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Invited Review

Sex Difference in OA: Should We Blame Estrogen?

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Abstract

Osteoarthritis (OA) is a leading cause of chronic pain and disability, not only in the United States but also worldwide. The burden of OA is higher in women than in men. Estrogen as a possible explanation for observed sex differences in OA has not been definitively established. The purpose of this review was to summarize the results from studies of estrogen, estrogen depletion and treatment, and their impact on knee, hip, hand, and spine OA. We conducted a targeted review of the literature using PubMed.

Although several studies show that hormone replacement therapy has the potential to be protective of OA for some joints, there are studies that showed no protective effect or even adverse effect. Taken together, the evidence for the protective effect of estrogen therapy depends on OA joint, OA outcome, and study design. Although this area has been studied for decades, more exclusively since the 1990s, there is a lack of high-quality experimental research in this topic. The lack of definitive conclusion on whether estrogen can play a role in the development in OA of either the knee, hip, spine, or hand is often in part due to the noncomparability of studies existing within the literature. Differences in diagnostic criteria, imaging modalities, populations studied, study designs, and outcome measures, as well as random error, have all contributed to inconclusive evidence. Future research on the role of estrogen in OA is needed, particularly as global demographic shifts in increasing overweight/obesity prevalence and ageing populations may contribute to widening OA-related health inequalities.

Keywords: Osteoarthritis, women's health, estrogen

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Introduction

Osteoarthritis (OA) is a leading cause of chronic pain and disability, not only in the United States but also worldwide.[1,2] The burden of OA is higher in women than in men.[3–5] Regardless of age, women have higher prevalence and incidence of hand and knee OA and higher incidence of hip OA compared with men[3,6]; there were no statistically significant differences between women and men in prevalent hip OA or spine OA. In addition, women have more severe knee OA, and the incidence of OA rises faster in women than in men after 50 years of age,[3,4,6–8] which coincides with onset of menopause and suggests a link between OA and estrogen. In fact, as early as 1925, Cecil and Archer published a case series of women who presented with pain and stiffness in the knees, and the overwhelming majority of these women were observed to be experiencing menopause; hence, they were called "arthritis of the menopause."[9] Of major interest are the possible mechanisms that drive sex differences in OA and whether sex hormone levels may influence the risk of developing or worsening of OA. Estrogen as a possible explanation for sex differences in OA has not been definitively established owing to the differential effect of sex hormones on different joint structures, the limited number of clinical studies of the effect of estrogen treatment for the prevention of development or worsening of OA in humans. Additionally, the results of studies of estrogen treatment from animal models have been conflicting. The purpose of this review is to summarize the current state of knowledge and summarize the results from studies of estrogen (endogenous and exogenous), estrogen depletion and treatment, and their impact on knee, hip, hand, and spine OA.

Sex Hormones and Osteoarthritis

Animal Studies

While much of the research on the effect of estrogen focuses on articular cartilage and the knee joint, studies of estrogen deficiency indicate that estrogen also affects other joint tissues related to OA, including periarticular bone, synovial lining, muscles, ligaments, and capsule.[10] in vitro studies have shown that age and estrogen dose can impact chondrocyte response to estrogen.[10] While estradiol seems to protect chondrocytes[11] and articular cartilage from damage,[12,13] high doses can have deleterious effects with increased inflammation.[14] Thus, these findings add to the complexity of the impact of estrogen.

To mirror the impact of menopause and estrogen deficiency on OA, much of the research on the effect of estrogen has been done on ovariectomized female animal models where there is much evidence of the negative impact of estrogen loss in mature female animals.[15–18] Research shows that ovary-intact female mice have less severe OA than ovariectomized female mice, suggesting that OA is associated with estrogen deficiency.[10,16,19] Studies have also shown that estrogen deprivation can directly lead to mild OA changes in healthy articular cartilage, and estrogen deficiency can also indirectly lead to OA by impairing muscle strength and impacting subchondral bone. Wu et al. used 3D visualization with propagation-based phase-contrast computed tomography imaging and were able to observe a decrease in cartilage volume, surface area, and thickness, as well as capture subchondral bone surface and trabecular bone loss among ovariectomized mice compared with controls.[17] Still, not all studies show consistent results. In a systematic review by Sniekers et al.,[19] 11 of 14 studies of sexually mature animals indicate that hormone depletion by ovariectomy in animal models suggests detrimental effect from cartilage degeneration and increase in cartilage stiffness and thickness, but two studies showed no effect, and one showed beneficial effect at 6 months but not at 1 or 12 months from estrogen depletion. As for estrogen treatment, only 11 out of 22 animal studies show protective effect of estrogen where incidence of spontaneous OA was reduced after estradiol treatment. Two of the 22 studies showed no effect, two showed unclear effect, and six showed detrimental effect, with increase in degeneration and cell death after estradiol treatment. While many of the studies from ovariectomized animal models show detrimental effect on joints and cartilage, studies of the efficacy of estrogen treatment in preventing onset or slowing progression of OA were inconsistent. More recently, estrogen deficiency has been shown to induce lumbar facet joint (LFJ) degeneration via both cartilage and subchondral bone loss in an ovariectomized female mouse.[20] Upon provision of exogenous estrogen, the LFJ degradation was reduced, degradation of cartilage was inhibited, and there was noticeable blood vessel and nerve ending growth.[20]

Main Points

- The effects of estrogen in joint tissues are complex and varied.
- Estrogen's interaction with other biological and environmental factors in osteoarthritis development requires more evidence to explain the sexual dimorphism observed.
- Hormone replacement therapy has the potential to protect against hip and knee osteoarthritis, but there is conflicting evidence suggesting that it may also be deleterious.
- There is a lack of conclusive evidence for the role of estrogen in the development of hand and spine osteoarthritis.

Human studies

In humans, onset and progression of OA involves not only numerous risk factors and multiple joint sites but also multiple complex pathways, including fluctuations in hormonal levels in relation to modulations of bones and joints.[21] Also, with regard to research in hormone replacement therapy, outcomes may not be the development of OA, but symptoms of OA or progression of OA. Recent work has elucidated possible "hormonal modulation of connective tissue homeostasis and sex differences" in risk for OA of the knee.[3] Sex hormones are produced not only in the gonads but also in connective tissues,[22] where the hormones are involved in signaling to the cell itself or to neighboring cells and serve autocrine and paracrine functions.[3] In addition, human chondrocytes in knee articular cartilage and cells in bones express receptors for estrogen, androgens, progesterone, and their metabolites in both males and females,[22] indicating that chondrocytes are responsive to the presence of hormones. Moreover, studies have shown that 17 β-estradiol can stimulate collagen production and proliferation of chondrocytes.[23] Among young females, the cyclic joint laxity in relation to sex hormone fluctuations has been implicated in the etiology of anterior cruciate ligament injury. The modulation of joint laxity during the menstrual cycle in females may influence positioning and function of the knee during high-risk maneuvers.[24] As such, the menstrual cycle and hormone fluctuation can lead to joint laxity and may predispose women to increased risk of joint injury, thus increasing risk of OA. Reproductive history has also been linked to risk of OA and knee replacement. For women of child-bearing age, a study in the Multicenter OA Study by Wise et al. found that parity of 5 or higher compared with parity of 1 has been shown to increase risk of newly developed radiographic knee OA, which also includes those with incident knee replacement.[25] Compared with nulliparous women in the Million Women Study, Liu et al. found that increasing parity increased the risk of knee replacement; for hip replacement, increased risk was found in women with parity of 4 or more.[26] In a group of middle-aged women in their 40s and 50s, Sowers et al.[27] found that women with lower levels of estradiol and lower levels of 2-hydroxyestrone were at increased risk for developing incident OA compared with counterparts with higher estradiol and 2-hydroxyestrone levels, respectively. As for women with menopause, it may also be depletion of estrogen that increased their risk for knee OA. Studies showed that premenopausal concentrations of 17β-estradiol have been found to prevent telomere shortening in articular chondrocytes that is associated with aging and age-related diseases, while postmenopausal concentrations do not.[28]

Sex differences can be seen with regard to both incident and prevalent OA. Among people without clinical knee OA, women have higher rates of cartilage loss and progression of cartilage defects at the knee over time compared with men.[29] Women also have worse tibial cartilage defects.[30] Thus, predisposition of OA at the knee in women compared with men may be in part due to more rapid loss of cartilage at the tibia and patella. For women participants in their late 40s or 50 years or older, depletion of estrogen may be a factor for the increased risk for cartilage loss and defects in women compared with men. Once affected by severe OA, sex differences were also found in synovial fluid levels and cellular expression of receptors to estradiol.[31] Male cells were more responsive to dihydrotestosterone, and female cells were more responsive to estradiol. Among people with symptomatic OA, differences between men and women were also observed between sex hormones and MRI structural changes.[32] In men, there were no longitudinal associations between sex hormones and cartilage volume, bone marrow lesions (BMLs), effusion-synovitis, or pain symptoms. Among women, however, increasing progesterone was associated with more cartilage volume, higher estradiol was associated with lower grade of BML, higher sex hormones, including estradiol, progesterone, and testosterone, were associated with less effusion-synovitis volume, and higher testosterone was associated with lower pain.

Observational epidemiologic studies of estrogen and OA, focusing on estrogen deficiency and estrogen replacement therapy (ERT)

Knee OA

Results are presented below for longitudinal or nested case control studies that examined estrogen in relation to knee OA.

Incident radiographic OA

Longitudinal data from a Michigan cohort suggest that pre- and peri-menopausal women who had the lowest tertile of

circulating serum estradiol (<47 pg mL^{-1}) had a 2-fold increased risk for developing incident radiographic OA compared with those from the middle tertile (47-77 pg mL^{-1}) over a 3-year period (OR = 1.88, 95% CI: 1.07–3.51).[33] Those women in the highest tertile (>78 pg mL^{-1}) showed no increased risk of developing incident OA (OR = 1.04, 95% CI: 0.52-2.09). Low urinary concentrations of 2-hydroxyestrone were also shown to be associated with an increased risk of incident knee OA (lowest tertile OR = 2.91, 95% CI: 1.49-5.68). Therefore, when a ratio of two urinary metabolites, 16α-hydroxyestrone and 2-hydroxyestrone, were assessed for incident knee OA, women in the highest tertile (<0.87 16α:2) showed a 2-fold increase in the odds of developing incident OA. However, using the same Michigan data,[27] the use of HRT was associated with a nonsignificant 2-fold increase in OA (OR = 2.56, 95% CI: 0.68-9.5), but estradiol in the same model was not associated (OR = 1.01, 95% CI: 0.99-1.01). Longitudinal data from the Framingham OA study showed that women who indicated use of postmenopausal ERT at two or more visits had a modest but statistically nonsignificant protective effects for both radiographic OA (OR = 0.71, 95% CI: 0.42-1.20) and severe radiographic OA (OR = 0.66, 95% CI: 0.33-1.32).[34] Data from the same Framingham OA cohort[35] showed that past users had a weak but statistically nonsignificant decreased risk for developing incident radiographic OA (OR = 0.80, 95% CI: 0.5-1.4). Current users had a moderate decreased risk of developing incident radiographic (OR = 0.4, 95% CI: 0.1-3.0), but the protective effect was not statistically significant. A case–control study using data from the Fallon Community Health Plan indicated that past use was inversely associated with the risk of incident OA (OR = 0.7; 95% CI: 0.3-1.9), while ongoing use of ERT was positively associated, but results were not statistically significant (OR = 1.4, 95% CI: 0.6-3.3). However, ongoing users of ERT in the same study showed that there was a 40% increased risk of developing incident OA when not adjusted for obesity, but the results were not statistically significant (OR = 1.4, 95% CI: 0.6-3.3). Evidence from a UK population study indicated that estrogen use was protective against large joint OA although this was not significant (OR = 0.31, 95% CI: 0.07-1.35).[36] Conversely, in a study of the Swedish Knee Arthroplasty Register, there was evidence of increased risk of knee OA in women who used estrogen therapy (RR = 1.8, 95% CI: 1.2-2.6).[37] The evidence, therefore, is conflicting and inconclusive.

Joint space narrowing or osteophytes

Data from the Chingford Study[38] showed that current users of HRT (n = 72) had a significant protective effect for prevalent knee OA as defined by Kellgren and Lawrence grade or osteophytes (OR = 0.31 (95% CI: 0.11-0.93)), and a similar but not statistically significant effect for moderate joint space narrowing of the knee (OR = 0.41 (95% CI: 0.05-3.15)); however, they were unable to stratify HRT use based on current versus ever users due to small numbers. When incident OA was examined, a statistically nonsignificant protective effect was seen with current ERT on incident knee osteophytes (OR = 0.41, 95% CI: 0.12-1.42).[38]

General OA

Results from the Ulm OA Study[39] showed that HRT users compared with nonusers had a modest 21% increased risk for bilateral OA and general OA; the OR (95% CI) is 1.21 (0.48-3.03) and 1.21 (0.53-2.74), respectively, which was not significant due to large confidence intervals. In a UK population, nodal generalized OA was shown to be moderately protective but statistically not significant (OR = 0.59, 95% CI: 0.19-1.89).[36]

Progression of OA

Current use of estrogen from the Framingham OA Study[35] also showed a trend toward decreased risk of progressive knee compared with never use (OR = 0.5, 95% CI: 0.1-2.9), but results were not statistically significant.

Knee replacement

Data from The Million Women Study[26] showed that past use and current use of postmenopausal hormone therapy were both associated with a significant increase in the incidence of knee replacement compared with never users, RR = 1.39 (95% CI: 1.29-1.49) and RR = 1.58 (95% CI: 1.48-1.69), respectively. In the HUNT study,[40] past use and current use of postmenopausal hormone therapy were associated with a significant increase in the incidence of knee replacement compared to never users HR = 1.42 (95% CI: 1.06-1.90) and HR = 1.25 (95% CI: 0.90-1.73), respectively. Conversely, data from the Singapore Chinese Health Study[41] showed that ever use of postmenopausal hormone therapy was not significantly associated with increased risk of total knee replacement (HR = 1.07, 95% CI: 0.86-1.34) compared to never users. Analysis of circulating levels of estradiol in men from the Melbourne Collaborative cohort study[42] stratified by overweight (BMI ≥ 25 kg m^{-2}) or normal weight (BMI < 25 kg m^{-2}) indicated no difference between those participants who underwent Total knee replacement (TKR) when compared with those who did not (overweight: HR, 1.00, 95% CI: 1.00-1.01, P = .26; normal weight: HR, 1.00, 95% CI: 0.99-1.02, P = .61). The study by Wise et al.[25] using data from the MOST Study found a statistically nonsignificant risk of knee replacement (RR = 1.3, 95% CI: 0.8-2.1) with estrogen use. Differences in results could be due to differences in study size and types of study populations, as well as differences in the types of covariates included in the adjusted models. For example, the Million Women study included 1.3 million women, whereas the MOST study included approximately 1,600 women. In addition, the Million Women Study was a population-based study, while the MOST Study was in people at high risk for OA; thus, differences in baseline risks in the reference groups could account for differences in magnitude of estimates of association and their confidence limits. It is also possible that certain studies adjusted for occupational hazards or joint injury while others did not. Finally, there could be differences in definition of hormonal replacement therapy or estrogen use.[25]

Hip OA

There are fewer studies of estrogen and sex-differences in hip OA. Longitudinal cohort or case–control studies are shown later. Results are inconsistent and inconclusive.

Hip OA

In a case–control study, Dennison et al.[43] found a protective effect of long-term HRT (≥5 years) with a reduced risk (OR = 0.6, 95% CI: 0.2-1.8), while short-term HRT use (<5 years) was associated with an increased risk of hip OA (OR = 1.7, 95% CI: 0.9-3.3); however, results were not statistically significant. In the Study of Osteoporotic Fracture cohort, Nevitt et al.[44] found that women who were current users of estrogen had a significant reduction in risk of any hip OA (OR = 0.62, 95% CI: 0.49-0.86). Current users also had a 46% lower risk of developing moderate to severe hip OA compared to never users (OR = 0.54, 95% CI: 0.33-0.88). Long-term current users of estrogen replacement (≥ 10 years) had a greater reduction in hip OA (OR = 0.57, 95% CI: 0.40-0.82), whereas women who used estrogen replacement for less than 10 years had a statistically nonsignificant reduction of 25% (OR = 0.75, 95% CI: 0.47-1.24). Conversely, a study of community dwelling women who used postmenopausal estrogen therapy showed that they were much more likely to have prevalent clinical hip OA (OR = 5.03, 95% CI: 1.70-14.84).[45] There is significant divergence between these studies as discussed in depth by Mühlen et al.,[45] and some of the factors suggested that may contribute to these differences include the difference in hip OA definition (ACR gold standard compared with other); the method by which it was diagnosed (radiographically in SOF compared with clinical examination in the community study)

and adjustment for confounders (SOF adjusted for age and body mass in odds ratio calculation).

Hip replacement

Data from The Million Women Study[26] showed that past use and current use of postmenopausal hormone therapy were associated with a statistically significant increase in the incidence of hip replacement RR = 1.13 (95% CI: 1.06-1.21) and RR = 1.38 (95% CI: 1.30-1.46), respectively. In the Nurses' Health Study,[46] ever user of HRT compared with never users were at borderline increased risk for Total hip replacement (THR) (HR = 1.2, 95% CI: 1.0-1.5). Data from the HUNT Study,[40] however, showed no association comparing past users with never users on risk for incident THR, HR = 1.03 (95% CI: 0.92-1.33), as were current users HR = 1.19 (95% CI: 0.92-1.53). Analysis of circulating levels of estradiol on the incidence of total hip arthroplasty in men in the Melbourne Collaborative Cohort Study[42] stratified by weight (BMI $\geq$ 25 kg m^{-2} or BMI $<$ 25 kg m^{-2}) showed no difference in risk of THR compared to those who did not have THR in either BMI group (HR, 1.00, 95% CI: 0.99-1.01], P = .41 for overweight group, HR, 0.99 [95% CI: 0.98-1.01], P = .22) for normal weight group.

Hand OA

The overall prevalence of radiographic hand OA reported in the literature ranges from 45 to 81%[47–49] and is consistently higher among women than men and increases with age. Women also have higher site-specific OA prevalence compared with men: distal interphalangeal (DIP) (52% vs 34%; OR: 2.1; 95% CI: 1.6-2.9), proximal interphalangeal (PIP) (23% vs 8%; OR = 2.5; 95% CI: 2.2-5.8) and thumb IP (44% vs 27%; OR: 2.1; 95% CI: 1.5-2.9), but not in the metacarpophalangeal and first carpometacarpal (CMC) joints which are higher amongst men.[49]

To-date, there have been a number of review articles focused on the risk factors and biological mechanisms of hand OA, with particular attention on the role of estrogen and menopause in the process.[50–52] Research conducted in this area has largely been cross-sectional, and study findings are conflicted. These highlight the dearth of prospective and experimental studies to uncover the role of estrogen, either estrogen deficiency or exogenous estrogen treatment through ERT or hormone replacement therapy on hand OA. Some studies indicate a protective effect, a deleterious effect, or no effect at all. A cross-sectional study of Tasmanian women found that short-term use of HRT (<5 years) was associated with hand OA severity, particularly the DIP, when compared to nonuse (P = .007) but was not present for long-term use (>5 years).[53] No difference has been observed with regard to mean number of osteoarthritic joints, painful joints, and nodal joints by HRT status use among women with either painful hand OA or "quiescent" hand OA.[54] HRT was statistically not significantly associated with OA at the DIP joint (OR = 0.48, 95% CI: 0.17-1.42) or for the CMC joint (OR = 0.94, 95% CI: 0.44-2.03) in the Chingford study,[55] and HRT was statistically not significantly associated with worsening radiographic hand OA scores among women with hand OA (OR = 0.54, 95% CI: 0.07-4.2).[27] Duration of postmenopausal estrogen has been shown to be associated with an increased likelihood of having hand OA in menopause for those women taking estrogen for more than 1 year (OR = 1.6, 95% CI: 1.05-2.3).[45] In the study by Cooley et al.,[53] current estrogen use was associated with increased risks of DIP OA, CMC OA, and Heberden's nodes, but only results for Heberden's nodes were statistically significant (DIP OR = 2.21, 95% CI: 0.88-5.51; CMC OR = 1.60, 95% CI: 0.76-3.39; Heberden's nodes OR = 3.02, 95% CI: 1.42-6.44). Ever use of estrogen therapy was associated with similar risks, but only results for Heberden's nodes were statistically significant (DIP OR = 2.10, 95% CI: 0.94-4.68; CMC OR = 1.41, 95% CI: 0.72-2.79; Heberden's nodes OR = 2.46, 95% CI: 1.34-4.49).

Data from the prospective Framingham Osteoarthritis Study indicated that age-standardized prevalence of hand OA was higher among women than men (44.2% vs 37.7%). No sex difference was observed in incidence after a 9-year follow-up period of those without radiographic hand OA at baseline, however of those with radiographic hand OA at baseline, incident hand OA and progression of $\geq$1 joint was higher among women (87.4% vs 79.1% and 71.5% and 61.3%, respectively).[56] Another prospective study investigated the course of hand OA over 2 years of follow-up in 172 individuals, specifically examining by menopausal stage.[57] They found that women in an early postmenopausal stage ($\leq$10 years) more often had radiological progression, joint space narrowing, and osteophyte progression, than those in a late postmenopausal stage. Other work by Wise et al.[58] examining the role of estrogen receptor-α and -β genes on hand OA found no significant association between hand OA and ESR1 or ESR2 SNPs. They further examined this relationship in a meta-analysis, combining Framingham data with Japanese data from Ushiyama et al.[59] Significant associations for heterozygosity of rs2234693 and rs9340799 for the risk of generalized OA and severe generalized OA in women were observed, providing support for the inherited risk of hand OA.

A nested case–control study using data from the UK Clinical Practice Research Datalink showed that when compared to women without recorded menopause, those with a recorded menopause were 42% at greater risk for incident hand OA.[58] Furthermore, findings suggest the timing of HRT initiation and cessation may be influential on hand OA risk. Current HRT users who initiated treatment within 3 months before or after menopause appeared to have a reduced risk of developing hand OA (aOR = 0.72, 95% CI: 0.55-0.96) compared to nonusers, while statistically nonsignificant trends in increased risk were observed when HRT commenced 3-36 months postmenopause (aOR = 0.97, 95% CI: 0.68-1.37) and more than 36 months postmenopause (aOR = 1.30, 95% CI: 0.69-2.43). While some of the findings around timing of HRT cessation were statistically nonsignificant, stopping HRT less than 18 months before hand OA diagnosis was suggestive of increased risk (aOR = 1.25, 95% CI: 0.86-1.81), with risk attenuating to the null as the time period between cessation and hand OA diagnosis increased.[60]

Spine OA

The reported prevalence of spine OA is complex and conditional on differences in diagnostic criteria, imaging modalities, as well as populations studied. Prevalence estimates of radiographic spine OA range from 55 to 76%, increase with age, and are higher among men when compared to women.[49,61–64] The prevalence of facet joint osteoarthritis (FJOA) ranges widely, with estimates increasing with age.[65–67] Mikkelsen et al.[68] found the prevalence of radiographic cervical FJOA was 19% among adults aged 45-64 years and 57% in adults 65 years and older. Suri et al.[67] found on CT imaging, that prevalence of moderate/severe lumbar FJOA was 36% among those <45, 67% in adults 45-64, and 89% in adults 65+ years old taking part in Framingham Heart Study. When compared to men, women were more likely to have FJOA on both radiography (OR = 1.52, 95% CI: 1.14-2.0) and lumbar CT (OR = 1.86, 95% CI: 1.09-3.18).[69] Disk space narrowing (DSN)/disk height narrowing (DHN) is another feature of spinal OA, and the prevalence ranges from 20 to 55%.[67,69–78] While the prevalence of DHN also increases with age at the thoracic and lumbar spine,[65] there is conflicting evidence of sex differences, with some studies showing no observed differences,[69,72,76,79] while others showed observed differences where prevalence was higher amongst women compared with men.[73,78]

The majority of studies examining risk factors for spinal OA have been observational in nature. In a cross-sectional study taken from the general South Korean population (KNHANES study), HRT-use was negatively associated with spinal OA, in that there was a lower prevalence of spinal OA among HRT users compared with never users. In addition, when compared to those without spinal OA, the duration of HRT use was also found to be important, being on HRT for more than 1 year resulted in greater reduction in odds of spinal OA (OR = 0.69), when compared to those on HRT for less than 1 year (OR = 0.74, $P < .05$).[80] Hassett et al.[71] examined known risk factors for lumbar spine disk degeneration in the Chingford Study, a prospective, population-based study of women only, finding that hormone replacement therapy and multiparity were not associated with progression of DSN or anterior osteophytes over a 9-year period. Jarraya et al. examined progression of DHN and FJOA over a 6-year period using CT images at baseline and follow-up to assess change in both the thoracic and lumbar spine. They found that more women than men experienced DHN progression in the thoracic spine, but this was not observed in the lumbar spine. Progression to moderate-to-severe FJOA was also higher in lumbar than thoracic spine for both genders proportionately.[65] Finally, a single case–control study examined the role of inflammation in lumbar OA. Forty-four postmenopausal women with estrogen deficiency and low back pain were examined, and increased hs-CRP levels were associated with increased odds of symptomatic lumbar OA (OR = 2.83, 95% CI: 1.07-8.78) and high level of IL-6 were also associated with increased risk of symptomatic lumbar OA (OR = 2.7, 95% CI: 0.99-8.3).

Trials of estrogen or estrogen as treatment of OA or symptoms and sequelae of OA

Symptoms of knee and hip OA

Very few randomized clinical trials have been conducted on the impact of estrogen as a treatment to prevent adverse outcomes in postmenopausal women, and none where OA or OA sequelae were the primary outcomes. The Women's Health Initiative (WHI) is a double-blind, placebo-controlled, randomized study, which was originally conducted to examine the impact of estrogen treatment on heart disease and stroke outcomes. An ancillary placebo-controlled, double-blind study where 10,739 women with a history of hysterectomy were randomized to receive either a daily oral conjugated equine estrogen (0.625 mg d^{-1}) or placebo control to examine the effects of estrogen alone compared with placebo on joint symptoms was evaluated after 1 and 3 years of treatment.[81] At baseline, about 77% of women in both arms had joint pain and 40% had joint swelling. After 1 year, 76% if those on estrogen treatment compared with 79% on placebo had joint pain, and the difference was even greater at year 3 of the study (76% vs 84%). Those on estrogen, however, had a higher proportion with joint swelling after 1 year (42% vs 39%) and the difference persisted at year 3 (41% vs 38%). These results from WHI were statistically significant and robust when analyses were done for both intent-to-treat and per protocol.

However, compared to the WHI trial, results from a knee OA substudy of the 4-year Heart and Estrogen and Progestin Replacement Study (HERS) were not statistically significant.[82] Results may have differed as this was a smaller placebo-controlled, randomized, double-blind study of 969 women that assessed the effect of conjugated estrogen (0.625 g d^{-1}) plus medroxy-progesterone acetate (2.5 mg d^{-1}) in a single daily tablet rather than just estrogen alone on postmenopausal women with documented coronary disease.[83] At the 4-year follow-up visit, 24% of the treated group compared with 26% of the placebo control had frequent knee symptoms (95% CI: –7.4% to 3.5%) and had almost identical Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score and disability score. Results per protocol did not change materially from that of intent-to-treat.

Total knee or hip replacement

With regard to end-stage OA and total hip and knee joint replacement, there appears to be a borderline statistically significant protective effect of estrogen alone on overall risk of total joint replacement, but not for estrogen-plus-progestin based on the two trials from the WHI study. When comparing the estrogen alone arm with its placebo control comparison group, those treated with estrogen were at decreased risk for overall total joint replacement (HR = 0.84, 95% CI: 0.70-1.00) and borderline decreased risk for hip (HR = 0.73, 95% CI: 0.52-1.03) and knee replacement (HR = 0.87, 95% CI: 0.71-1.07). When data were analyzed per protocol, there were more statistical power and stronger decreased risk for overall total joint replacement (HR = 0.73, 95% CI: 0.58-0.93) and hip replacement (HR = 0.55, 95% CI: 0.35-0.88), and borderline decreased risk for knee replacement (HR = 0.80, 95% CI: 0.61-1.05). When comparing the estrogen-plus-progestin arm with its placebo control comparison group, those treated with estrogen-plus-progestin had no association for overall total joint replacement (HR = 0.99, 95% CI: 0.82-1.20), or with hip replacement (HR = 1.14, 95% CI: 0.83-1.57) and knee replacement (HR = 0.91, 95% CI: 0.72-1.15). Results did not change materially when analyzed per protocol.

Gaps: The Complex Interaction of Sex Hormones and Other Factors as Potential Explanation for Sex-Differences

As risk factors of OA are multifactorial and may impact OA differently depending on specific joints, potential factors may also modify or interact with sex hormones in relation to mechanisms that lead to OA. For example, mechanical contributors may contribute to sex differences. Research by Thaler et al.[84] implicates possible interaction between shear stress from mechanical loading and exposure to estradiol in degradation of the connective tissue in the knee joint that could explain differences between men and women in the development of OA. Also, the interaction between vitamin D and sex hormones is sex-specific in relation to cell activities in the bones. For example, male chondrocytes were more responsive to vitamin D, while female chondrocytes were more responsive to estradiol.[85] In addition, estradiol affects signaling of female osteoblasts differently than male osteoblasts, while vitamin D has similar impact.[86] There is also suggestion that endogenous hormones and reproductive factors, including parity and increased weight gain, may impact inflammatory pathways and mechanical environment, leading to increased risk for knee and/or hip OA.[3,21,32]

More research is needed given multifactorial risk factors for joint-specific OA and lack of understanding in possible mechanisms owing to the complexities and chronic nature of OA. Many of the studies that show protective effect of hormone replacement therapy on OA were based on observational epidemiologic studies. Potential biases including self-selection, survival bias, or recall bias, as well as residual or uncontrolled confounding may favor estrogen users in relation to OA outcomes. There is still a paucity of randomized clinical trials examining the effect of HRT on OA, and none where OA is the primary outcome of interest. This is possibly due to the fact that the risks may outweigh the benefits of HRT, as the use of HRT has been shown to increase risk for coronary heart disease, stroke, pulmonary embolism, and breast cancer in women treated with estrogen and progestin.[87,88] Thus, while we can say that more RCTs are needed to conclusively say whether HRT can prevent the development or slow down progression of OA, we need to weigh the risks and benefits of HRT in relation to the complexity of these conditions and the interaction among hormones, reproductive factors, and life style factors.

Conclusion

In summary, while several studies show that HRT has the potential to be protective of OA for some joints, there are studies that showed no protective effect or even adverse effect. In the WHI study, women receiving estrogen treatment had significantly lower rates of hip and knee joint replacements.[89] A cross sectional analysis found that postmenopausal women on long-term estrogen treatment had significantly reduced risk of any radiographic hip OA.[82] Yet, a prospective study of estrogen treatment in postmenopausal women increased the risk for hip and knee joint replacements.[26] Also, longitudinal studies show no statistically significant risk or reduction in radiographic severity of knee or hand OA.[34,35,55] Taken together, the evidence for the protective effect of estrogen therapy depends on OA joint, OA outcome, and study design.

Although this area has been studied for decades, more exclusively since the 1990s, there is a lack of experimental research in this topic. The lack of definitive conclusion on whether estrogen can play a role in the development in OA of either the knee, hip, spine, or hand may be in part due to the noncomparability of studies existing within the literature. Differences in diagnostic criteria, imaging modalities, populations studied, study designs, and outcome measures, as well as random error, have all contributed to inconclusive evidence. Advancement in diagnostic imaging (e.g., fast field cycling MRI) may offer solutions to answering the question at hand, particularly with importance of unpicking genetic and lifestyle factors that are also known to play a role in joint degradation and subsequent OA development. Understandably, randomized controlled trials remain the gold standard of experimental study design; however, they are a costly and involve a lengthy process as time until OA diagnosis can be considerable. There are circumstances where for ethical reasons, estrogen or hormone replacement therapy may not be warranted as the benefits fail to outweigh the risk of cardiovascular and cancer events, and results may reflect differences in participant recruitment and selection, as well as measurement issues. Capitalizing on pharmacology drug registers, drug trials, as well as real world evidence collected in electronic medical records may provide timely data to better unpick the relationship between estrogen and OA.

Research examining the role of estrogen on OA has, to date, focused on certain periods of life, particularly before and after the menopause in women and as it relates to HRT. The complexity of estrogen throughout the life course as it relates to modifiable lifestyle factors such as parity/birth control use, chronic conditions (e.g., thyroid disease and osteoporosis), overweight/obesity, and occupational/leisure activities is an area for future research. In addition, most of what is known about the relationship between estrogen and OA is based on research conducted in predominately white American and Western European populations, and although more research is now being published out of Asia, there are very little data in this topic from Africa or Latin/South America. There is no current drug for the prevention of OA or progression of OA. Total joint replacement has been the most cost-effective treatment for end-stage OA. Future studies into the effectiveness of alternative strategies to treat and manage OA are much needed.

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