	[75]
Randomized.	SOP, 273, 4 weeks.	BL17, BL20, BL23, EX-B2, Ashi points, BL40 and GB34. EA and moxibustion.	VAS decreased; SF-36 and clinical efficacy improved.	[76]
Randomized.	POP, 72, 3 months.	Warm acupuncture method: BL11, BL23, ST36. If kidney deficiency, GV4 and KI3 were punctured. If spleen deficiency, SP6 and BL20 were included. If blood stasis, BL17 and SP6 were included. Seven-needle method: following the bladder first lateral line of the back. Cupping method: following the bladder first lateral line of the back. Retaining cupping method: GV14, BL23 and point of pain.	BMD increased; VAS, TCM symptoms scores and QOL scale scores decreased.	[77]
Randomized.	POP, 40, 10 days per course, 3 courses.	GV14, ST36, BL23, BL26, and Ashi points. Bamboo-circled salt moxibustion was applied CV8.	Lower back pain scores decreased; BMD increased.	[78]
Randomized.	OP, 98, 3 months per course, 2 courses.	Group 1: EX-B2, BL25, BL23, BL20, BL32. Group 2: CV4, ST36, ST34, CV6, SP6, CV12, CV8. The two groups were alternately acupunctured with moxibustion.	Effective rate: 95.9%; BMD increased; ICS decreased.	[79]
Randomized. Triple-blind Trial.	SOP, 76, 4 weeks per course, 2 courses.	KI10, KI3, KI4, KI7, BL67. Treatment with acupoint plaster therapy with midnight-noon ebb-flow hour-prescription method.	Effective rate: 85.7%; VAS, ODI, TCM symptoms scores and QUALEFFO-41 decreased.	[80]
Randomized.	SOP, 60, 6 months.	Option 1: GV14, BL11, BL18. Option 2: CV12, CV17, ST36. Option 3: BL20, BL23, GV4. Option 4: CV8, CV4. The four groups of acupoints were acupunctured in turn. Medicinal-cake-separated moxibustion.	ICS and β-CTX decreased; BMD and PINP increased.	[81]
Randomized.	PMOP, 48, 3 months.	Bilateral BL23, BL20, BL21, KI3, BL11, GB39, SP6. EA at BL23 and BL20.	PCS scores and MCS scores increased; VAS, TCM symptoms scores decreased.	[82]
Randomized.	PMOP, 60, 3 months.	BL20, bilateral, BL23, bilateral, co-treatment with mild moxibustion.	VAS, TCM symptoms scores, TRACP-5b, DKK-1 and RANKL decreased; BGP, BALP and OPG increased.	[83]
Randomized.	OP, 70, not known.	The main acupoints: GV4, GV9, GV3, GV20, GV14. The matching acupoints: SP6, ST36, BL31, BL32, BL23, BL18, BL20, CV6, CV4, KI3.	Effective rate: 91.43%; VAS reduced, QOL and BMD increased.	[84]
Randomized.	PMOP, 65, 3 months.	The main acupoints: BL23, GV4, CV4, CV6. The matching acupoints: KI3, ST36, CV12, KI6, GB39, SP6. Warm needling.	Effective rate: 90.90%; BMD and Vit D increased.	[85]

Table 1. Continued

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Not identified.	POP, 70, 6 weeks.	ST36, LU5, BL23, BL18, GB21. Warm needling plus Tuina.	Effective rate: 94.29%; VAS decreased.	[86]
Not identified.	OP, 80, one week per course.	The main acupoints: GV4, GV3, GV14. The matching acupoints: SP6, ST36, BL23, BL20, CV4.	Effective rate: 92.5%; BMD increased; VAS decreased.	[87]
Randomized. Triple-blind Trial.	OP, 56, 15 days per course, 3 courses.	EX-B2, BL18, BL20, BL21, BL23, ST36, CV4, CV6.	Effective rate: 96.4%; ICS, IL-6 and BGP decreased; BMD increased.	[88]
Randomized.	POP, 56, 4 weeks of treatment and 1 month follow-up.	BL20, BL23, GV3, and GV4. Thunder-fire moxibustion.	VAS and the Young's modulus value decreased; BP, GH, SF, MH increased.	[89]
Randomized.	POP, 182, once every 2 days, 3 months.	GV20, BL11, ST36, BL18, BL23, BL20, warm needling. KI3, SP6, GV14, GV4, GB39, EX-B2, GV3, etc, co-treatment with mild moxibustion.	Effective rate: 90.1%; BMD, osteocalcin increased; VAS score decreased.	[90]
Not identified.	PMOP, 72, 3 months.	BL18, BL23, SP6, GB34, CV4, ST36, BL11, GB39. Warm needling.	BMD and E2 increased.	[91]
Randomized.	OP, 100, 60 days.	KI3, CV4, CV6, BL20, BL18, BL23, BL32, BL31, ST36, SP6.	Effective rate: 96%; BMD increased; VAS and adverse reaction rate decreased.	[92]
Randomized. Open trial.	POP, 60, 4 weeks.	BL20, BL23, GV3, GV4. Thunder-fire moxibustion.	VAS, ODI score, multi-cleft muscle Young's modulus value and TCM symptoms scores reduced.	[93]
Randomized.	OP, 88, one week per course.	BL11, GV3, ST36, SP6, EX-B2, GV4, KI3.	Effective rate: 93.2%; VAS score decreased; BMD increased.	[94]
Not randomized.	SOP, 32, 10 days per course, 3-6 courses.	GV9, GV20, GV4, GV3, BL23, GB39, ST36, SP6, CV4, CV6, BL20, and KI3, co-treatment with mild moxibustion.	Effective rate: 93.7%.	[95]
Randomized.	POP, 200, 3 months.	BL11, BL23, ST36, GB39, warm needling. BL18, GB34, SP6. CV4 only mild moxibustion.	Effective rate: 92%; BMD increased; BGP and VAS score decreased.	[96]
Randomized. Single-blind Trial.	POP, 100, 30 days.	ST36, BL20, BL23, GV4. Heat-sensitive point moxibustion combined with EA.	Effective rate: 94%; pain scores decreased; BMD improved.	[97]
Randomized.	POP, 100, 5 weeks.	BL23, BL18, BL11 and EX-B2. Heat-sensitive moxibustion combined with acupuncture and EA.	Effective rate after 1 month: 92%, effective rate after 3 months: 100%; Pain relieved; CTX, NTX, PYR and BGP decreased; OPG and IGF-1 increased.	[98]
Randomized.	POP, 60, 4 weeks.	GV3, GV4, BL18, BL23 and BL25. Co-treatment with thunder-fire moxibustion and vibration training.	VAS scores, Young's modulus of multifidus muscle decreased; 5 dimensions of SF-36 improved.	[99]

Table 1. Continued

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Randomized. Single-blind trial.	POP, 72, 3 months.	BL23, GB25, BL20, LR13, BL18, LR14, BL11, GB39, ST36, and GB34.	Effective rate: 93.75%; BMD increased; VAS score, ODI score, SAS score and TCM symptoms score improved.	[100]
Randomized.	OP, 180, 10 days.	CV6, CV4, ST36, ST34, SP6.	Effective rate: 94.44%; Clinical symptoms improved.	[101]
Randomized.	POP, 72, 3 months.	BL11, BL23, ST36. If kidney deficiency, GV4 and KI3 were punctured. If spleen deficiency, SP6 and BL20 were punctured. If blood stasis, BL17 and SP6 were punctured.	Effective rate: 91.18%; Pain relieved; Clinical symptoms and QOL improved; ICS and β-CTX decreased; BMD and PINP increased.	[102]
Randomized. Double-blind trial.	PMOP, 104, 3 months.	BL11, BL23 and ST36. If kidney Yang and spleen-kidney Yang deficiency, GV4 and GB34 were punctured. If liver-kidney Yin deficiency, SP6 and KI3 were punctured. If kidney deficiency and blood stasis, SP6 and BL17 were punctured.	BMD, E2, FSH, BGP, BALP, TAC, AOPP, PPARγ, β-catenin, FoxO3a, VAS, TCM syndrome scores and QOL improved.	[103]
Randomized. Double-blind trial.	PMOP, 70, 3 months and 1 month follow-up.	BL23, SP6, RN4, BL18, BL11, GB39, ST36 and BL20. Acupoint thread embedding.	SF-MPQ, symptom score, OQOLS and ECOS-16 improved.	[104]
Randomized	PMOP, 31, 12 weeks	BL23, BL20, RN4, ST36, SP6, and GB39 were punctured. Oral Calcium carbonate D3	Effective rate: 83.87%; TCM syndrome scores, E2, FSH, LH levels improved. GH/IGF-1 axis improved	[105]
Randomized	OP, 47, 6 months	KI3, BL52, Ashi point, EX-B2, BL23, BL40 were punctured. GV4 were Moxibustion. Co-treatment with alendronate sodium and the Bushen Zhuanggu decoction.	Effective rate: 95.74%; TCM syndrome scores, BMD, Ca improved. VAS, ALP declined.	[106]
Randomized	SOP, 30, 3 weeks per course.	BL28, BL25, BL23, BL20, DU3, RN4, GV4. Co-treatment with the decoctions.	The levels of BMD, and Ca improved. PTH, VAS deceased.	[107]
Randomized	SOP, 30, 7 days per course, 5 courses.	BL20, BL21, BL23. Co-treatment with Qianggu capsule.	Effective rate: 96.66%, VAS decreased, and the SF-36 score increased,	[108]
Randomized	OP, 40, twice a week, 10 times per course, 3 courses.	BL23, BL20, GV4, ST36, SP6, and DU20. Co-treatment with Chinese medicine decoction.	Effective rate: 97.5%.	[109]
Randomized	POP, 30, 2 weeks per course	BL23, GV4, BL11, GB39, BL20, and Ashi point. Sodium Tanshinon IIA silate	BMD and E2 improved.	[110]
Randomized	OP, 40, twice a day.	LI15, LI11, ST36, SP6, GB34, BL40, Lumbar region point. Co-treatment with Duzhong Bushen Jiangu decoction. Warm acupuncture and moxibustion	Lower pain score, BMD improved.	[111]
Not randomized	OP, 56, once a day, 6 days per course, half a year.	BL23, GV4, Ashi point, KI3. Co-treatment with Bushen Zhuanggu decoction.	BMD, OC, Ca improved, ALP, t P1NP, CTX-1, β-CTX decreased.	[112]
Randomized	PMOP, 66, 6 months	BL23, ST36, BL11, GB39, SP6, GB34, BL18. Co-treatment with the Bugu Pill.	Effective rate: 98.4%.	[113]
Randomized	SOP, 34, 5 weeks	DU3, GV4, DU9, co-treatment with Chinese medicine.	Effective rate: 97.06%.	[106]

Table 1. Continued

Study design	Type of OP; number of patients; treatment duration	Acupoints selection	Key results	Ref.
Randomized	SOP, 55, treatment duration unknown.	Ashi point, SP10, ST34, ST35, ST35, LR7, BL40, BL39, GB34, KI10. Warm acupuncture combined with rehabilitation training	Effective rate: 90%. BMP-2. BMD, TGF-β improved.	[114]
Randomized	PMOP, 54, 1 month.	Point (T11, L1, L3, L5) Embedding thread. BL23, BL25, BL40, KI3, Acupoint drug injection	Effective rate: 92.59%.	[115]
Randomized	PMOP, 40, once a day, 10 days per course, 1 month.	BL23, SP6, BL18, GV4, Moxibustion heat-sensitizing acupoints combined with risedronate sodium tablets	Effective rate: 94.7%. TCM clinical syndrome scores improved	[116]
Randomized	PMOP, 40, once a week, 6 months.	BL23, BL20 ST36, BL23, RN12, RN4. Caltrate D was given orally, combined with embedding thread.	Effective rate: 100%.	[117]
Randomized	PMOF, 20, 3 times a week, 4 weeks per course, 3 months.	BL23, ST36, BL11, BL18, RN4, Warming-needle moxibustion combined with Pulsed Electromagnetic Fields.	Effective rate: 95%.	[118]
Randomized	PMOF, 43, 3 months	BL23, ST36, RN4, GV14. Warming-needle moxibustion combined with the Bushen Tongluo formula.	Serum levels of sOC and sBAP improved. sCTx, uNTx/Cr declined.	[119]
Randomized	OP, 39, 8 weeks	BL23, ST36, BL11, GB39, GV4. Warming-needle moxibustion combined with Alendronate Sodium	Effective rate: 94.87%.	[120]
Randomized	POP, 50, 6 months	BL40, KI3, BL23, BL18, BL11, and GB39. Warming-needle moxibustion combined with the Gukang capsules	Effective rate: 92%.	[121]
Randomized	POMP, 40, 1 month	BL18, BL11, BL23, GB39, BL40, GB34, ST36, RN4. Warming-needle moxibustion combined with nourishing Yin and nourishing marrow formula.	Effective rate: 97.5%.	[122]
Randomized	OP, 30, 5 times a week, 8 weeks.	GV4, GV3, CV4, BL23, ST36. Heat-sensitive moxibustion combined with alendronate sodium tablet and calcium carbonate and vitamin D3 tablet.	The VAS scores, ODI scores and TCM clinical symptom scores decreased	[123]
Randomized	SOP, 64, once a day, 6 months.	BL23, GV4, BL20, BL25, ST25 and ST36, *Wentong* acupuncture combined with oral administration of vitamin D calcium chewable tablets and calcitriol capsules.	Effective rate: 85.9%.	[124]
Randomized	POP, 29, 3 times per week, 4 weeks	ST36, GB34, BL18, BL20, BL23 Oral Caltrate combined with EA.	The motor functions and muscle state improved.	[125]

Table 2. The ten most used acupoints for acupuncture on osteoporosis management

Order	Acupoint	Chinese Pinyin name	Frequency of appearances	Percentage (%)
1	BL23	*Shenshu*	98	89.9
2	ST36	*Zusanli*	71	65.1
3	BL20	*Pishu*	54	49.5
4	BL11	*Dazhu*	50	45.9
5	CV4	*Guanyuan*	48	44.0
6	GV4	*Mingmen*	46	42.2
7	SP6	*Sanyinjiao*	45	41.3
8	KI3	*Taixi*	34	31.2
9	BL18	*Ganshu*	33	30.3
10	GB39	*Xuanzhong*	29	26.6

syndrome differentiation and treatment in the basic theory of TCM [130,131]. For example, GV4 and KI3 acupoints were always punctured for patients with kidney deficiency. For patients with spleen deficiency, BL20, SP9, and SP6 acupoints were stimulated. In addition, BL18, SP6, and KI3 acupoints were acupunctured for patients with Yin deficiency of the liver and kidney. For patients with Yang deficiency of the spleen and kidney, BL20, ST36, GV4, and GB34 acupoints were acupunctured. Furthermore, BL17 and SP6 were acupunctured for patients with blood stasis.

Of the 109 clinical trials, the numbers of enrolled patients were usually between 30 to 100, while the treatment duration was between 1 to 6 months. Although the courses of treatment were generally more than one month, the observation duration was relatively short. Therefore, there is still a lack

of corresponding studies on the long-term efficacy and side effects of acupuncture for OP.

The efficacy of acupuncture for OP was widely investigated in the 109 clinical trials. The criteria for clinical efficacy were usually defined as the following: (1) Clinical recovery, defined as the disappearance or almost disappearance of clinical symptoms and signs, increased BMD, and the decreased syndrome score (≥ 95%); (2) Obvious effect, defined as the significant improvement of clinical symptoms and signs, increased BMD, and decreased syndrome score (≥ 70%, < 95%); (3) Effective, defined as the improvement of clinical symptoms and signs, no increase in BMD, and reduced syndrome scores (≥ 30%, < 70%); (4) Inefficacy, defined as no significant improvements in clinical symptoms and signs, and reduced syndrome scores (< 30%) [132]. The accumulating evidence demonstrated that acupuncture treatment not only increased BMD but also improved clinical symptoms. The clinical efficacy was generally above 70%, even higher than 95%. However, a few studies were conducted to elucidate the underlying mechanisms. In addition, micro-computed tomography (CT) was more acute than dual-energy X-ray absorptiometry (DXA) in evaluating bone alterations [133]. Thus, future clinical trials are suggested to employ micro-CT to investigate the efficacy of acupuncture. Moreover, estrogen levels were reported to be increased in several clinical trials after acupuncture treatment, which may raise the concerns of potential side effects of this non-drug management.

In summary, the clinical efficacy of acupuncture for OP treatment has been demonstrated by different groups. Generally, the acupoints, BL23, ST36, BL20, BL11, CV4, GV4, SP6, KI3, BL18, and GB39, are chosen for OP management. Even though most of the clinical trials were randomized, well-controlled and multi-center trials were not conducted, which may undermine the evidence. In addition, a larger sample size and prolonged treatment course should be considered. Moreover, investigations observing the possible long-term efficacy, side effects, and compliance in applying acupuncture for OP management are still yet to be conducted.

With the development of artificial intelligence technology, in the future, care providers should consider incorporating this technology into OP management, which may contribute to an optimized individual prevention and treatment protocol, improve patient compliance, and consequently increase the efficiency of acupuncture for OP management [134].

2. Preclinical advances in using acupuncture for OP treatment

In preclinical studies, female Sprague-Dawley (SD) and Wistar rats were usually used for studying the anti-OP effects of acupuncture. Generally, the acupoints governor, conception, bladder, kidney, and stomach meridians were acupunctured. In detail, BL23, ST36, CV4, GV4, BL11, SP6, GB39, BL20, and BL17 were commonly chosen acupoints in these studies. Acupuncture approaches included conventional acupuncture, electro-acupuncture (EA), laser acupuncture, and moxibustion. Each acupoint was punctured for 10-30 minutes once a day for 2 weeks to 4 months [135-141].

In addition, Zhang et al. [142] found that traditional Chinese countermeasures of "bird-pecking and revolving moxibustion on twelve Beishu points" administered to ovariectomized (OVX) rats for 90 days decreased the levels of urinary hydroxyproline and bone alkaline phosphatase, as well as increased BMD. In this study, the acupoints for cyclotron moxibustion were BL13, BL14, BL15, BL18, BL19, BL20, BL21, BL22, BL23, BL25, BL27, and BL28. The points for bird-pecking moxibustion included BL15, BL20, and BL23. In another study, Shao et al. [143] found that EA treatment at the BL23 and BL20 acupoints could downregulate the expression of histone deacetylase 2 (HDAC2) and histone 3 (H3) and upregulate the expression of acetylated H3, which further increased BMD, bone mass, and trabecular bone, and promoted trabecular bone rod-like changes in OVX rats.

Moreover, OVX female New Zealand rabbits were used to evaluate the efficacy of acupuncture on bone quality [144]. The results revealed that EA treatment at BL20, BL23, and ST36 may prevent bone loss through the upregulation of plasma estradiol (E2) levels and downregulation of osteoprotegerin (OPG) ligand expression.

The current findings of the preclinical studies have elucidated some underlying mechanisms whereby acupuncture exhibits an anti-OP effect. Firstly, acupuncture may regulate the hypothalamic-pituitary-gonadal (adrenal) axis. One study showed that acupuncture and moxibustion at B11, GV14, GV4, GB39, BL17, and ST36 (retaining needle 30 minutes/treatment every 4 days, 6 courses) in OVX rats increased serum levels of E2, parathyroid hormone (PTH), and bone gla protein (BGP) [145]. In another study, EA treatment at BL20, BL21, BL23, BL24, CV4, ST36, BL17, and BL11 (15 minutes/treatment, 6 days per week for 8 weeks) increased serum levels of E2 and insulin-like growth factor-1 in OVX SD rats [146]. In addition, acupuncture and moxibustion with bilateral BL11, BL23, BL20, and GV4 (retaining needle 30 minutes/treatment, 10 times/course for 6 courses) elevated E2, PTH, and calcitonin levels, promoted femoral BGP mRNA expression, and consequently improved calcium metabolism and bone homeostasis in OVX rats [147].

Secondly, acupuncture may decrease the levels of pro-inflammatory factors contributing to the inhibition of osteoclastogenesis and the improvement of bone metabolism. It was demonstrated that EA treatment inhibited mRNA and protein expression of tibial interleukin (IL)-6 in OVX

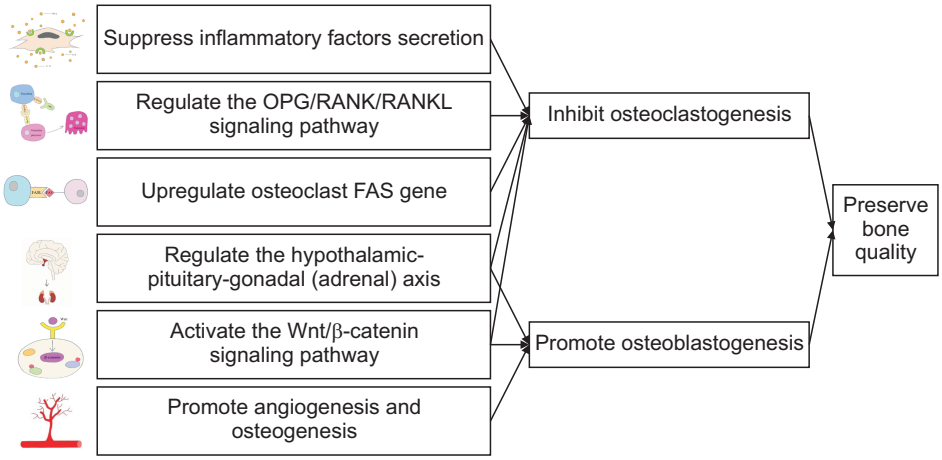

Fig. 2 The mechanisms behind the action of acupuncture for osteoporosis treatment. Acupuncture may preserve bone quality by promoting osteoblastogenesis and inhibiting osteoclastogenesis via regulating the hypothalamic-pituitary-gonadal (adrenal) axis, inhibiting pro-inflammatory factors, activating the Wnt/β-catenin signaling pathway, modulating the OPG/RANK/RANKL signaling pathway, activating osteoclast FAS gene, and promoting angiogenesis and osteogenesis.

rats [146]. In addition, acupuncture at bilateral ST36 (once a day with twirling for 1 minute, no needle left, 5 times/course every 3 days for 4 courses) reduced serum IL-1β levels in osteoporotic female Wistar rats [148]. Moreover, moxibustion at GV20, GV14, GV3, and GV4 (once a day, 7 days/course for 2 courses) reduced serum levels of IL-6 and tumor necrosis factor (TNF)-α, and increased transforming growth factor (TGF)-β1 levels in osteoporotic Wistar rats [149].

Thirdly, acupuncture may activate the canonical Wnt/β-catenin pathway, promoting osteoblastogenesis and enhancing bone strength. It was demonstrated that EA treatment at CV4 for one month promoted the proliferation and differentiation of osteoblasts by upregulating the expression levels of β catenin, Wnt3a, and Runx2 in OVX rats [150]. In addition, a study conducted by Zhou et al. [151] showed that EA treatment at ST36 and SP6 for 12 weeks increased the expression of low-density lipoprotein receptor-related protein 5 (LRP5) and β-catenin mRNA in OVX rats. Moreover, Zheng et al. [152] demonstrated that EA treatment at GV4/GV6 or BL20/BL23 for 90 days upregulated the protein expression of LRP5, β-catenin, and Runx2 in OVX rats.

Fourthly, acupuncture may modulate osetoprotegerin (OPG)/ receptor activator of NF-κB ligand (RANKL)/ receptor activator of NF-κB (RANK) signaling pathway. It is known that OPG inhibits osteoclastogenesis by competitively binding with RANK, interfering with the binding of RANKL to RANK [153]. In a study conducted by Huang [153]. EA treatment at BL20, BL21, BL23, BL24, CV4, ST36, BL17, and BL11 (15 minutes/time, 6 days per week for 8 weeks) increased OPG and RANKL levels in OVX rats. In addition, Zheng et al. [152] found that EA treatment at GV4/GV6 or BL20/BL23 increased the ratio of OPG to RANKL in OVX rats. Moreover, Pan [154] demonstrated that EA treatment at GB34, GB30, GB39, and GB25 (20 minutes/treatment, 10 times/course every 5 days for 6 courses) increased the serum OPG/RANKL ratio in OVX rats.

Lastly, acupuncture may effectively increase the apoptosis of osteoclasts and promote angiogenesis and osteogenesis. Liu et al. [155] found that acupuncture and moxibustion treatment at BL11, GV4, GB39, and ST36 (30 minutes/treatment, 10 days/course every 6 days for 6 courses) decreased tibial fatty acid synthase (FAS) expression, and increased the expression of TGF-β1 and vascular endothelial growth factor (VEGF) mRNA in OVX rats, which further promotes blood vessel and bone formation.

In addition, acupuncture may inhibit bone resorption by promoting osteoclasts apoptosis, angiogenesis, and osteogenesis. Of note, the long-term efficacy and safety of acupuncture for OP management deserves further investigation.

In brief, acupuncture was demonstrated to preserve bone quality in OVX rats and rabbits through the regulation of the hypothalamic-pituitary-gonadal (adrenal) axis and the Wnt/β-catenin and OPG/RANKL/RANK signaling pathways, as well as the promotion of osteoclasts apoptosis, angiogenesis, and osteogenesis (Fig. 2).

CONCLUSIONS

Acupuncture has been demonstrated to exert certain therapeutic effects on OP in both preclinical and clinical studies. New acupoint stimulation methods, such as EA, may also contribute to protection against OP. Acupuncture at the top ten commonly used acupoints or in conjunction with other

acupoints may achieve good clinical efficacy against OP. However, there is still a lack of investigations on the long-term efficacy of acupuncture for OP management. In addition, an upregulation of E2 levels in response to acupuncture treatment may indicate potential side effects of long-term management. Due to the paucity of high-quality studies, the efficacy of acupuncture for OP management and its potential side effects should be evaluated by further investigation. In the future, large randomized controlled trials may further demonstrate the effect of acupuncture on OP management. Also, the standardization of acupoint selection will help clinical management.

Although there is a breakthrough in elucidating the mechanisms of acupuncture against OP, the advancement of animal experiments at the preclinical level is currently lacking. There are still some controversies about the correspondence of acupoints between humans and animals, which may limit the translation of basic research into clinical trials and affect the complete understanding of the molecular mechanisms of acupuncture for OP management.

OP is a chronic metabolic disease and thus needs a long-term drug intervention. However, the current anti-OP drugs may have limited effectiveness due to the high risk of side effects for long-term management. The poor compliance and persistence with current anti-OP medications also suggest that a new intervention for OP management is needed. Interestingly, the accumulating evidence indicates that acupuncture may provide a new non-drug intervention option to protect against OP. With further advances in experimental investigation and clinical trials, acupuncture may gain increasing attention in the prevention and treatment of OP.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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