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REVIEW

Efficacy and safety of elcatonin in postmenopausal women with osteoporosis: a systematic review with network meta-analysis of randomized clinical trials

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Abstract

Summary The present systematic review aimed to evaluate bone mineral density (BMD) change and complication rates of elcatonin on treating postmenopausal osteoporosis. The result confirmed efficacy of elcatonin and safety in combination therapies of elcatonin (C-E).

Introduction Postmenopausal osteoporosis is an important issue in global aging trends. One treatment of osteoporosis is elcatonin, a kind of calcitonin. However, it has been challenged for long time because of safety. Many trials investigated on this topic, but they were designed differently. Those designs can be categorized in monotherapy of elcatonin (M-E) and C-E. Unfortunately, no synthesized evidence dealt this topic.

Methods This study systematically identified target trials from six important databases and only included randomized controlled trial for synthesis. Two investigators assessed quality of eligible trials using the Cochrane Risk of Bias Tool, and they independently extracted data. Network meta-analysis performed Peto odds ratio (POR, used for dealing with zero cell) or weighted mean difference (WMD, for continuous data) with 95% confidence intervals (CI) and consistency *H*.

Results Sixteen trials recruiting 2754 women with postmenopausal osteoporosis were included in our study. Elcatonin therapies and non-elcatonin medications had comparable fracture rates and bone mineral density change. Yet, C-E (WMD, − 18.93; 95% CI, − 23.97 to − 13.89) and M-E (WMD, − 13.72; 95% CI, − 19.51 to − 7.94) had significantly lower pain score than non-elcatonin medications. However, M-E (POR = 8.413, 95% CI, 2.031 to 34.859) and non-elcatonin medication (Peto OR, 7.450; 95% CI, 1.479 to 37.530) had significantly higher complication rates than placebo. No evidence detected inconsistency and small study effect in this network model.

Conclusions Based on current evidence, C-E may be considered for treating postmenopausal osteoporosis because it benefits on pain relief and complications. Moreover, it shows comparable fracture rate and bone mineral density change as compared with anti-osteoporosis and calcium supplements. Nevertheless, further trials are needed to investigate formula and dosages of elcatonin.

Keywords Calcitonin · Elcatonin · Osteoporosis

Abbreviations

BMD	Bone mineral density
CI	Confidence interval
C-E	Combination therapy of elcatonin
LFK	Luis Furuya-Kanamori
M-E	Monotherapy of elcatonin
POR	Peto odds ratio
RCT	Randomized clinical trial

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Introduction

Osteoporosis, a skeletal disorder compromising bone strength, is a disease predisposing to an increased risk of fracture [1]. A common manifestation of osteoporosis, vertebral fracture, usually decreases quality of life because of back pain and disability [2], and it is recommended to be treated in early stage [3]. Furthermore, the incidence of osteoporosis increases with age, and it is commonly seen in the elderly population [4]. Finding a better way to treat osteoporosis is an important issue in global aging trends. For instance, there were about 12.8 million elderly postmenopausal women with osteoporosis in Japan by 2010 [5]. This serious public health problem is not only in Asia but also in America. There were about 1.4 million adults with osteoporosis in Canada and 10 million adults with osteoporosis in the USA.

However, how to provide a better healthcare to postmenopausal women with osteoporosis is still controversial. There are several courses of treatment for osteoporosis, even combined medication. In past decades, many therapeutic agents were used to treat osteoporosis. These agents mainly relied on the effect of increasing bone mineral density, preventing fractures, relieving back pain, or suppression of osteoclast activity. The proper selection of different drugs for treating osteoporosis is open for debate. One of therapies for osteoporosis is elcatonin, a derivative of calcitonin from eel [6]. Elcatonin is known to increase bone mineral density, to inhibit bone resorption and process a central analgesic effect [7, 8]. It can reduce fracture pain and improve quality of life in senile or postmenopausal osteoporosis [9].

Unfortunately, there was no synthesized evidence for safety and efficacy of elcatonin in postmenopausal women with osteoporosis. Therefore, the aim of this study was to compare the safety and efficacy of elcatonin with other therapeutic agents for osteoporosis.

Methods

This study reported evidence selection, quality assessment, and network meta-analysis according to the PRISMA guidelines. The study protocol is registered on online platform PROSPERO, and the registry number is CRD42018092845. (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018092845).

Eligible criteria

According to the aim of this study, the eligible criteria for this systematic review should be as follows: (1) randomized clinical trial (RCT); (2) patients with osteoporosis; (3) comparing the effects or safety of elcatonin (eel). The exclusion criteria should be as follows: (1) trial recruiting male; (2) patients with diseases that were not only osteoporosis; or (3) comparing elcatonin with surgery.

Search strategy and evidence selection

This study identified RCT on the topic of effects and safety of elcatonin in patient with osteoporosis from six electronic databases. The six databases were the Cochrane Library database (including Cochrane Central Register of Controlled Trials), EMBASE, Ovid MEDLINE, PubMed (including MEDLINE), ScienceDirect, and Web of Science. We built primary search strategy in PubMed and adapted the search strategy to the other databases before October 29, 2018 (Supplementary File 1). The search strategy involved relevant terms of elcatonin, osteoporosis, and osteoporotic in free-text and medical subject headings (e.g. MeSH term in PubMed, and Emtree in Embase) with appropriate Boolean algebras. The search strategy did not restrict language and publication date.

After potential references were identified from databases through the search strategy, two investigators (WCC and YNK) selected evidence through two steps with eligible criteria. In the first step, they took evidences into the second step for further review when title and abstract met the inclusion criteria. In the second step, they retrieved full text for further review and reviewed the full texts of remaining references. The investigators removed the reference that meets the exclusion criteria. Any disagreement during the evidence selection was resolved by a third reviewer.

Quality assessment

To assess the biases of the trials included in this study, two investigators (WCC and YNK) individually completed the critical appraisal using the Cochrane Risk of Bias Tool. The Risk of Bias Tool consists of seven items for assessing six potential biases including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The seven methodological items are allocation generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective report, and other bias. Any disagreement during the critical appraisal was resolved by a third reviewer.

Data extraction

Two independent investigators extracted relevant information and outcome data respectively. They identified not only characteristics of study and baseline information of participants in each trial but also clinical outcome data. The relevant information included age, weight, and body mass index. The outcome data involved fracture, bone mineral density, and complication. The primary endpoints in our study were fracture and complication. These two outcomes were dichotomous data. Regarding the complication, we extracted nausea, digestive symptom, flushing, respiratory symptom, headache, and mastalgia. The secondary outcomes were bone mineral density change and pain score (visual analog scale). The bone mineral density change and pain score were continuous data. The bone mineral density was usually measured by dual-energy X-ray absorptiometry in the eligible studies.

Statistics and quantitative synthesis

The quantitative synthesis of this study applied Bucher method network meta-analyses. The analysis used Peto odds ratio (POR) in random effects model, because the quantitative synthesized outcomes, fractures and complications, were binary data with zero cell. The effect size was performed with 95% confidence interval (CI). It is statistically significant in all analyses when 95% CI crosses the cut point value 1. For continuous outcome, pain score was analyzed in inverse variance heterogeneity model through using mean and standard deviation. This method overcomes some limitations in fixed effects model and random effects model [10]. We estimated standard deviation from CI by using RevMan version 5.3 according to the Cochrane handbook [11]. The result was performed in weighted mean differences (WMD). Inconsistency in the network meta-analysis was examined by H statistics. H statistics can detect inconsistency among direct comparison and indirect comparisons in a network meta-analysis. H statistics proves minimal inconsistency when the value is lower than 3 and detects severe inconsistency when the value is higher than 6. When H statistics value is between 3 and 6, there is a modest inconsistency in the network meta-analysis. Small study bias in meta-analysis was examined by Doi plot with Luis Furuya-Kanamori (LFK) index [10]. These analyses were conducted using MetaXL for Microsoft Windows.

Results

Our search strategy retrieved 551 potential references, in which 167 were duplicated. In the remaining 384 references, we excluded 352 records after title and abstract screening and completed 32 full-text reviews. Last, we included 18 eligible references from 16 RCTs [2, 3, 12–27]. The process of study selection is shown in Fig. 1.

Characteristics and quality of included studies

A total of 16 eligible RCTs recruited 2754 postmenopausal women with osteoporosis in China [17, 24–27], Italy [12, 13, 18, 20], Japan [2, 3, 14–16, 22, 23], and Spain [19, 21] before 2015 (Table 1). We divided the treatments in these RCTs into four categories: monotherapy of elcatonin ($n = 331$), combination therapies of elcatonin ($n = 915$), non-elcatonin therapies ($n = 1446$), and placebo ($n = 62$). The combination therapies of elcatonin usually used elcatonin plus calcium [12, 18, 19, 21]. The non-elcatonin therapies mainly consisted of anti-osteoporosis drugs [2, 15, 16, 18, 23, 25]. Elcatonin was usually provided by intramuscular injections at a dose of 20 units weekly in the eligible trials. The quality of these RCTs is shown in Supplementary File 2. The mean age of postmenopausal women in each RCT was from 48 to 83 years old.

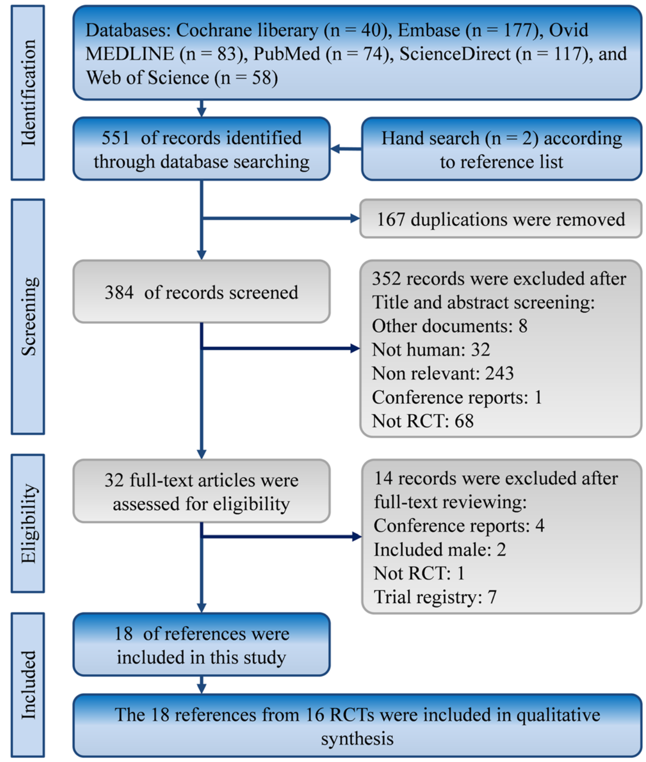

Fig. 1 Flowchart of the systematic review and meta-analysis according to PRISMA guidelines. RCT, randomized controlled trials

Fracture rate

There were three outcomes for efficacy of elcatonin in our study, and they were fracture rate, bone mineral density, and pain score. For the first outcome of efficacy, a total of six RCTs reported fracture rate [3, 14, 16, 17, 19, 22]. These trials formed an adjusted indirect comparison based on 1873 postmenopausal women with osteoporosis. Three of them compared combination therapies of elcatonin with non-elcatonin therapies [17, 19, 22], and the other three trials compared monotherapy of elcatonin with non-elcatonin therapies (Fig. 2a) [3, 14, 16]. The pooled result showed no significant differences among the three groups (Supplementary File 3). The estimates were not only insignificant but also small effect sizes. The inconsistency test for this result showed few inconsistent in the network meta-analysis ($H = 1$).

Table 1 Characteristics of the included studies

Location	Region		Sample size	Elcatonin dosage		Age			
						M-E	C-E	N-E	Placebo
Part A									
Astengo et al. (1994) [12]	Italy		75	40 IU IM		N/A	80.76 ± 6.23 83.12 ± 5.43	81.24 ± 5.83	N/A
Consoli et al.(1991) [13]	Italy		20	N/A		70 ± 5	N/A	N/A	61 ± 8
Endo et al.(2017) [14]	Japan		228	20 units; once/week		77.26 ± 6.55	N/A	77.26 ± 6.30	N/A
Fujita et al. (1999) [15]	Japan		30	20 units; once/week		69.8 ± 2.0	N/A	63.5 ± 2.4	N/A
Hongo et al. (2015) [2]	Japan		45	20 units; once/week		N/A	70.9 ± 6.7	70.8 ± 7.0	N/A
Iwamoto et al. (2011) [16]	Japan		194	20 units; once/week		81.9 ± 6.4	N/A	77.7 ± 7.2	N/A
Li et al. (2013) [17]	China		453	20 units; once/week		N/A	65.0 ± 7.3	65.1 ± 7.6	N/A
Lobianco et al. (1992) [18]	Italy		90	40 U; once/month		N/A	54.8/61.3	58.4	N/A
Lozano et al. (2000) [19]	Spain		55	40 U		N/A	52.59 ± 3.89	51.43 ± 2.79	N/A
Meschia et al. (1992) [20]	Italy		104	40 IU IM twice/week		55.1 ± 4.3	52 ± 5.1	49.3 ± 4.8	53.3 ± 4
Pérez et al. (1996) [21]	Spain		104	40 IU once/3 days		N/A	50 ± 5	48 ± 6 50 ± 4	50 ± 5
Sugimoto et al. (2018) [22]	Japan		869	20 units		N/A	75.5 ± 5.7	N/A	75.5 ± 5.7
Tanaka et al. (2016) [3]	Japan		107	20 units IM; once/week		74.3 ± 5.4	N/A	75 ± 5.4	N/A
Tanaka et al. (2017) [23]	Japan		51	20 units IM; once/week		75.5 ± 6.8	78.1 ± 6.7	72.6 ± 7.0	N/A
Zhang et al. (2009) [27]	China		205	20 units IM; once/week		N/A	65.78 ± 7.62	64.70 ± 7.67	N/A
Zhang et al. (2013) [25]	China		124	20 units IM		N/A	N/A	N/A	N/A
Part B									
Location	Duration (days)	Weight				Body mass index			
		M-E	C-E	N-E	Placebo	M-E	C-E	N-E	Placebo
Astengo et al. (1994) [12]	365	N/A	54.6 ± 10.32/52.82 ± 9.99	52.76 ± 8.77	N/A	N/A	24.64 ± 4.28/23.75 ± 4.41	23.09 ± 3.98	N/A
Consoli et al. (1991) [13]	180	69 ± 12	N/A	N/A	66 ± 6	NR	N/A	N/A	NR
Endo et al. (2017) [14]	42	NR	N/A	NR	N/A	NR	N/A	NR	N/A
Fujita et al. (1999) [15]	365	46.7 ± 2.4	N/A	49.9 ± 1.9	N/A	NR	N/A	NR	N/A
Hongo et al. (2015) [2]	180	N/A	48.6 ± 6.8	47.2 ± 4.9	N/A	N/A	21.9 ± 2.7	20.8 ± 2.1	N/A
Iwamoto et al. (2011) [16]	180	46.3 ± 6.4	N/A	49.6 ± 8.1	N/A	20.9 ± 2.3	N/A	22 ± 3.2	N/A
Li et al. (2013) [17]	535	N/A	56.5 ± 9.1	55.3 ± 8.5	N/A	N/A	23.4 ± 3.3	23.1 ± 3.1	N/A
Lobianco et al. (1992) [18]	365 (330)	N/A	68.1/65.7	63.5	N/A	N/A	NR	NR	N/A
Lozano et al. (2000) [19]	720	N/A	61.89 ± 10.2	65.35 ± 11.97	N/A	N/A	NR	NR	N/A
Meschia et al. (1992) [20]	365	NR	NR	NR	NR	26.8 ± 3.1	26 ± 2	26.3 ± 2.7	25.6 (3.3)
Pérez et al. (1996) [21]	365	N/A	62.3 ± 6.1	64.1 ± 6.8/60.2 ± 5.6	62.0 ± 7.0	N/A	NR	NR	NR
Sugimoto et al. (2018) [22]	1008	N/A	50.5 ± 8.0	N/A	50.3 ± 7.7	N/A	23.3 ± 3.4	N/A	23.2 ± 3.3
Tanaka et al. (2016) [3]	180	46.4 ± 4.9	N/A	47.0 ± 5.0	N/A	21.3 ± 1.8	N/A	21.4 ± 1.7	N/A
Tanaka et al. (2017) [23]	180	46.6 ± 5.8	45.1 ± 4.0	48.1 ± 4.9	N/A	20.9 ± 2.2	21.1 ± 1.3	21.6 ± 1.9	N/A
Zhang et al. (2009) [27]	180	N/A	56.55 ± 9.11	56.59 ± 8.67	N/A	N/A	23.60 ± 3.29	23.38 ± 3.17	N/A
Zhang et al. (2013) [25]	365	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

M-E monotherapy of elcatonin, *C-E* combined therapy of elcatonin, *N-E* none elcatonin medication

Bone mineral density

Eleven of the 16 included RCTs performed information about bone mineral density change [2, 3, 12, 13, 17–20, 22, 25, 27]. Unfortunately, these RCTs presented the outcome data differently. Therefore, a qualitative synthesized table for these results is better than an inappropriate meta-analysis. In Table 2, the 10 RCTs showed six comparisons among monotherapy of elcatonin, combination therapies of elcatonin, non-elcatonin medications, and placebo. The first comparison was between combination therapies of elcatonin and monotherapy of elcatonin. In this comparison, there was only one RCT published in 1992 [20]. The RCT indicated that combination therapies of elcatonin improved more bone mineral density than monotherapy of elcatonin. Yet, this evidence was only based on a small sample size which is 26 participants in each group.

The second comparison was between combination therapies of elcatonin and non-elcatonin therapies (inflammatory drugs or anti-osteoporosis drugs). This comparison consisted of eight RCTs that were published between 1992 and 2015 [2, 12, 17–20, 25, 27]. Half of these RCTs demonstrated no significant differences in bone mineral density improvement between combination therapies of elcatonin and non-elcatonin therapies [2, 12, 18, 19], but four RCTs showed some significant differences in subgroup comparisons [17, 20, 25, 27]. Three of the four RCTs from Asia found some outcomes on L1 to L4 with statistical significance. Those outcomes showed that non-elcatonin therapies had a better improvement in bone mineral density than combination therapies of elcatonin significantly [17, 25, 27], but these differences were only on L1 to L4. These reports were based on 782 postmenopausal women with osteoporosis. By contrast, another RCT from Europe showed that combination therapies of elcatonin had a more improvement in bone mineral density than non-elcatonin therapies significantly [20]. The evidence from Europe was only based on 52 participants.

The third comparison comparing combination therapies of elcatonin to placebo was reported by two RCTs from Asia and Europe [20, 22]. The result showed combination therapies of elcatonin had a significantly better outcome on bone mineral density change than placebo in the outcomes on lumbar bone mineral density change, but it had no significant benefit on neither hip nor femoral neck bone mineral density change. This outcome was based on 333 postmenopausal women.

The fourth comparison comparing monotherapy of elcatonin to non-elcatonin therapies was reported by two RCTs from Asia and Europe [3, 20]. These two RCTs recruited 159 postmenopausal women and indicated that monotherapy of elcatonin was not superior to non-elcatonin therapies.

The fifth comparison was to compare monotherapy of elcatonin with placebo. There were two RCTs from Europe before 2000 [13, 20]. These two evidences had similar trend that monotherapy of elcatonin had a more improvement in bone mineral density than placebo, although one of the two RCTs did not find significant difference [13]. These results were from 62 postmenopausal women.

The sixth comparison, the comparison of non-elcatonin therapies and placebo, was only based on one RCT from Europe [20]. The RCT showed that non-elcatonin therapies were superior to placebo. However, this RCT found the result from 52 participants.

Pain score (visual analog scale)

There were six trials mentioning pain relief [2, 3, 14, 16, 17, 23], but there were only two of them reporting complete information of visual analog score [14, 23]. These trials randomized 264 patients into monotherapy of elcatonin, combination therapies of elcatonin, and non-elcatonin therapies and formed a complete network (Fig. 2b). The estimates showed that patients receiving combination therapies of elcatonin had significantly lower pain score than those receiving monotherapy of elcatonin (WMD, − 5.21; 95% CI, − 10.31 to − 0.10) and non-elcatonin therapies (WMD, − 18.93; 95% CI, − 23.97 to − 13.89). Moreover, the pooled analysis also demonstrated that patients in monotherapy of elcatonin had lower pain score than those in non-elcatonin therapies (WMD, − 13.72; 95% CI, − 19.51 to − 7.94). Few inconsistencies were detected in the network model ($H = 1$) (Supplementary File 4).

Complications

Nine of the eligible RCTs formed a complete network meta-analysis among monotherapy of elcatonin, combination therapies of elcatonin, non-elcatonin therapies, and placebo (Fig. 2c and Supplementary File 5). This network meta-analysis consisted of 2075 postmenopausal women from Asia and Europe [2, 12–14, 17, 18, 20, 22, 27]. The consistency model showed that placebo had the lowest complication rates among comparators. Moreover, complication rates in non-elcatonin therapies (Peto OR, 7.450; 95% CI, 1.479 to 37.530) and monotherapy of elcatonin (Peto OR, 8.413; 95% CI, 2.031 to 34.859) were significantly higher than those in placebo. These outcomes comparing placebo with medical interventions were consistent between direct and indirect comparisons ($H = 1$). Regarding the two significant outcomes, the results of the consistency model were consistent with direct comparisons. For one, in the comparison between monotherapy of elcatonin and placebo, the consistency model (Peto OR, 8.413) consisted with direct comparison (Peto OR, 9.316). In further test, no evidence showed heterogeneity in the direct comparison of monotherapy of elcatonin and placebo (I-square = 0%). For another, in the comparison between non-elcatonin therapies and placebo, the consistency model (Peto OR, 7.450) consisted with direct comparison (Peto OR, 8.004) though the direct comparison had no statistical

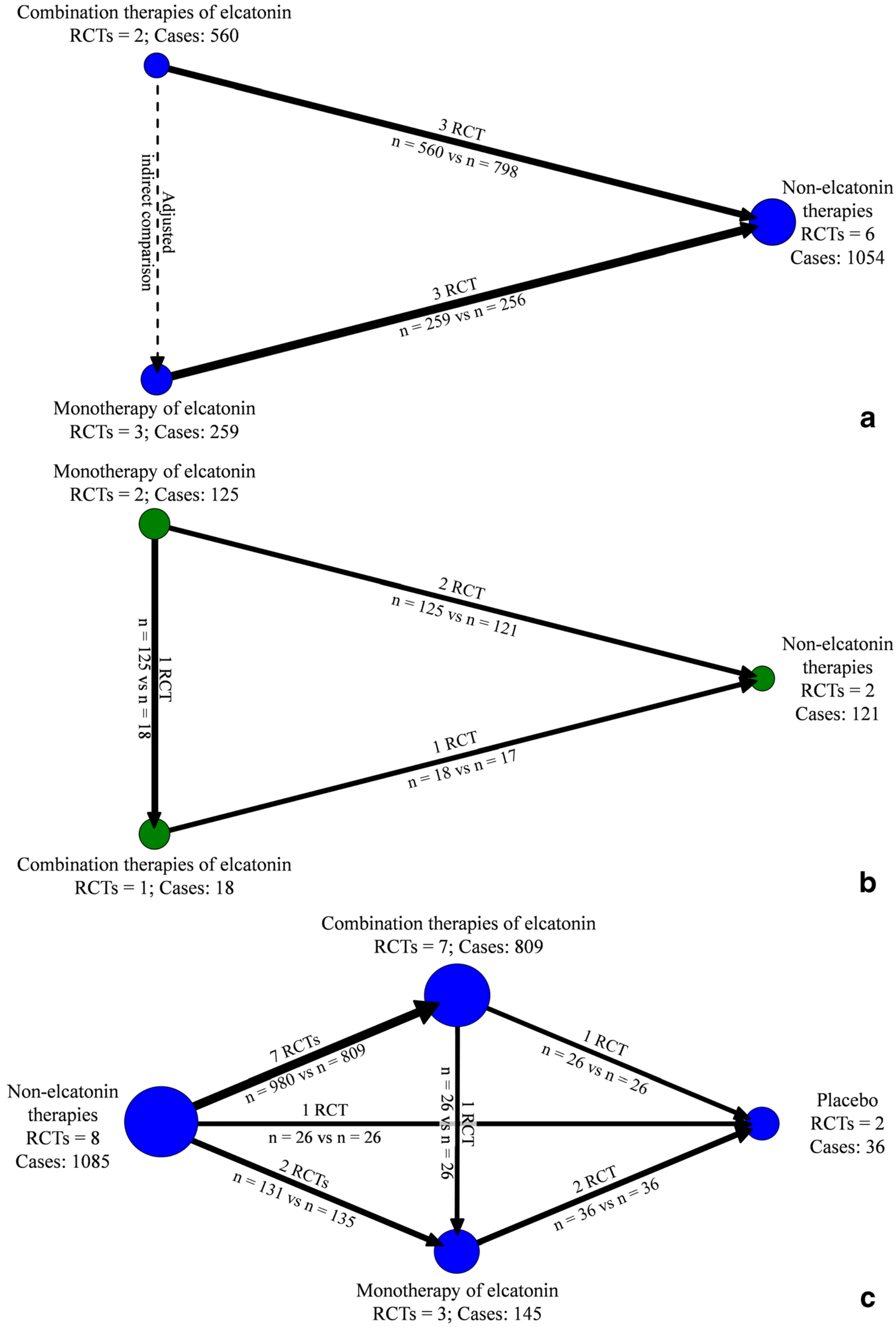

Fig. 2 Network plots. **a** Fracture rates. **b** Pain score. **c** Total complications

significance (Table 3). However, heterogeneity cannot be estimated in the direct comparison of non-elcatonin and placebo, because there was only one RCT in this pairwise meta-analysis.

Although there was no statistical significance among the three medical interventions, some interesting trends could be observed in the consistency model. Among the comparison of combination therapies of elcatonin, monotherapy of elcatonin, and non-elcatonin therapies, the effect sizes showed that combination therapy of elcatonin seems to have the lowest complication rates when it was compared with monotherapy of elcatonin (Peto OR, 0.469; 95% CI, 0.090 to 2.436) and non-elcatonin therapies (Peto OR, 0.740; 95% 0.154 to 3.558). Similar trends

Table 2 Summary of bone mineral density among treatments

Comparisons	Outcome		Comparison between groups
	Left	Right	
C-E versus M-E			
Meschia 1992 [20]	0.88 → 0.98*	0.82 → 0.84	C-E was better*
C-E versus N-E			
Astengo 1994 [12]	0.455 → 0.479* 0.449 → 0.465	0.454 → 0.447	C-E seems better?
Hongo 2015 [2]	Proximal femur: 0.610 → 0.622* (↑1.9%)	Proximal femur:0.616 → 0.632* (↑2.9%)	N-E seems better
	lumbar spine: 0.693 → 0.715* (↑3.5%)	Lumbar spine:0.682 → 0.724* (↑6.3%)	N-E seems better
Li 2013 [17]	L1–L4: ↑2.7%	L1–L4: ↑9.5%	N-E was better*
	Femoral neck: ↑?%	Femoral neck: ↑2.6%	N-E seems btter
Lobianco 1992 [18]	↑5.1%	↑5.0%	C-E seems better?
Lozano 2000 [19]	L1–L4: 0.786 → 0.781	L1–L4: 0.798 → 0.783	C-E seems better?
	Femoral: 0.691 → 0.680	Femoral: 0.733 → 0.717	C-E seems better?
Meschia 1992 [20]	0.88 → 0.98*	0.82 → 0.85*	C-E was better*
Zhang 2013 [25]	L2–L4: 0.763 → 0.788*	L2–L4: 0.737 → 0.795*	N-E was better*
	Troch: 0.523 → 0.513	Troch: 0.511 → 0.509	N-E seems better?
	Femoral neck: 0.657 → 0.647	Femoral neck: 0.651 → 0.650	N-E seems better?
	Wand's tri: 0.451 → 0.444	Wand's tri: 0.459 → 0.461	N-E seems better?
Zhang 2009 [27]	L1–L4: ↑1.55%*	L1–L4: ↑5.51%*	N-E was better*
	Femoral neck: ↑0.11%	Femoral neck: ↑0.65%	N-E seems better
C-E versus placebo			
Meschia 1992 [20]	0.88 → 0.98*	0.83 → 0.79*	C-E was better*
Sugimoto 2018 [22]	Lumbar: ↑2.13%	Lumbar: − 0.58%	C-E was better*
	Hip: − 2.45%	Hip: − 4.06%	C-E seems better
	Femoral neck: − 1.95%	Femoral neck: − 3.78%	C-E seems better
M-E versus N-E			
Meschia 1992 [20]	0.82 → 0.84	0.82 → 0.85*	N-E seems better
Tanaka 2016 [3]	L2–L4: 0.947 → 0.969* (↑2.3%)	L2–L4: 0.948 → 0.955(↑0.78%)	M-E seems better
	Total hip: 0.792 → 0.810* (↑2.32%)	Total hip: 0.779 → 0.796* (↑2.24%)	M-E seems better
	Femoral neck: 0.783 → 0.803* (↑2.48%)	Femoral neck: 0.773 → 0.773 (↓0.06%)	M-E seems better
M-E versus placebo			
Consoli 1991 [13]	0.557 → 0.575*	0.542 → 0.529*	M-E seems better?
Meschia 1992 [20]	0.82 → 0.84	0.83 → 0.79*	M-E was better*
N-E versus placebo			
Meschia 1992 [20]	0.82 → 0.85*	0.83 → 0.79*	N-E was better*

M-E monotherapy of elcatonin, *C-E* combined therapy of elcatonin, *N-E* none elcatonin medication, *ND* no data. *Significant difference; ? without statistics

can be found in direct comparisons. In the direct comparison of combination therapies of elcatonin and monotherapy of elcatonin, combination therapies of elcatonin have lower effect size in complication rates (Peto OR, 0.120; 95% CI, 0.012 to 1.232). In the direct comparison of combination therapies of elcatonin and non-elcatonin therapies, combination therapies of elcatonin also show smaller effect size in complication rates (Peto OR, 0.768; 95% CI, 0.557 to 1.057). Overall, the inconsistency test for the comparisons of combination therapy of elcatonin showed low inconsistent in the network meta-analysis ($H = 1.089$). The small study effect for the network meta-analysis can be only tested in the outcome from the comparisons of combination therapies of elcatonin. The LFK index of asymmetry showed little asymmetry for small study effect (LFK index = − 0.96) (Fig. 3).

Table 3 Summary of network meta-analysis for total complications

Model	Monotherapy of elcatonin		Non-elcatonin therapies		Placebo	
	Peto OR	95% CI	Peto OR	95% CI	Peto OR	95% CI
Combination therapies of elcatonin						
Direct	0.120	0.012 to 1.232	0.768	0.557 to 1.057	1.000	0.020 to 50.397
Consistency	0.469	0.090 to 2.436	0.740	0.154 to 3.558	2.156	0.357 to 13.019
Monotherapy of elcatonin						
Direct	NE	NE	0.730	0.158 to 3.361	*9.316**	*1.718 to 50.514*
Consistency	NE	NE	1.358	0.355 to 5.198	*8.413**	*2.031 to 34.859*
Non-elcatonin therapies						
Direct	NE	NE	NE	NE	8.004	0.474 to 135.139
Consistency	NE	NE	NE	NE	*7.450**	*1.479 to 37.530*

Peto OR Peto odds ratio, *NE* no estimate, * Statistical significance

Discussion

In this study, we investigated the efficacy and safety of elcatonin in postmenopausal women with osteoporosis. Through systematic search, we found 16 RCTs recruiting 2754 participants and observed that combination therapies of elcatonin, monotherapy of elcatonin, and non-elcatonin therapies had similar effects on fracture prevention. Yet, our evidence showed the elcatonin therapies had better pain relief than non-elcatonin therapies. Furthermore, our qualitative synthesis portrayed a picture showing better outcomes in bone mineral density change when medications were compared with placebo. However, placebo had the lowest complication rates among the four groups. Among the three medical interventions, combination therapies of elcatonin had the smallest effect size in complication rates than non-elcatonin therapies and monotherapy of elcatonin.

Base on the heterogeneity of the results in 11 RCTs, including bone mineral density of different parts of bones and various measurements, we cannot conduct a meta-analysis that shows which has a better effect on bone mineral density change in all four kinds of treatments. The combination therapies of elcatonin may have benefits on bone mineral density change to patients with osteoporosis. There was a substantial increase in bone mineral density among patients receiving either elcatonin alone or combination therapies of elcatonin. These regiments may contribute to firmer bone and reduce fracture risk. It is known that bone metabolism is changed during healing of vertebral or hip fractures, leading to an increase risk of secondary fractures [28]. Therefore, whether using elcatonin alone or combination therapies of elcatonin, initiating a treatment of osteoporosis with acute vertebral fracture is important in clinical practice.

In addition to anti-osteoporosis effect, elcatonin has greater efficacy than non-steroidal anti-inflammatory drugs in relieving pain and improving quality of life in patients with recent vertebral fractures, which are the most common type of osteoporotic fractures [14]. It is mainly attributed to elcatonin's analgesic effect that may be understood by the hypothesis of analgesic mechanisms of calcitonin, because calcitonin can reduce pain via a direct effect on the central nervous system [29, 30].

Although the evidences we included showed that elcatonin had benefit to bone mineral density change in patients with osteoporosis, elcatonin appeared to have some minor complications. The few and mild side effects were reported, including hypersensitivity reaction, nausea, facial flushing, or others. Nevertheless, in our results, elcatonin therapies seem to have lower complication rates than non-elcatonin therapies. That is to say, non-elcatonin therapies, including estrogen,

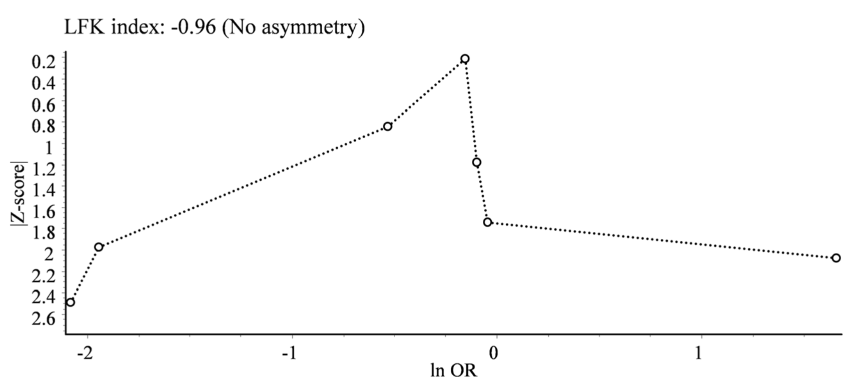

Fig. 3 Doi plot for publication bias

anti-inflammatory, and other anti-osteoporosis drugs, do not have a higher tolerability that elcatonin possessed, and may lead to higher complication rates. Those complications involved nausea, vomiting, gastrointestinal symptoms, and gynecological disease.

Moreover, our study showed combination therapies of elcatonin had a lower trend in complication rates than monotherapy of elcatonin. The possible reasoning should be understood in the complementary effect between elcatonin and other interventions including vitamin D, calcium, anti-osteoporosis drugs, estrogen, or medroxyprogesterone.

Elcatonin that was listed as one of calcitonin, may be concerned to increase risk of cancer, because a report by the European Medicines Agency (EMA) showed calcitonin has been associated with cancer in long-term usage in 2012 [31]. The increase in cancer rates ranged from 0.7 to approximately 2.4%. Therefore, the EMA withdrew salmon calcitonin from the market and limited the duration of other forms of calcitonin product. That is to say, EMA's decision was based on the study investigating the safety of salmon calcitonin, which was the most common form of calcitonin in the past decades. However, elcatonin is different from salmon calcitonin in its structure [14]. There were almost no reports of cancer in using of elcatonin, and there was no report of cancer incidence in the RCTs we included in this systematic review.

To our knowledge, this study had at least two advantages. The first, this study is the first systematic review with network meta-analysis that investigates the efficacy and safety of elcatonin therapies for postmenopausal women with osteoporosis. The second, our outcome is estimated from network meta-analysis without serious inconsistency and small study bias.

Though our study had some important advantages, it had some limitations. Firstly, combination therapies of elcatonin and non-elcatonin therapies were complex. For one, regarding the combination therapies of elcatonin, there were different combination designs in the RCTs we included. In this category, elcatonin was combined with vitamin D, calcium, anti-osteoporosis drugs, estrogen, or medroxyprogesterone. For another, the non-elcatonin therapies consisted of anti-osteoporosis drug, anti-inflammatory, estrogen, medroxyprogesterone, and calcium. There is a conceptual heterogeneity in this network meta-analysis. However, we did not detect inconsistency or high heterogeneity in this network meta-analysis. For clinical practice, the findings should be interpreted carefully and be translated cautiously. For instance, we did not find fracture rate in the trials comparing elcatonin with anti-osteoporosis drugs, but elcatonin was compared with anti-inflammatory and calcium. That is to say, our evidence cannot prove comparable result of fracture rate between elcatonin and anti-osteoporosis drugs though we found a comparable result of bone mineral density change between elcatonin and anti-osteoporosis drugs. Secondly, the RCTs included in this study used different dosages. As we were challenged by paucity and complexity of details on dosage, our network meta-analysis cannot conduct further analysis. In clinical practice, further choices should be made according to patients' characteristics. Thirdly, most of the eligible RCTs in this systematic review reported short-term outcomes (between 1 month and a year), and there was only one trial reported results more than 2 years. Although our results are consistent with the long-term report, long-term effects of elcatonin should be confirmed in the future. Since elcatonin is still used around the world, further randomized controlled trials are needed for clarifying the safety on different therapies and usages.

Conclusion

On the basis of current evidence, in summary, elcatonin therapies appeared to be an option with acceptable tolerability for postmenopausal women with osteoporosis because elcatonin therapies did not have serious complications, especially combination therapies of elcatonin. Moreover, elcatonin therapies had lower pain score than non-elcatonin therapies though elcatonin therapies had comparable fracture rate and bone mineral density change as compared with non-elcatonin. Although elcatonin may be an available choice for postmenopausal women with osteoporosis, further RCTs are needed to guarantee how to use elcatonin in different formulas and dosages.

Compliance with ethical standards

Conflicts of interest None.

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