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REVIEW ARTICLE

The efficacy and safety of menatetrenone in the management of osteoporosis: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Summary In our systematic review and meta-analysis, we comprehensively evaluated menatetrenone in the management of osteoporosis. We found that menatetrenone decreased the ratio of undercarboxylated osteocalcin to osteocalcin (ucOC/OC) and improved lumbar BMD compared with placebo based on the 18 studies assessed. However, its benefit in fracture risk control was uncertain.

Introduction We performed a systematic review and meta-analysis of the efficacy and safety of menatetrenone in managing osteoporosis.

Methods PubMed, Cochrane Library, Embase, ClinicalTrials.gov, and three Chinese literature databases (CNKI, CBM, Wanfang) were searched for relevant randomized controlled trials (RCTs) published before October 5, 2017, comparing menatetrenone with other anti-osteoporotic drugs or placebo in treating osteoporosis. The pooled risk ratio (RR) or mean difference (MD) and 95% confidence interval (CI) were calculated using fixed-effects or random-effects meta-analysis.

Results Eighteen RCTs (8882 patients) were included. Pooled analyses showed that menatetrenone was more effective than placebo in improving lumbar bone mineral density (BMD) (five studies, $N = 658$, MD = 0.05 g/cm^2, 95% CI 0.01 to 0.09 g/cm^2) and decreasing ucOC/OC (two studies, $N = 75$, MD = − 21.78%, 95% CI − 33.68 to − 9.87%). Compared with placebo, menatetrenone was associated with a nonsignificantly decreased risk of vertebral fracture (five studies, $N = 5508$, RR = 0.87, 95% CI 0.64 to 1.20). Evidence on other anti-osteoporotic drugs as comparators was limited and revealed no significantly different effects of menatetrenone on BMD or fracture risks. Furthermore, compared with placebo, menatetrenone significantly increased the incidence of adverse events (AEs) (two studies, $N = 1949$, RR = 1.47, 95% CI 1.07 to 2.02) and adverse drug reactions (four studies, $N = 6102$, RR = 1.29, 95% CI 1.07 to 1.56). However, no significant difference in the incidence of serious AEs was found between menatetrenone and placebo.

Conclusions Menatetrenone significantly decreases ucOC and might improve lumbar BMD in osteoporotic patients. However, its benefit in fracture risk control is uncertain.

Keywords Menatetrenone · Osteoporosis · Efficacy · Safety · Meta-analysis

S. Su and N. He contributed equally to this work.

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Introduction

Osteoporosis is a progressive disease with reduced bone density and quality, and the risk of fracture is greatly increased as bones become more porous and fragile [1]. There were an estimated nine million osteoporotic fractures worldwide in 2000. Among these cases, 1.6 million were at the hip, 1.7 million were at the forearm and 1.4 million were clinical vertebral fractures [2]. Hip fracture is generally considered the most serious type of osteoporotic fracture. Twenty percent of patients die of complications in the first year following a hip fracture, and nearly 50% of patients are not independently mobile [3]. As the world population ages, it is estimated that

the annual number of hip fractures will increase to between 4.5 and 6.3 million by 2050 [2, 4]. By 2050, more than 50% of all osteoporotic fractures worldwide will occur in Asia, where the aging population is rapidly growing [5]. The 2015 World Health Organization (WHO) Report on Aging and Health announced that musculoskeletal disorders, including osteoporosis, increase social and economic burdens worldwide [6], making the prevention and treatment of osteoporosis a major public health goal.

The ultimate goal of osteoporosis management is to prevent osteoporosis-related fractures and improve quality of life. However, this goal is challenging and requires critical efforts worldwide. Several medications have been used for the prevention and treatment of osteoporosis, including calcium, vitamin D, bisphosphonate, parathyroid hormone, raloxifene, nasal calcitonin, and vitamin K [7]. Menatetrenone is the form of a synthetic vitamin K_2 that is chemically identical to menaquinone-4. It has been widely used in Japan since its marketing in 1995. It has been reported that vitamin K_2 could increase bone mass and reduce bone resorption [8]. Vitamin K_2 affects the carboxylation of osteocalcin (OC), which plays a role in bone mineralization [8]. In addition, vitamin K_2 inhibits programmed cell death and maintains the number of osteoblasts [9].

Several published systematic reviews and meta-analyses evaluated vitamin K's efficacy in preventing and treating osteoporosis [10–16]. However, those studies analyzed vitamin K_1 and vitamin K_2 together [10, 11, 15]. Additionally, different doses of vitamin K_2 were incorporated [10–12]. Some of the studies did not separate patients taking vitamin K for osteoporosis prevention from those taking vitamin K for osteoporosis treatment and bundled them into a single analysis [10–12], and some studies enrolled only postmenopausal women [13, 16]. The effect of vitamin K_2 (menatetrenone) on adults with diagnosed osteoporosis remains a matter of controversy and is still uncertain. Thus, we undertook a systematic review and meta-analysis to comprehensively evaluate menatetrenone in the management of osteoporosis by analyzing different osteoporosis-related parameters.

Methods

This systematic review and meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [17] and is presented per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [18].

Literature search

We searched PubMed, Cochrane Library, Embase, China National Knowledge Internet (CNKI), CBM, Wanfang Data (WanFang), and ClinicalTrials.gov from their respective inception dates to October 5, 2017. The search terms were "vitamin K," "vitamin K_2," "menatetrenone," "menaquinone," and "osteoporosis." Both Medical Subject Headings (MeSH) terms and text words were used. The search strategies are detailed in Online Resource 1. The reference lists of the retrieved articles and related reviews were also examined manually for additional studies. No language or date restriction was applied.

Eligibility criteria

RCTs were eligible according to the following inclusion criteria: (1) conducted in adults with osteoporosis, (2) compared menatetrenone (treatment group) with placebo or other active anti-osteoporotic drugs (control group), and (3) explicitly reported at least one of the following outcomes: vertebral fracture, nonvertebral fracture, hip fracture, fracture, lumbar bone mineral density (BMD), undercarboxylated osteocalcin (ucOC), ucOC/OC, adverse events (AEs), adverse drug reactions, serious AEs, gastrointestinal AEs, skin and subcutaneous tissue disorders, or prothrombin time (PT). Menatetrenone could be used as monotherapy or part of a combination therapy in the management of osteoporosis. To achieve an unconfounded comparison, planned interventions were required to be identical between the treatment and control groups, except the use of menatetrenone.

Study selection

Two reviewers independently screened the titles and abstracts of the studies initially identified for potential eligibility. Then, a full-text review was performed to determine the final list of included studies. Any disagreement was resolved by discussion between the two reviewers or by consulting a third reviewer.

Data extraction

We extracted the following data: study characteristics (the first author's name, year of publication, country, and sample size), participant characteristics (age, sex, baseline BMD, and baseline ucOC), interventions, controls, efficacy and safety outcomes, and trial duration. If outcomes were reported at multiple follow-up points, we used the data from the longest follow-up. The number of decimal digits was reported per the Official Positions of the International Society for Clinical Densitometry (ISCD) (https://www.iscd.org/) if possible. If the primary study did not satisfy the requirements of ISCD, relevant data were extracted, consistent with the reporting in the primary study. Data extraction was performed by two reviewers independently. Discrepancies were addressed by

discussion between the two reviewers or consultation with a third reviewer if necessary.

Quality assessment

The methodological quality of each included study was assessed by two researchers independently, and disagreements were resolved by discussion or by consulting a third researcher. The potential risk of bias in the RCTs was assessed according to the Cochrane risk of bias tool [17]. The included trials were graded as high, moderate, or low quality based on the following criteria: (1) a trial was considered low quality if either randomization or allocation concealment was estimated to have a high risk of bias, regardless of the risk of other items; (2) a trial was considered high quality when both randomization and allocation concealment were estimated to have a low risk of bias and when all other items were estimated to have low or unclear risk of bias; or (3) a trial was considered moderate quality if it did not meet the criteria for high or low risk [19].

Statistical analysis

Risk of bias was assessed by Review Manager software (RevMan Version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis was performed using STATA (version 14; Stata Corp., College Station, TX, USA). For dichotomous outcomes, the pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel method or the DerSimonian and Laird method. Pooled mean differences (MDs) and 95% CIs were calculated for continuous outcomes using the inverse variance method or the DerSimonian and Laird method. The χ^2 test and I^2 value were used to determine the heterogeneity between the included studies. If $I^2 < 50\%$ and $P > 0.1$, a fixed-effect model was adopted; otherwise, a random-effects model was used for statistical analysis. For efficacy and safety evaluations, menatetrenone was compared with each individual arm separately in studies with multiple comparators. Sensitivity analysis was performed by excluding each study from the analysis to examine whether a single study had a significant influence on the summary estimates, using STATA's user-written function "metaninf" [20]. Additionally, another sensitivity analysis was performed by focusing on trials recruiting only postmenopausal women with osteoporosis for efficacy evaluation. Potential publication bias was assessed by a funnel plot when sufficient data were available. For some outcomes for which data were scant or meta-analysis was not adoptable, only descriptive analysis was conducted.

Results

Search process and eligible studies

Of the 3023 potentially relevant published reports identified, 61 reports proved potentially eligible after removing duplicates and screening abstracts. After full text screening, 18 RCTs with 8882 participants were ultimately included in the systematic review and meta-analysis [21–38]. The detailed search process is described in Fig. 1.

Study characteristics

Of the 18 RCTs, 12 were conducted in Japan [21–32], 5 were conducted in China [33–37], and 1 was conducted in Indonesia [38]. Eleven trials used menatetrenone as an add-on or part of a combination therapy [24, 27, 29, 31–38], five trials used it as a monotherapy [21, 23, 25, 28, 30], and two used it as both a monotherapy and part of a combination therapy [22, 26]. The menatetrenone dose of 17 studies was 45 mg/day [22–38], whereas one study used 90 mg/day [21]. Eleven trials compared menatetrenone with negative comparators (placebo or no additional anti-osteoporotic drug) [21, 24, 27, 29, 31, 32, 34–38], while four used other active anti-osteoporotic drugs as comparators [23, 25, 30, 33] and three used both negative and active comparators [22, 26, 28]. The participants of 13 studies consisted solely of postmenopausal women with osteoporosis [22, 24–33, 37, 38]. The patients' mean age was between 53.4 and 75.8 years, and the trial duration ranged from 2 weeks to 4 years. The trial duration of the studies included was not less than 24 weeks, except for the study by Miki [27]. Different treatment groups of each included trial were well balanced with respect to demographic and clinical characteristics. A summary description of the studies is shown in Table 1.

Overall, all of the included studies were of adequate quality. Seventeen trials were of moderate quality [21–25, 27–38], and the remaining one study was of low quality [26]. The risk of bias of the studies is detailed in Online Resource 2.

Efficacy evaluations

Summary results from meta-analyses for dichotomous and continuous efficacy outcomes are summarized in Figs. 2 and 3, respectively.

Menatetrenone versus placebo/no additional drug

Fourteen trials compared the efficacy of menatetrenone versus placebo or no additional anti-osteoporotic drugs [21, 22, 24, 26–29, 31, 32, 34–38]. Vertebral fracture was reported in 5 studies with 5508 participants [24, 28, 29, 31,

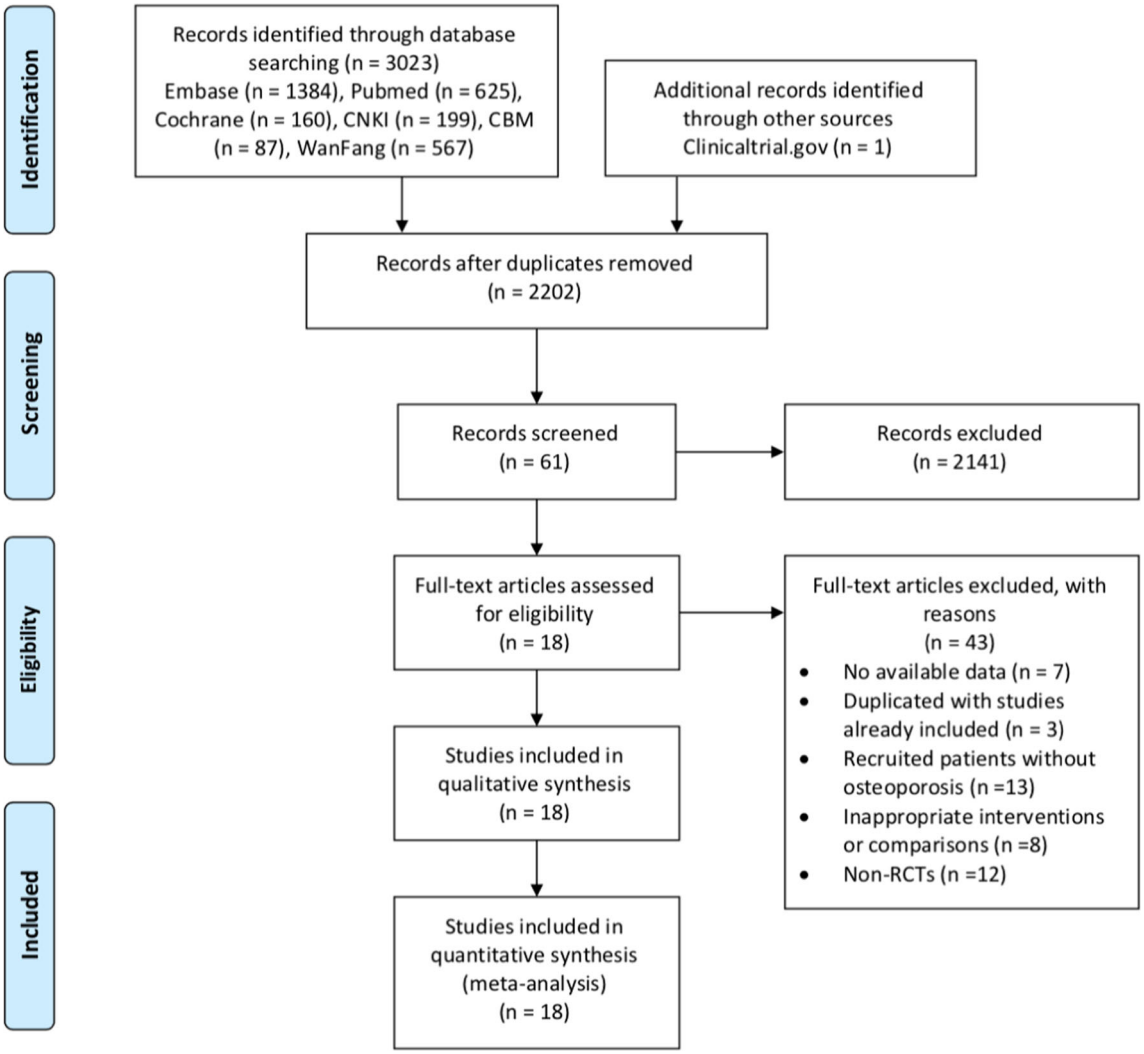

Fig. 1 Flow chart of the study search process

32], and there was no significant association between menatetrenone use and vertebral fracture (RR = 0.87, 95% CI 0.64 to 1.20, $P = 0.39$) (Figs. 2 and 4). Three studies with 2196 patients reported nonvertebral fracture [24, 28, 32], but no significant difference in this outcome was observed (RR = 0.67, 95% CI 0.39 to 1.16, $P = 0.15$) (Fig. 2; Online Resource 3). Two studies enrolling 322 patients reported hip fracture [24, 28], and our meta-analysis demonstrated no significant difference between menatetrenone and placebo or no additional drug (RR = 0.26, 95% CI 0.03 to 2.33, $P = 0.23$) (Fig. 2; Online Resource 3). Three studies with 6079 patients reported the incidence of fracture [24, 29, 32], showing that menatetrenone nonsignificantly decreased the risk of fracture (RR = 0.78, 95% CI 0.48 to 1.25, $P = 0.30$) (Fig. 2; Online Resource 3).

Five studies including 658 patients reported the changes in lumbar BMD (g/cm^2) from baseline to the study endpoint [24, 26, 35–37]. Our analysis revealed a significant increase in lumbar BMD associated with menatetrenone (MD = 0.05 g/cm^2, 95% CI 0.01 to 0.09 g/cm^2, $P = 0.01$) (Fig. 3; Online Resource 3). In addition, analysis of five studies [21, 22, 24, 26, 38] ($N = 391$) revealed a significantly greater percent increase in lumbar BMD from baseline for menatetrenone compared with placebo or no additional anti-osteoporotic drug (MD = 2.11%, 95% CI 0.91 to 3.32%, $P = 0.0006$) (Fig. 3; Online Resource 3).

Three studies including 2038 participants reported the change in ucOC [31, 32, 38], and our analysis showed nonsignificantly decreased ucOC in the menatetrenone group compared with the placebo or no additional drug (MD = − 1.17 ng/ml, 95% CI − 2.82 to 0.49 ng/ml, $P = 0.17$) (Fig. 3; Online Resource 3). Two studies ($N = 75$) reported the change in ucOC/OC with menatetrenone as part of a combination therapy [27, 31]. Analysis of these two studies showed that the menatetrenone group had a significantly lower ucOC/OC than the placebo or no additional drug group (MD = − 21.78%, 95% CI − 33.68 to − 9.87%, $P = 0.0003$) (Fig. 3; Online Resource 3).

Table 1 Characteristics of the included RCTs

Study	Country	Characteristics of patients	Number of patients	Mean age	Gender (male/female)	Baseline lumbar BMD (g/cm^2)		Baseline ucOC (ng/ml)
						Intervention	Control	Intervention
Orimo 1992 [23]	Japan	Patients with postmenopausal or senile osteoporosis	546	45(8%) < 60 years	33/513	NR	NR	9.03#
Orimo 1998 [21]	Japan	Patients with osteoporosis	80	72.1	4/45	NR	NR	12.6#
Iwamoto 2000 [22]	Japan	Postmenopausal women with osteoporosis	50	63.5	0/50	0.677	0.697	NR
			42	64.7	0/42	0.682	0.691	NR
Shiraki 2000 [24]	Japan	Elderly women with osteoporosis	241	67.2	0/241	0.747	0.756	13.0#
Iwamoto 2001 [25]	Japan	Postmenopausal women with osteoporosis	47	65.7	0/47	0.246*	0.254*	NR
Ushiroyama 2002 [26]	Japan	Postmenopausal women with vertebral BMD < 0.98 g/cm^2	172	53.4	0/126	0.820	0.872	NR
						0.876	0.864	NR
						0.876	0.872	NR
Miki 2003 [27]	Japan	Elderly women with osteoporotic fracture(s) and low lumbar BMD	20	75.8	0/20	0.713	0.726	2.8
Ishida 2004 [28]	Japan	Postmenopausal women with osteoporosis	396	68.0	0/396	0.44*	0.44*	NR
Purwosunu 2006 [38]	Indonesia	Postmenopausal women with osteoporosis	69	60.8	0/69	0.792	0.766	6.3
Inoue 2009 [29]	Japan	Postmenopausal women with osteoporosis	4378	69.6	0/4378	NR	NR	NR
Shiraki 2009 [30]	Japan	Postmenopausal women with osteoporosis	109	68.6	0/109	0.690	0.710	5.6
Jiang 2014 [33]	China	Postmenopausal women with osteoporosis	236	64.4	0/236	0.805	0.794	2.7
Kasukawa 2014 [31]	Japan	Postmenopausal women with osteoporosis	101	74.7	0/101	0.286*	0.305*	5.7
						−5.4~	−4.9~	
Liu 2015 [34]	China	Patients with primary or secondary osteoporosis	20	58.3	2/18	−2.9^	−2.7^	NR
Hu 2017 [35]	China	Elderly patients with osteoporosis	122	63.2	43/79	0.80	0.78	NR
Luo 2017 [36]	China	Osteoporotic patients with femoral intertrochanteric fracture	150	62.2	74/76	0.70	0.70	NR
Tanaka 2017 [32]	Japan	Women over 65 years of age with osteoporosis	1983	75.3	0/1983	−3.2^	−3.2^	5.8
Zhuang 2017 [37]	China	Postmenopausal women with osteoporosis	120	67	0/120	0.79	0.78	NR

Study	Baseline ucOC (ng/ml)	Background therapy	Interventions	Controls	Trial duration	Outcomes
	Control					
Orimo 1992 [23]	8.59#	None	Menatetrenone 45 mg/day	Alfacalcidol 1 μg/day	48 weeks	1,9,10
Orimo 1998 [21]	12.2#	None	Menatetrenone 90 mg/day	Placebo	24 weeks	5,9,12,13
Iwamoto 2000 [22]	NR	Alfacalcidol 0.75 μg/day	Menatetrenone 45 mg/day	No additional drugs	2 years	5
	NR	None	Menatetrenone 45 mg/day	Calcium lactate 2 g/day		
Shiraki 2000 [24]	12.6#	Calcium 150 mg/day	Menatetrenone 45 mg/day	No additional drugs	2 years	1–6
Iwamoto 2001 [25]	NR	None	Menatetrenone 45 mg/day	Calcium lactate 2 g/day Etidronate 200 mg/day	2 years	2,11
	NR	Alfacalcidol 1 μg/day	Menatetrenone 45 mg/day	No additional drugs	2 years	5,6

Table 1 (continued)

Ushiroyama 2002 [26]	NR	None	Menatetrenone 45 mg/day	No additional drugs		
	NR	None	Menatetrenone 45 mg/day	Alfacalcidol 1 μg/day		
Miki 2003 [27]	3.2	Calcium aspartate 600 mg/day	Menatetrenone 45 mg/day	No additional drugs	2 weeks	8
Ishida 2004 [28]	NR	None	Menatetrenone 45 mg/day	No additional drugs Etidronate 200 mg/day Alfacalcidol 1 μg/day	2 years	2–4
Purwosunu 2006 [38]	5.4	Calcium carbonate 1500 mg/day	Menatetrenone 45 mg/day	Placebo	48 weeks	5,7
Inoue 2009 [29]	NR	Calcium aspartate 1.2 g/day	Menatetrenone 45 mg/day	No additional drugs	4 years	1,2,10,13
Shiraki 2009 [30]	5.4	None	Menatetrenone 45 mg/day	Calcium aspartate 1200 mg/day (133.8 mg of calcium)	6 months	5,7,9,10
Jiang 2014 [33]	2.4	Calcichew (contains 500 mg of calcium)	Menatetrenone 45 mg/day	Alfacalcidol 0.5 μg/day	1 year	1,2,4,6,7,9
Kasukawa 2014 [31]	7.7	Risedronic acid (17.5 mg/week)	Menatetrenone 45 mg/day	No additional drugs	1 year	2,7,8
Liu 2015 [34]	NR	Vitamin AD 300 units/day + Caltrate D 1.5 g/day	Menatetrenone 45 mg/day	No additional drugs	12 months	12
Hu 2017 [35]	NR	Caltrate D 600 mg/day + salmon calcitonin	Menatetrenone 45 mg/day	No additional drugs	6 months	6.13
Luo 2017 [36]	NR	Caltrate D orally 600 mg/day	Menatetrenone 45 mg/day	No additional drugs	1 year	6
Tanaka 2017 [32]	6.0	Risedronic acid (2.5 mg/day or 17.5 mg/week)	Menatetrenone 45 mg/day	No additional drugs	2 years	1–3,7,9–11,13
Zhuang 2017 [37]	NR	Calcium **c**arbonate and **v**itamin D_3 chewable tablets	Menatetrenone 45 mg/day	No additional drugs	6 months	6

Outcomes: 1, fracture; 2, vertebral fracture; 3, nonvertebral fracture; 4, hip fracture; 5, lumbar bone mineral density (%); 6, lumbar bone mineral density (g/cm^2); 7, undercarboxylated osteocalcin (ucOC); 8, ucOC/OC; 9, adverse events; 10, severe adverse events; 11, gastrointestinal adverse events; 12, prothrombin time; 13 adverse drug reactions

BMD bone mineral density, *ucOC* undercarboxylated osteocalcin, *NR* not reported

#Baseline OC

^ Vertebral bone mineral density (T-score)

*Forearm bone mineral density (g/cm^2)

~ Forearm bone mineral density (T-score)

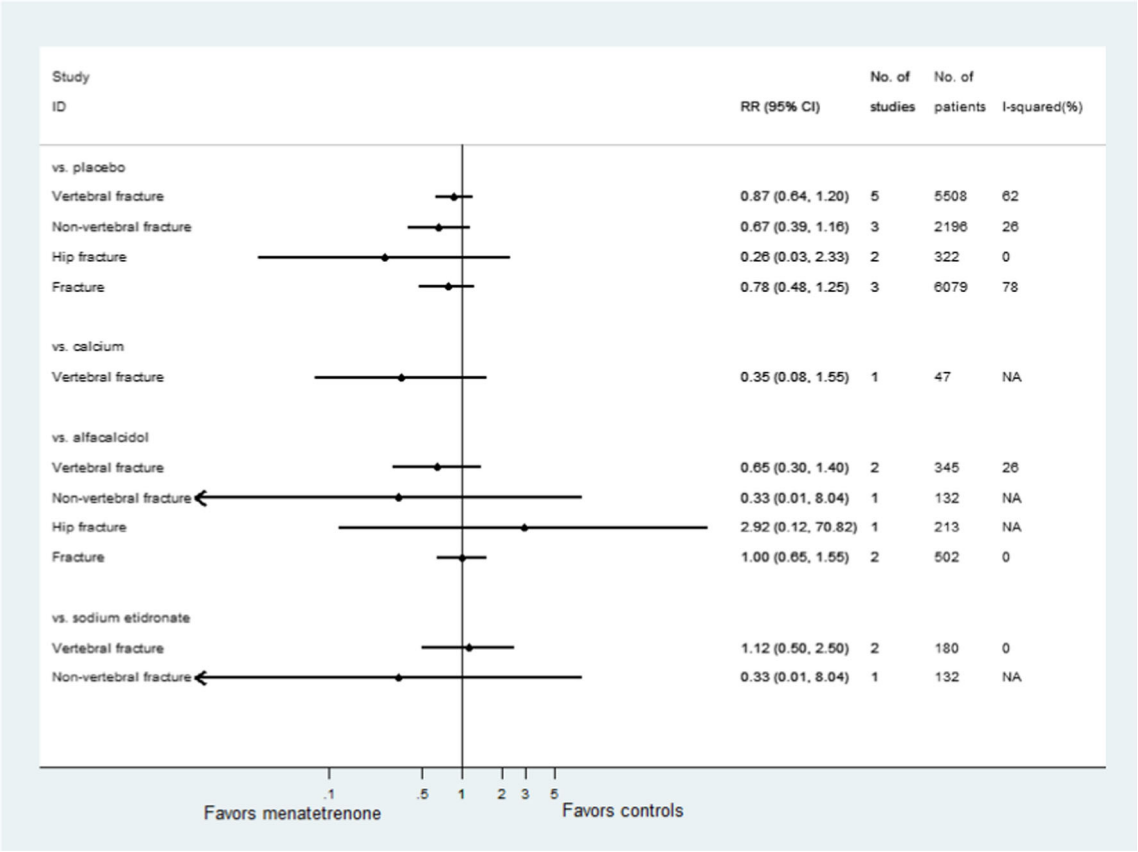

Fig. 2 Summary results of the meta-analyses for dichotomous variables

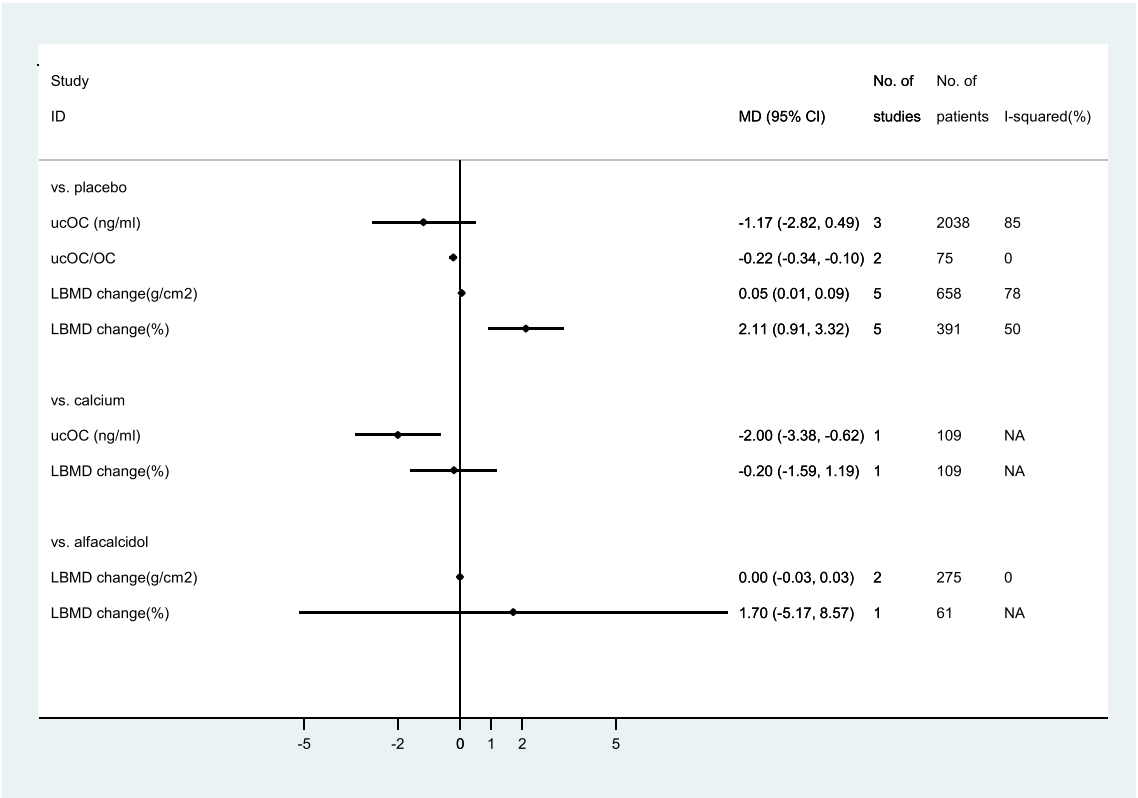

Fig. 3 Summary results of the meta-analyses for continuous variables

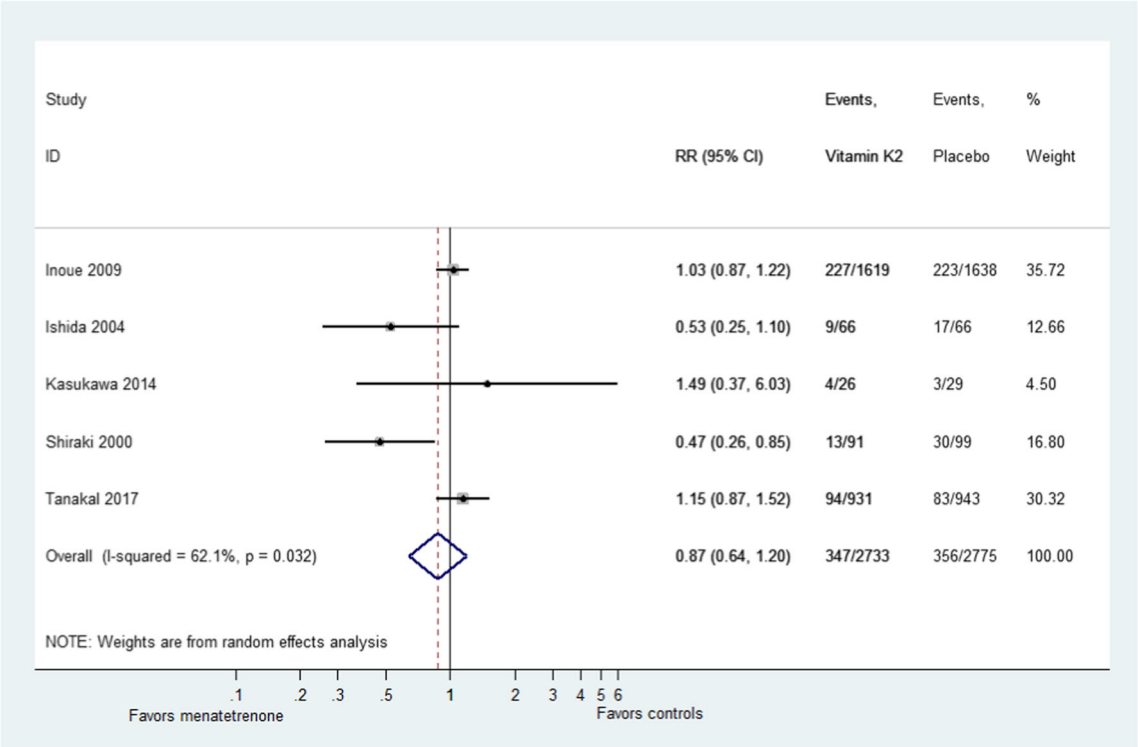

Fig. 4 Meta-analysis comparing the risk of vertebral fracture between menatetrenone and placebo

Menatetrenone versus alfacalcidol

Four studies compared menatetrenone with alfacalcidol in terms of efficacy in osteoporosis management [23, 26, 28, 33]. Compared with alfacalcidol, menatetrenone was not associated with a significantly different risk of vertebral fracture (2 studies [28, 33] with 345 patients, [RR = 0.65, 95% CI 0.30 to 1.40, P = 0.27]) or facture (2 studies [23, 33] with 502 patients, [RR = 1.00, 95% CI 0.65 to 1.55, P = 0.99]) (Fig. 2; Online Resource 3). Additionally, Ishida et al. [28] reported that one forearm fracture occurred in the alfacalcidol group (N = 66), while there was no nonvertebral fracture in the menatetrenone group (N = 66). Jiang et al. [33] further reported that one patient in the menatetrenone group (N = 108) but no patients in the alfacalcidol group (N = 105) suffered hip fracture.

Two studies including 275 patients showed no significant difference in lumbar BMD change (g/cm^2) between menatetrenone and alfacalcidol [26, 33] (MD = 0.00 g/cm^2, 95% CI − 0.03 to 0.03 g/cm^2, P = 0.63) (Fig. 3; Online Resource 3). Additionally, Jiang et al. [33] demonstrated a significantly greater decrease in serum ucOC levels for menatetrenone (N = 108) compared with alfacalcidol (N = 105) (− 82.3% vs. − 34.8%, P < 0.001).

Menatetrenone versus calcium

Three studies compared menatetrenone with calcium, and only descriptive analysis was performed [22, 25, 30]. Iwamoto et al. [25] found that menatetrenone had a trend toward a lower incidence of vertebral fracture compared with calcium (2/23 vs. 6/24). In terms of surrogate outcomes, Iwamoto et al. [22] demonstrated that the mean percent increase in lumbar BMD was significantly greater in the menatetrenone group (N = 22) than in the calcium group (N = 20) (0.90% vs. − 0.79%, P < 0.01). Shiraki et al. [30] investigated menatetrenone's effect on the percent changes in lumbar BMD and ucOC. They illustrated no significant difference in the percent change in BMD from baseline between menatetrenone and calcium (0.5 ± 0.5% vs. 0.7 ± 0.5%). However, the serum level of ucOC was significantly lower in the menatetrenone group than in the calcium group (MD = − 2.00 ng/ml, 95% CI − 3.38 to − 0.62 ng/ml, P = 0.005).

Menatetrenone versus sodium etidronate

Two studies including 180 participants reported vertebral fracture [25, 28], and our analysis revealed no significant difference in the risk of vertebral fracture between menatetrenone and sodium etidronate (RR = 1.12, 95% CI 0.50 to 2.50, P = 0.97) (Fig. 2; Online Resource 3). Concerning nonvertebral fractures, Ishida et al. [28] showed that one forearm fracture occurred in the etidronate group (N = 66), but no nonvertebral fracture was found in patients treated with menatetrenone (N = 66).

Safety evaluations

Menatetrenone increased the incidence of AEs [21, 32] ($n = 2$, $N = 1949$, RR = 1.47, 95% CI 1.07 to 2.02, $P = 0.02$, Online Resource 4) and adverse drug reactions [21, 29, 32, 35] ($n = 4$, $N = 6102$, RR = 1.29, 95% CI 1.07 to 1.56, $P < 0.01$, Online Resource 4) compared with placebo or no additional drug. However, no significant difference in serious AEs, gastrointestinal AEs or skin, and subcutaneous tissue disorders was detected between menatetrenone and placebo (Table 2, Online Resource 4). Data on all active anti-osteoporotic drugs were scant, and no significant difference compared with menatetrenone was found for all outcomes concerned (Table 2).

Prothrombin time was reported in two studies [21, 34]. Orimo et al. [21] showed no significant difference in PT between menatetrenone and placebo (pretreatment 11.94 ± 0.39 s vs. 12.11 ± 0.21 s, $P = 0.73$; posttreatment 11.77 ± 0.28 s vs. 11.74 ± 0.23 s, $P = 0.94$). Liu et al. [34] demonstrated that PT in the menatetrenone group ($n = 10$) was 10.68 ± 0.64 s at baseline and 10.90 ± 0.47 s after 1 year of treatment, showing no significant difference ($P > 0.05$). Finally, none of the included RCTs reported the occurrence of coagulation disorders.

Publication bias assessment and sensitivity analysis

The number of included studies in each meta-analysis was not adequate for a proper assessment of publication bias. Sensitivity analysis using the "metaninf" function [20] revealed that for the comparison of menatetrenone and placebo, the significant difference in BMD (g/cm^2) was attenuated when the study by Zhuang et al. [37] was excluded from the analysis. Additionally, the result of pooled analysis of ucOC became significant when the study by Purwosunu et al. [38] was excluded. Sensitivity analysis concerning other outcomes showed no outliers. Detailed results are presented in Online Resource 5. Additionally, sensitivity analysis focusing on trials with postmenopausal osteoporosis showed no significant differences in efficacy from the overall analyzed population (Online Resource 6).

Discussion

In this systematic review and meta-analysis of RCTs, we comprehensively analyzed menatetrenone's efficacy and safety in the management of osteoporosis. Meta-analyses showed that compared with placebo or no additional drug, menatetrenone was effective in decreasing ucOC/OC and improving lumbar BMD. Additionally, a decreasing trend in ucOC, vertebral fracture, nonvertebral fracture, hip fracture, and fracture was observed for menatetrenone in comparison with placebo. Menatetrenone appeared to lead to lower ucOC than calcium and alfacalcidol did. However, no significant effect of menatetrenone on the risk of vertebral fracture or nonvertebral fracture was found relative to the effect of active comparators.

Vitamin K is a cofactor of the enzyme gamma-carboxylase, which converts three glutamic acid (Glu) residues to gamma-carboxyglutamic acid (Gla) [8, 39]. Osteocalcin, also known

Table 2 Summary of menatetrenone's safety

Safety-related outcomes	Number of studies	Number of patients	RR (95% CI)	*P*
Adverse events				
vs. placebo	2	1949	1.47 (1.07, 2.02)	0.02
vs. calcium	1	121	1.19(0.34,4.22)	0.79
vs. alfacalcidol	2	390	1.09(0.63,1.89)	0.75
Adverse drug reactions				
vs. placebo	4	6102	1.29 (1.07, 1.56)	< 0.01
Serious adverse events				
vs. placebo	2	5905	0.96 (0.77, 1.20)	0.72
vs. calcium	1	121	Not estimable (zero events)	
vs. alfacalcidol	1	546	Not estimable (zero events)	
Gastrointestinal adverse events				
vs. placebo	1	1874	1.60 (0.97, 2.65)	0.07
vs. calcium	1	47	0.21 (0.01, 4.12)	0.30
vs. sodium etidronate	1	48	0.08 (0.00, 1.40)	0.08
Skin and subcutaneous tissue disorders				
vs. placebo	1	1874	2.79 (0.89, 8.72)	0.08
vs. calcium	1	47	Not estimable (zero events)	
vs. sodium etidronate	1	47	Not estimable (zero events)	

as osteoblastspecific noncollagenous protein hormone, is a protein in bone containing Gla. Thus, vitamin K is essential for OC carboxylation. Without this modification, OC becomes ucOC, which lacks the structural integrity and ability to bind to the mineral hydroxyapatite. Therefore, vitamin K supplementation has the potential to decrease ucOC and improve bone quality [8, 39].

The ultimate goal of osteoporosis treatment is to reduce the incidence of fracture. Some studies reported that BMD and ucOC levels were associated with the incidence of fracture [40–43]. Thus, both serum ucOC levels and BMD are considered to be surrogate endpoints in clinical trials [40–42]. In terms of vitamin K, several cross-sectional studies have reported that vitamin K status had a positive correlation with BMD and negative correlations with ucOC and fracture risk [44, 45]. Our study showed that compared with placebo, menatetrenone significantly decreased ucOC levels and improved BMD, which was consistent with the theory that vitamin K could improve bone quality [8, 39]. However, its benefit for fracture risk control was not yet validated in the treatment of osteoporosis. This inconsistency in results between surrogate endpoints and fracture incidence could presumably be explained by the fact that bone quality is not solely reflected by BMD and ucOC, as additional factors such as the shape of bone, other bone turnover markers, microarchitecture, and degree of mineralization also reflect bone quality [46]. In addition, the incidence rate of fracture was low, and only a few trials studied menatetrenone's effect on fracture. As such, the statistical power was too small to detect an actual difference in the incidence of fracture. On the other hand, nine of the trials included in our study [22, 25, 26, 28, 29, 34–37] did not report patients' baseline vitamin K, ucOC, or OC levels. It was possible that at least some of these enrolled participants did not have vitamin K deficiency or a high level of ucOC upon enrollment. For such patients, menatetrenone would not have had much effect. Additionally, the background therapies were different between trials and possibly influenced the relative effect of menatetrenone on fracture. For example, the magnitude of reduced risk of vertebral fracture in the studies by Kasukawa [31] and Tanaka [32] was less obvious than that in the other three studies [24, 28, 29], as shown in Fig. 4. We assumed that this finding was because risedronic acid was given to both the intervention and control groups in these two studies. Additionally, although our analysis showed that menatetrenone-associated benefits for fracture were statistically nonsignificant, an obvious decreasing trend was definitely shown. More prospective RCTs of sufficiently large sample sizes are needed to further explore whether menatetrenone reduces the risk of fracture and, if so, the conditions under which menatetrenone could produce this effect.

Menatetrenone's safety was also evaluated in our study. As vitamin K is involved in the biosynthesis of several blood coagulation factors, a great concern of the synthetic form of vitamin K is its potential to induce a tendency toward thrombosis. Our results demonstrated no significant decrease in PT, and no coagulation disorder event was reported. In summary, the hemostatic balance remains stable with menatetrenone. Concerning other AEs, no significant difference in serious AEs was detected between menatetrenone and placebo. However, compared with placebo, menatetrenone resulted in increased AEs and adverse drug reactions. In the review of the studies reporting the specific AEs or adverse drug reactions, we found that gastrointestinal disorders and skin/subcutaneous tissue disorders were the two most common AEs, which were relatively not serious and could be resolved after taking action. Overall, the limited evidence showed that menatetrenone's tolerability may be acceptable.

This study is valuable to both current clinical practice and future clinical research. First, the mechanism of action of menatetrenone is different from that of other first-line anti-osteoporotic drugs. Thus, menatetrenone can be used as part of a combination therapy for patients at high risk of fractures. Previous studies showed that menatetrenone possibly had a synergistic effect with vitamin D [26] in improving bone health. Second, the available evidence suggests that OC-related markers are the key bone turnover markers for monitoring the effect of menatetrenone. However, the clinical implications of ucOC as a bone turnover marker require further research. For example, studies can be designed to investigate the ucOC cutoff value for osteoporotic patients who would need intervention. Additionally, studies focused on interventions guided by ucOC or vitamin K levels will be helpful in identifying the optimal conditions for menatetrenone usage. Third, ucOC has recently been investigated as a mediator of glucose regulation [47]. From the perspective of safety, future studies should pay attention to menatetrenone's effect on glucose regulation.

To the best of our knowledge, this is the first systematic review and meta-analysis of RCTs focusing on the effect of menatetrenone in the treatment of osteoporosis. Unlike previous studies [12, 13, 16], we included trials without patient age or sex limitations per the indication of menatetrenone. In the efficacy evaluation, sensitivity analysis was performed by focusing solely on postmenopausal osteoporosis, and no significant difference from the results of the overall analysis was found. Additionally, menatetrenone was used to treat osteoporosis rather than prevent osteoporosis in all trials. Furthermore, we analyzed each control arm separately rather than bundling them together into a single control group. For the safety outcomes, AEs and adverse drug reactions were assessed separately because they have different definitions. In this case, clinical heterogeneity and several potential confounders were controlled to the greatest extent possible.

Nevertheless, limitations of this systematic review and meta-analysis should also be considered. First, all of the

studies were undertaken in Asia, indicating that these findings may not be applicable elsewhere and that the generalizability of the results is limited. Second, subgroup analysis based on whether menatetrenone was used as monotherapy or as part of a combination therapy was not performed due to an inadequate number of studies for each outcome and different background therapies in combination therapy studies. Additionally, in some of the included studies, patients were not blinded to the interventions, which could bring uncertainty and potential bias to the interpretation of the results. Above all, menatetrenone's effect in the management of osteoporosis remains investigational. More well-designed RCTs reporting baseline vitamin K and ucOC levels are needed to assess the robustness of our findings.

In conclusion, the findings of this systematic review and meta-analysis suggest that menatetrenone decreases ucOC significantly and might improve BMD. However, its benefit in fracture risk control is still uncertain. Further studies need to be performed to investigate the proper conditions for prescribing menatetrenone.

Compliance with ethical standards

Conflicts of interest None.

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