META ANALYSIS

Meta-Analysis of Estrogen in Osteoarthritis: Clinical Status and Protective Effects

Xiaohui Yang, MD; Kun Yan, MD; Qianlong Zhang, MD; Alimujiang Yusufu, MD; Jian Ran, BS

ABSTRACT

Context • Osteoarthritis (OA) impacted over 5-million people worldwide in 2018, with an incidence second only to diabetes and hypertension. Clinical research has had difficulty in finding methods to treat OA quickly and effectively. More and more researchers have begun to explore the effects of estrogen (ER) on OA.

Objective • The study intended to conduct a meta-analysis of studies using ER in OA, aiming to confirm the potential value of ER, laying a foundation for follow-up research, and providing new choices for the treatment of OA.

Design • The research team performed a literature review searching PubMed for clinical studies on the application of ER for the OA treatment or on the improvement of joint pain that: (1) were published after the year 2000, and (2) had participants who used ER compared to other treatment methods. The research team selected studies for analysis after independent screening by two members of the team, based on inclusion and exclusion criteria and a methodological quality evaluation. The meta-analysis used RevMan V5.3 software.

Intervention • The research team included eight studies with 11 689 participants, with 5776 participants who received ER treatments becoming the intervention group, and with 5913 participants who received other treatments becoming the control group.

Outcome Measures • The outcome measures included the selected studies' results related: (1) to changes in the bone marker, collagen cross-linked C-telopeptide type I (CTX-1); (2) to the levels of bone Gla protein (BGP); (3) to joint-pain relief, and (4) to subjective scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a visual analogue scale (VAS) for pain, and the Short-Form 36 (SF-36).

Results • The meta-analysis found that the CTX-II level was significantly lower ($P < .0001$) and the BGP level was significantly higher ($P = .07$) in the EG group than the levels in the control group. Similarly, the number of participants with joint pain in the ER group was significantly lower than that of the control group ($P = .01$), and a significant difference existed between the groups in the subjective scores ($P = .02$).

Conclusion • ER can exert varying degrees of positive effects on OA and can effectively ameliorate the pathological process in OA patients, and it may become an alternative for OA treatment in the future, providing patients with better health and life quality. (*Altern Ther Health Med.* 2023;29(1):224-230).

Xiaohui Yang, MD, Associate chief physician; **Kun Yan, MD,** Resident physician; **Qianlong Zhang, MD,** Master's degree in reading; **Alimujiang Yusufu, MD,** Master's degree in reading; **Jian Ran, BS,** Botanic physician; Department of Orthopedics, the Sixth Affiliated Hospital of Xinjiang Medical University, Urumchi, China.

Corresponding author: Jian Ran, BS
E-mail: ranjian830002@163.com

Osteoarthritis (OA) is one of the most common diseases of joint tissues and mainly involves articular-cartilage damage that can eventually lead to articular-cartilage fibrosis, fractures, and defects.[1] With middle-aged and older adults being most affected, OA impacted over 5-million people worldwide in 2018, with an incidence second only to diabetes and hypertension.[2,3] OA has seriously endangered the quality of life of millions of older adults all over the world.[4]

In recent years, the incidence of OA has risen. Glyn-Jones et al's survey found that more than 50% of people aged over 65 suffer from OA to different degrees.[5] OA may present with mild joint pain and redness only at the early stage of illness, but if not controlled in a timely and effective manner, can result in joint deformity, fractures, and loss of joint mobility.[6]

Individuals with severe cases may even develop massive necrosis of joint tissues, for which joint replacement or amputation is the only option for control of disease

progression.[7] At that stage, physical therapy, such as acupuncture, electrical stimulation, or hydrotherapy, is still the primary treatment for pain control and symptom remission for OA in clinics.[8]

Modern clinical research has had difficulty in finding methods to treat OA quickly and effectively. In the face of the increasingly high incidence of OA, finding a more effective treatment as soon as possible has become a global focus for clinical research.

ER and OA

More and more researchers have begun to explore the effects of ER on OA. Recently, Gokhale et al found a significantly higher incidence of OA in 50-year-old women than in men, suggesting that estrogen (ER) deficiency may increase the occurrence of OA.[9] Robinson et al found that the ER content in joint fluid was positively correlated with the ER level in blood; when the ER level in the body decreases, the ER level in joint fluid decreases correspondingly, thus affecting the whole joint both physiologically and pathologically.[10] Keita-Alassane found that ER can decrease the surgical pain of OA in rats.[11]

Karsdal et al found that ER can improve the activity of OA chondrocytes.[12] Arao and Korach found that ER not only affects protein and mRNA synthesis in aromatase, which results in chondrocyte metabolism alterations, but also promotes ER generation in articular chondrocytes to participate in intra-articular cellular metabolism.[13] Those researchers proposed that chondrocytes mainly expressed ER-α and ER-β after interfering with the synthetic metabolic pathway of ER.

The research on ER and OA isn't all positive. For instance, Chen et al indicated that the intervention of excessive doses of ER in vitro can significantly inhibit the synthesis of DNA and proteoglycan in mandibular chondrocytes, reduce cartilage thickness in extracellular matrix, and upregulate C-terminal telopeptides of collagen type II (CTX-II), interleukin 1 beta (Il-1β), IL-6, and IL-8, thus promoting cellular inflammatory responses.[14] Rossouw et al indicated that the use of ER might be a risk factor for hip replacement in OA patients.[15] It's precisely because of the controversy that it's important to confirm the exact impact of ER on OA as soon as possible.

ER Receptors

A study by van der Eerden et al found ER receptors, ER-alpha (ER-α) and ER-beta (ER-β), in articular chondrocytes,[16] confirming that ER is the target site in articular cartilage and indicating that ER supplementation may be a potential treatment option for OA.

ER receptors are mainly divided into membrane estrogen receptors (mERs) and nuclear estrogen receptors (nERs), according to different distribution positions.[17]

mERs. The mERs are mainly distributed on the endoplasmic reticulum and cell membranes. After binding with ER, the corresponding ion-channel status and enzyme activity change can enhance the mitosis and protein-kinase activity of phosphatidylinositol 3-kinase (PIK3). The mERs are also known as the rapid non-genomic effector channel due to the reaction's extremely rapid occurrence.[18] However, mERs mainly exist in breast, heart, ovary, and neurolymphatic tissues, so their influence on OA may not be significant.[19]

nERs. The two nERs, nER-α and nER-β, mainly play a role in the nucleus, and the two receptors share multiple domains, each of which directs the hormone to interact and perform its function.[20] The nER-α gene chromosome is located at 6q25.1-2 and contains 7 introns and 8 exons, with a chromosome size of about 140 000.[21] The nER-β gene karyotype is located on chromosome14q23.2-3 and contains 8 exons, with a chromosome size of about 40 000.[22] Both nuclear receptors have a strong affinity for ER and can better regulate target cells and influence the inflammatory release of cells after binding with ER.[23]

However, also known as the slow genome-effect channel, nERs have a slower reaction time that usually takes more than several hours.[24] This suggests the need for a relatively stable and continuous treatment cycle when applying ER to the treatment of OA.

Current Study

Due to the lack of authoritative clinical guidelines for reference, controversy about the clinical application of ER in OA is still great.

Consequently, the current research team intended to conduct a meta-analysis of studies using ER in OA, aiming to confirm the potential value of ER, laying a foundation for follow-up research, and providing new choices for the treatment of OA.

METHODS

Procedures

The research team performed a literature review on the application of ER for the OA treatment or on the improvement of joint pain.

Eligibility criteria. The research team retrieved all studies related to OA and ER. The research team included studies that: (1) included patients treated with ER or ER-related drugs in vitro; (2) included patients with OA or other manifestations of bone and joint pain; (3) set no limitations as to age or gender; (4) used treatment methods that included in vitro ER or ER-related medications; (5) included patients treated with ER successfully, providing complete experimental results; and (6) included clinical trials or randomized controlled trials.

The research team excluded studies: (1) for which the team couldn't contact the researchers to obtain the original data, (2) that lacked clear criteria for efficacy assessment, (3) that had obvious design defects and logic errors, (4) that had a follow-up success rate lower than 70%, or (5) that were conducted before 2000.

Retrieval strategy. The research team used PubMed to search for clinical research on the application effects of ER on

OA, with the search keywords being osteoarthritis, estrogen, knee, joints, cartilage, and bone density and the study types being clinical trials and randomized controlled trials. At the same time, the team manually checked relevant periodical literature records to obtain more references.

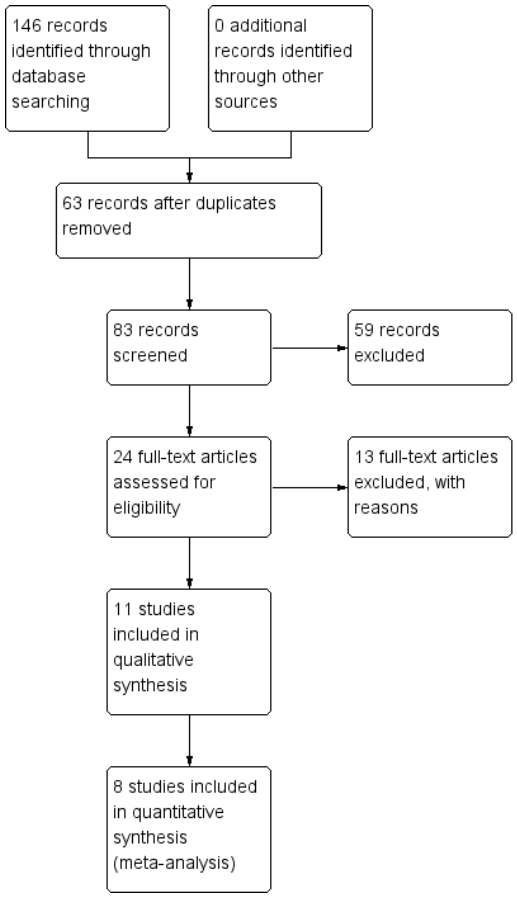
The search formula was: ((((“estrogens”[All Fields] OR “estrogens”[MeSH Terms] OR estrogen[Text Word]) OR (“osteoarthritis”[MeSH Terms] OR osteoarthritis[Text Word])) AND ((“estrogens”[All Fields] OR “estrogens”[MeSH Terms] OR estrogen[Text Word]) OR (“knee”[MeSH Terms] OR “knee joint”[MeSH Terms] OR knee[Text Word]))) AND ((“estrogens”[All Fields] OR “estrogens”[MeSH Terms] OR estrogen[Text Word]) OR (“joints”[MeSH Terms] OR joints[Text Word]))) AND ((“estrogens”[All Fields] OR “estrogens”[MeSH Terms] OR estrogen[Text Word]) OR (“cartilage”[MeSH Terms] OR cartilage[Text Word]))) AND ((“estrogens”[All Fields] OR “estrogens”[MeSH Terms] OR estrogen[Text Word]) OR (“bone density”[MeSH Terms] OR bone density[Text Word])).

Literature screening. After removing duplicates using the EndNote X9 literature management software (Thomson Scientific, Stanford, Connecticut, USA), two members of the research team screened the documents according to the eligibility criteria and cross-checked the screening results to determine the final inclusion results. If any disagreement occurred during the verification process, the two researchers had a third researcher review the results for discussion and a decision.

Literature-quality evaluation. The research team evaluated the quality of the included articles using guidelines from the Cochrane Handbook for Systematic Reviews of Interventions[25] to determine the studies’ use of random-sequence generation, allocation concealment, blinding, withdrawal, and loss during follow-up.

Outcome measures. The outcome measures included the selected studies’ results related: (1) to changes in the bone marker, collagen cross-linked C-telopeptide type I (CTX-1); (2) to the levels of bone Gla protein (BGP); (3) to joint-pain relief, and (4) to subjective scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[26] a visual analogue scale (VAS) for pain, and the Short-Form 36 (SF-36).[27]

Figure 1. Flow Chart of Literature Screening



Intervention

For the included studies, the participants receiving ER treatments became the intervention group, the ER group, and participants receiving other treatments became the control group.

Outcome Measures

CTX-II. CTX-II is the main organic component of cartilage and is one of the most effective biochemical indicators for OA. The higher the CTX-II, the more severe the OA.

BGP. BGP is synthesized by osteoblasts and odontoblasts and plays an important role in regulating bone calcium metabolism. It is a new biochemical marker for studying bone metabolism. The higher the BGP, the better the bone calcium metabolism of the bones.

WOMAC.[26] A rating scale developed by Bellamy specifically for assessing the severity of arthritis. The higher the score, the more severe the arthritis.

VAS. VAS is the most widely used subjective pain evaluation method in clinical practice. The higher the VAS, the more significant the pain.

SF-36.[27] SF-36 is a universal measurement scale developed by the American Medical Outcomes Study (MOS) group, which includes 8 dimensions and is used to reflect the quality of life of patients. The higher the score, the better the quality of life.

Statistics Analysis

The research team used RevMan V5.3 (Cochrane Collaboration Network) to statistically analyze the data, and conducted the Chi-square (χ^2) to test heterogeneity. For weighted merging, the team used a fixed-effect model when $I^2 \leq 50\%$ and a random-effects model (REM) when $I^2 > 50\%$. $P < .05$ indicated statistical significance.

RESULTS

Literature Retrieval

The research team preliminarily retrieved 146 related articles. After using the software to remove duplicates and

Table 1. Basic Characteristics of Included Studies. The outcome measures were: (1) changes in the bone marker, collagen cross-linked C-telopeptide type I (CTX-1); (2) levels of bone Gla protein (BGP); (3) joint-pain relief, and (4) subjective scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[26] a visual analogue scale (VAS) for pain, and the Short-Form 36 (SF-36).[27]

	Control Group		ER Group		
	Age Mean ± SD	Participants n	Age Mean ± SD	Participants n	Outcome Measures
Christgau et al, 2004[28]	57.4 ± 4.1	21	56.9 ± 3.8	71	1,3
Cirillo et al, 2006[29]	-	5196	-	5076	3
Nevitt et al, 2001[30]	-	542	-	427	3,4
Ravn et al, 2004[31]	54.5 ± 2.6	25	55.4 ± 2.8	50	1,2,3
Seo et al, 2012[32]	56.6 ± 2.4	32	57.0 ± 2.6	30	2,3
Song et al, 2004[33]	-	32	-	32	2,3,4
Stanosz et al, 2009[34]	52.3 ± 3.5	25	52.7 ± 3.2	50	1,2
Wong et al, 2017[35]	-	40	-	40	3,4

Abbreviations: ER, estrogen.

manually reading titles, abstracts, and full texts, the research team included 8 articles[28-35] comprising 11 689 participants, including 5776 treated with ER, the ER group, and 5913 treated with other methods, the control group (Figure 1).

Literature's Basic Characteristics

Except for Songet al's study[33] on the treatment of ER in OA patients (data not shown), the other studies all focused on the effects of ER or ER-related drugs on joint symptoms and cartilage tissues, with the participants all being women. Table 1 shows the included studies, providing the mean ages and number of participants, and identifying the outcome measures that the studies used. The methodological quality of the literature, as identified by the Cochrane guidelines was Grade B. See Figure 2 for the risk of bias for the included studies.

CTX-II

Three studies[28,31,34] evaluated the influence of ER on CTX-II, with heterogeneity existing among groups ($I^2 = 97\%$), and the research team used REM for the analysis. Figure 3 shows that the ER group had significantly lower CTX-II levels postintervention than the control group did ($P < .0001$).

BGP

Four studies[31-35] evaluated the influence of ER on BGP levels, with heterogeneity existing among the groups ($I^2 = 81\%$), and the research team used REM for analysis. Figure 4 shows that the ER group had significantly higher BGP levels postintervention than the control group did ($P = .07$).

Joint Pain

Seven articles[28-33,35] evaluated the influence of ER on joint pain, with heterogeneity existing among the groups ($I^2 = 54\%$), and the research team used REM for analysis. Figure 5 shows that the ER group had significantly fewer

Figure 2. Risk of Bias Diagram of the Literature

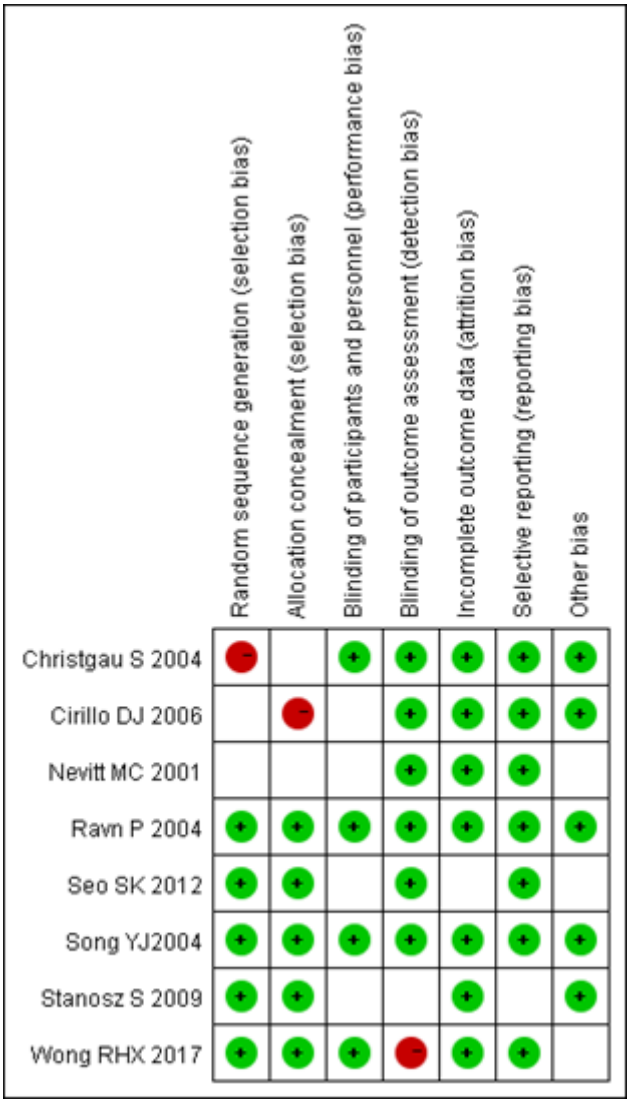
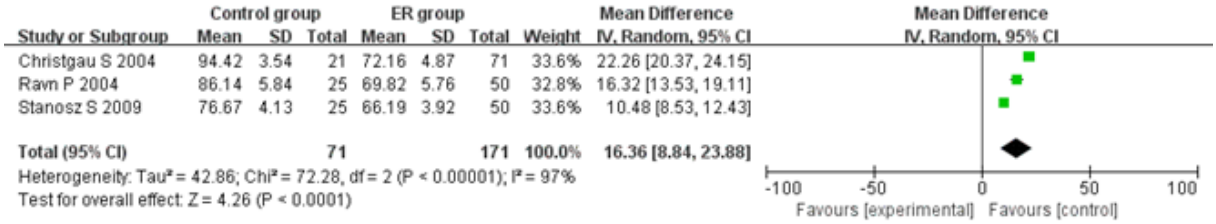
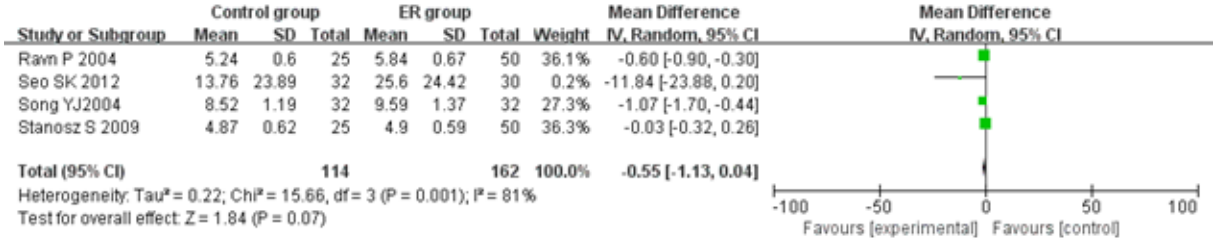


Figure 3. Meta-analysis of the Influence of ER on CTX-I



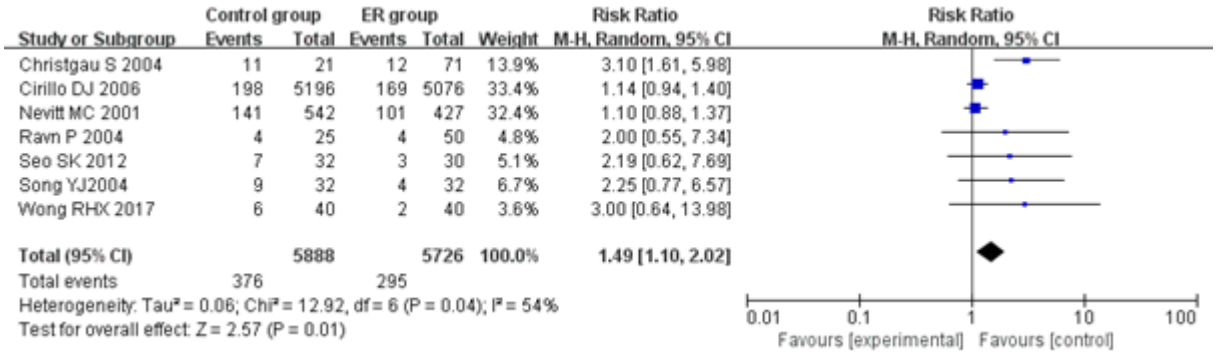
Abbreviations: CTX-I, collagen cross-linked C-telopeptide type I; ER, estrogen.

Figure 4. Meta-analysis of the Influence of ER on BGP



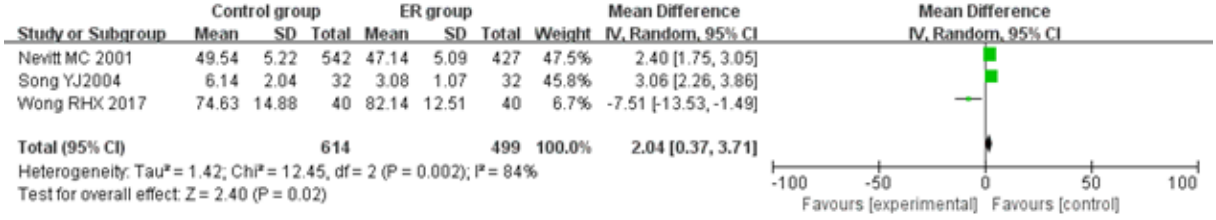
Abbreviations: BGP, bone Gla protein; ER, estrogen.

Figure 5. Meta-analysis of the Influence of ER on Joint Pain



Abbreviations: ER, estrogen.

Figure 6. Meta-analysis of the Influence of ER on Subjective Scores



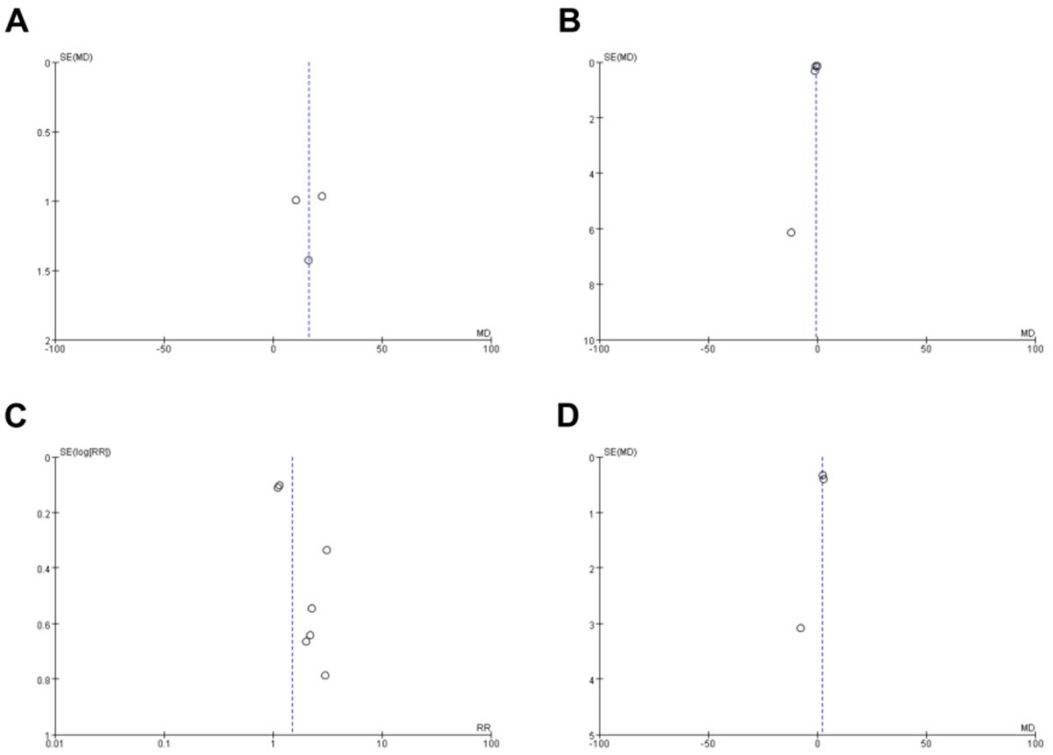
Abbreviations: ER, estrogen.

participants with joint pain postintervention than the control group did ($P = .01$).

Subjective Scores

Three studies[30,33,35] evaluated the changes in participants' subjective scores after ER application, among which Nevitt et al[30] conducted a WOMAC survey, Song et al[33] conducted a VAS survey and Wong et al[35] conducted a SF-36 survey (data not shown). Heterogeneity was present among the groups, and the research team used REM for the analysis ($I^2 = 84\%$). Figure 6 shows that the ER group's subjective scores were significantly different postintervention from those of the control group ($P = .02$).

Figure 7. Funnel Plot. Figure 7A shows the influence of ER on CTX-II; Figure 7B shows the influence of ER on BGP; Figure 7C shows the influence of ER on joint pain; and Figure 7D shows the influence of ER on subjective scores.



Abbreviations: BGP, bone Gla protein; CTX-I, collagen cross-linked C-telopeptide type I; ER, estrogen.

Publication Bias

The analysis of the influence of ER on CTX-II, BGP, joint pain, and subjective scores showed significant heterogeneity, so the research team determined the consistency of the results by changing to the fixed-effect model. That model didn't significantly alter the results for ER, confirming their reliability (data not shown: (1) CTX-II—MD = 16.51, 95% CI = approximately 15.29 to 17.73 and $P < .001$; (2) BGP—MD = -0.39, 95% CI = approximately -0.59 to -0.19 and $P < .05$; (3) joint pain—MD=1.21, 95%CI= approximately 1.05 to 1.39) and $P < .05$; and (4) subjective scores—MD = 2.59, 95% CI = approximately 2.09 to 3.10 and $P < .05$.

Finally, the research team drew funnel plots to detect any bias in the observed indicators. The funnel plot was basically symmetrical, indicating a small bias in the included literature (Figure 7).

DISCUSSION

The current review included studies using ER and involving OA. The analysis revealed that the use of ER contributed to varying degrees of improvement in CTX-II, BGP, joint pain, and subjective scores, suggesting that ER has great potential in future treatment of OA.

Not all past studies have indicated favorable effects for ER on OA. The current research team feels that this result may relate to Clusan et al's[19] suggestion that the influence of mERs on OA may not be significant because they mainly exist in breast, heart, ovary, and neurolymphatic tissues.

The current research team feels that nERs, on the other hand, are the key to the treatment of OA with ER at present, because as Pettersson and Gustafsson found,[23] both nuclear receptors have strong affinity for ER and can regulate target cells and influence the inflammatory release of cells after binding with ER recognition.[23]

Cirillo et al's, included in the current review, lasted only one month,[29] which may be one reason for its unsatisfactory effects because the participants' pathological changes hadn't been stably controlled at that point.

The research team feels that the differences in the effects of ER may be closely related to the regional distribution of population, medication duration, medication dosage, sample size, and disease site and believes that it's worth carrying out more in-depth and comprehensive experimental analyses to achieve the clinical popularization of ER.

The current review may be biased in selection, implementation, and measurement, because some of the included studies didn't give detailed descriptions of research methods, allocation concealment, or blinding. In addition, all of the studies analyzed were published, and the review lacks evidence from nontraditional literature sources. Therefore, in a follow-up study, the current research team needs to include more relevant data to conduct a more

comprehensive meta-analysis and obtain more accurate experimental results.

CONCLUSION

ER can exert varying degrees of positive effects on OA and can effectively ameliorate the pathological process of OA in patients, and it may become an alternative for OA treatment in the future, providing patients with better health and life quality.

ACKNOWLEDGMENT

The Natural Science Foundation of Xinjiang Uygur Autonomous Region supported the review (Grant No.2019D01C244) supported the study.

AUTHORS' DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

REFERENCES

1. Xia B, Di Chen, Zhang J, Hu S, Jin H, Tong P. Osteoarthritis pathogenesis: a review of molecular mechanisms. *Calcif Tissue Int*. 2014;95(6):495-505. doi:10.1007/s00223-014-9917-9
2. Mandl LA. Osteoarthritis year in review 2018: clinical. *Osteoarthritis Cartilage*. 2019;27(3):359-364. doi:10.1016/j.joca.2018.11.001
3. Sacitharan PK. Ageing and Osteoarthritis. *Subcell Biochem*. 2019;91:123-159. doi:10.1007/978-981-13-3681-2_6
4. Nelson AE. Osteoarthritis year in review 2017: clinical. *Osteoarthritis Cartilage*. 2018;26(3):319-325. doi:10.1016/j.joca.2017.11.014
5. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. *Lancet*. 2015;386(9991):376-387. doi:10.1016/S0140-6736(14)60802-3
6. Taruc-Uy RL, Lynch SA. Diagnosis and treatment of osteoarthritis. *Prim Care*. 2013;40(4):821-836, vii. doi:10.1016/j.pop.2013.08.003
7. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet*. 2011;377(9783):2115-2126. doi:10.1016/S0140-6736(11)60243-2
8. Abramoff B, Caldera FE. Osteoarthritis: Pathology, diagnosis, and treatment options. *Med Clin North Am*. 2020;104(2):293-311. doi:10.1016/j.mcna.2019.10.007
9. Gokhale JA, Frenkel SR, Dicesare PE. Estrogen and osteoarthritis. *Am J Orthop*. 2004;33(2):71-80.
10. Robinson JL, Johnson PM, Kister K, Yin MT, Chen J, Wadhwa S. Estrogen signaling impacts temporomandibular joint and periodontal disease pathology. *Odontology*. 2020;108(2):153-165. doi:10.1007/s10266-019-00439-1
11. Keita-Alassane S, Otis C, Bouet E, et al. Estrogenic impregnation alters pain expression: analysis through functional neuropeptidomics in a surgical rat model of osteoarthritis. *Naunyn Schmiedebergs Arch Pharmacol*. 2022;395(6):703-715. doi:10.1007/s00210-022-02231-5
12. Karsdal MA, Byrjalsen I, Leeming DJ, Christiansen C. Tibolone inhibits bone resorption without secondary positive effects on cartilage degradation. *BMC Musculoskelet Disord*. 2008;9(1):153. doi:10.1186/1471-2474-9-153
13. Arao Y, Korach KS. The physiological role of estrogen receptor functional domains. *Essays Biochem*. 2021;65(6):867-875. doi:10.1042/EBC20200167
14. Chen J, Kamiya Y, Polur I, et al. Estrogen via estrogen receptor beta partially inhibits mandibular condylar cartilage growth. *Osteoarthritis Cartilage*. 2014;22(11):1861-1868. doi:10.1016/j.joca.2014.07.003
15. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333. doi:10.1001/jama.288.3.321
16. van der Eerden BC, Gevers EF, Löwik CW, Karperien M, Wit JM. Expression of estrogen receptor alpha and beta in the epiphyseal plate of the rat. *Bone*. 2002;30(3):478-485. doi:10.1016/S8756-3282(01)00703-7
17. Nalvarte I, Varshney M, Inzunza J, Gustafsson JA. Estrogen receptor beta and neural development. *Vitam Horm*. 2021;116:313-326. doi:10.1016/bs.vh.2021.02.007
18. Divekar SD, Tiek DM, Fernandez A, Riggins RB. Estrogen-related receptor β (ERRβ) - renaissance receptor or receptor renaissance? *Nucl Recept Signal*. 2016;14(1):e002. doi:10.1621/nrs.14002
19. Clusan L, Le Goff P, Flouriot G, Pakdel F. A closer look at estrogen receptor mutations in breast cancer and their implications for estrogen and antiestrogen responses. *Int J Mol Sci*. 2021;22(2):E756. doi:10.3390/ijms22020756
20. Pfaff D, Waters E, Khan Q, Zhang X, Numan M. Minireview: estrogen receptor-initiated mechanisms causal to mammalian reproductive behaviors. *Endocrinology*. 2011;152(4):1209-1217. doi:10.1210/en.2010-1007
21. Nelson ER, Habibi HR. Estrogen receptor function and regulation in fish and other vertebrates. *Gen Comp Endocrinol*. 2013;192:15-24. doi:10.1016/j.ygcen.2013.03.032
22. Bai Z, Gust R. Breast cancer, estrogen receptor and ligands. *Arch Pharm (Weinheim)*. 2009;342(3):133-149. doi:10.1002/ardp.200800174
23. Pettersson K, Gustafsson JA. Role of estrogen receptor beta in estrogen action. *Annu Rev Physiol*. 2001;63(1):165-192. doi:10.1146/annurev.physiol.63.1.165
24. Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. *Steroids*. 2014;90:13-29. doi:10.1016/j.steroids.2014.06.012
25. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10:ED000142. doi:10.1002/14651858.ED000142
26. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes*. 2003;1(1):17. doi:10.1186/1477-7525-1-17
27. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483. doi:10.1097/00005650-199206000-00002
28. Christgau S, Tankó LB, Cloos PA, et al. Suppression of elevated cartilage turnover in postmenopausal women and in ovariectomized rats by estrogen and a selective estrogen-receptor modulator (SERM). *Menopause*. 2004;11(5):508-518. doi:10.1097/01.WCB.0000121484.18437.98
29. Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis Rheum*. 2006;54(10):3194-3204. doi:10.1002/art.22138
30. Nevitt MC, Felson DT, Williams EN, Grady D. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2001;44(4):811-818. doi:10.1002/1529-0131(200104)44:4<811::AID-ANR137>3.0.CO;2-F
31. Ravn P, Warming L, Christgau S, Christiansen C. The effect on cartilage of different forms of application of postmenopausal estrogen therapy: comparison of oral and transdermal therapy. *Bone*. 2004;35(5):1216-1221. doi:10.1016/j.bone.2004.07.017
32. Seo SK, Yang HI, Lim KJ, et al. Changes in serum levels of cartilage oligomeric matrix protein after estrogen and alendronate therapy in postmenopausal women. *Gynecol Obstet Invest*. 2012;74(2):143-150. doi:10.1159/000339934
33. Song YJ, Lin SQ, Wu ZH, Weng XS, Qiu GX, Chen FL. [Effect of combined continued hormone replacement therapy on knee osteoarthritis symptom of postmenopausal women]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2004;26(5):571-575.
34. Stanosz S, Zochowska E, Safranow K, Sieja K, Stanosz M. Influence of modified transdermal hormone replacement therapy on the concentrations of hormones, growth factors, and bone mineral density in women with osteopenia. *Metabolism*. 2009;58(1):1-7. doi:10.1016/j.metabol.2008.07.016
35. Wong RHX, Evans HM, Howe PRC. Resveratrol supplementation reduces pain experience by postmenopausal women. *Menopause*. 2017;24(8):916-922. doi:10.1097/GME.0000000000000861