Female hormonal factors and osteoarthritis of the knee, hip and hand: a narrative review

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Female hormonal factors and osteoarthritis of the knee, hip and hand: a narrative review

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ABSTRACT
Osteoarthritis is a leading cause of disability with no cure. The incidence of osteoarthritis is sexually dimorphic: women have a higher rate of osteoarthritis than men after the age of 50. Research has investigated the contribution of sex hormones, reproductive factors and hormone supplementation to osteoarthritis. It has been recognized that different joints are susceptible to different risk factors for osteoarthritis. We reviewed the evidence for the effect of endogenous sex hormones, reproductive factors and hormone supplementation on joint-specific osteoarthritis of the knee, hip and hand. Although the role of these hormonal factors in the pathogenesis of osteoarthritis is complex, data suggest that endogenous hormones and reproductive factors have a role in the pathogenesis of osteoarthritis, especially knee osteoarthritis, with uncertainty for the effect of exogenous hormones. From the available data, it is hard to conclude whether this is a direct effect of hormonal factors, or whether other factors related to these hormonal factors, i.e. obesity and inflammation, have a role in this association. Further studies should consider the mediation effect of body weight and inflammation, change in body weight throughout life, circulatory levels of all endogenous hormones and circulatory levels of hormones after hormone supplementation in this complex relationship.

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KEYWORDS
Sex hormones; reproductive factors; menarche; parity; menopause; oral contraceptive pills; hormone replacement therapy

Introduction
Osteoarthritis (OA), the most common joint disorder, is a leading cause of disability in the adult population. The joint manifestations are well characterized, including progressive loss of articular cartilage, osteophyte formation, subchondral bone remodeling, and mild to moderate inflammation of the synovial lining. The etiology of OA is multifactorial, being impacted by aging, genetic predisposition, abnormal biomechanics, obesity, and trauma1. OA is also influenced by co-morbidities such as cardiovascular disease, metabolic syndrome, and diabetes2.

Women have a higher prevalence and incidence of OA than men after the age of 50 years3, around the same age of the menopausal transition in women4. Explaining the dramatic increase in OA risk in women after menopause has been a challenging research question for many years. It has been hypothesized that women are protected by their female sex hormones, particularly estrogens, up until menopause, after which their estrogen levels decline. Reproductive factors, i.e. menarche, parity, and menopause, may play a role in the risk of OA by influencing lifetime or acute exposure to estrogen and/or other sex hormones. Similarly, exogenous hormone supplementation, i.e. combined hormonal contraception (CHC)/hormonal contraception (HC) and postmenopausal hormone replacement therapy (HRT), might modify OA risk by altering hormone levels.

Emerging evidence suggests that different joints are susceptible to different risk factors for OA. The knee joint is more affected by obesity-associated metabolic and inflammatory factors and mechanical loading5,6. Obesity-associated inflammation is a strong risk factor for hand OA6. In contrast, obesity has a weak or inconsistent associations with hip OA7. The purpose of this review is to evaluate the potential of reproductive hormones, reproductive history and hormone supplementation to influence OA. Thus, in this review, we examined the effect of endogenous sex hormones, reproductive factors and exogenous hormone supplementation (CHC/HC during active reproductive life and postmenopausal HRT) on joint-specific OA, focusing on OA of the knee, hip and hand.

Endogenous hormones and osteoarthritis
Endogenous sex hormones may have unique effects on lifetime risk of OA incidence and progression by preserving articular cartilage and subchondral bone8,9. The availability of a free fraction of sex hormones depends on the circulating levels of binding globulin, mainly sex hormone binding globulin (SHBG). High SHBG levels may indeed decrease the free fraction of estrogen. Estrogen increases hepatic synthesis of SHBG, and a high level of SHBG is therefore considered as a sign of a high level of estrogenization. Although
observational studies have examined the association between endogenous sex hormones and SHBG and OA\textsuperscript{10-12}, the nature of their influence in OA pathogenesis remains uncertain. Although one cross-sectional study showed higher estradiol levels were associated with an increased prevalence of radiographic knee OA\textsuperscript{13}, two cohort studies showed that a lower estradiol concentration was associated with an increased risk of developing radiographic knee OA\textsuperscript{10} and knee arthroplasty for OA\textsuperscript{14}. One cross-sectional study showed that a higher SHBG concentration was associated with increased tibial and patellar cartilage loss\textsuperscript{11}, while a cohort study showed no association between SHBG concentration and knee arthroplasty for OA\textsuperscript{14}. Two studies reported no associations of dehydroepiandrosterone sulfate, androstenedione and testosterone with tibial and patellar cartilage loss\textsuperscript{11} or knee arthroplasty for OA\textsuperscript{14}. One cohort study found no association between estrone and knee arthroplasty\textsuperscript{14}. Only one cohort study examined the association between endogenous sex hormones and the risk of hip OA\textsuperscript{14}. A lower concentration of androstenedione and a higher concentration of SHBG were associated with an increased risk of hip OA\textsuperscript{14}. Two studies reported no associations of dehydroepiandrosterone sulfate, androstenedione and testosterone with tibial and patellar cartilage loss\textsuperscript{11} or knee arthroplasty for OA\textsuperscript{14}. One cohort study found no association between estrone and knee arthroplasty\textsuperscript{14}. Overall, the data for an association of endogenous hormones and OA are inconclusive, with some longitudinal data to support the notion that low estrogen levels are associated with increased risk of knee OA. However, the paucity of data makes it hard to conclude whether estrogen or other endogenous sex hormones are involved in the pathogenesis of joint-specific OA. Furthermore, it should be noted that the frequently used radioimmunoassay methods for free circulating estradiol lack sufficient sensitivity and precision compared to gas chromatography/tandem mass spectrometry, which might be considered in further studies\textsuperscript{15}. While examining the effect of estrogen in the pathogenesis of OA, it should be kept in mind that there is a complex relationship among the endogenous sex hormones that should be taken into account. For example, estrone is a reservoir for estradiol in the circulation and, similarly, dehydroepiandrosterone sulfate is a reservoir for circulating dehydroepiandrosterone, which is a precursor for androstenedione, estrone and estradiol production\textsuperscript{14}. Only one study has examined the associations between the endogenous hormones and joint-specific OA\textsuperscript{14}.

**Hormone receptors and osteoarthritis**

Estrogen acts via the estrogen receptor (ER), which has two isoforms: ER\textsubscript{a} and ER\textsubscript{b}. In human articular tissue, both ER types are expressed by the chondrocytes\textsuperscript{16}, subchondral osteoblasts\textsuperscript{17}, synovial lining cells\textsuperscript{18}, ligament and fibroblasts\textsuperscript{19}. In vitro and in vivo experiments have shown that ER\textsubscript{a} and ER\textsubscript{b} antagonize each other in bone and in other tissues\textsuperscript{20}. Though several studies have reported associations between polymorphisms in ER\textsubscript{a} and ER\textsubscript{b} and OA with inconclusive associations of these two phenomena\textsuperscript{21}, no previous study has examined the associations between ER expressions in joint-specific different articular tissues and OA. Similarly, the availability of endogenous hormones in the synovial fluid should be explored while examining the relationship of endogenous hormones with joint-specific OA. Furthermore, there are androgen receptors in osteoblasts and chondroblasts\textsuperscript{22-26}. However, current data do not provide enough evidence on how androgen receptors and androgens work, which is another area of investigation.

Since women may not follow the same patterns of endogenous hormonal distributions, studies that aim to assess the role of these hormones in OA risk should not assume a uniform trajectory among all women. This assumption will most likely bias or dilute the findings on OA risk related to endogenous sex hormones. Furthermore, long-term exposure to endogenous hormones at multiple time points should be considered rather than a single time point since the hormonal concentrations keep changing. Studies should consider both between-women and within-women variations in endogenous hormones over the life span.

**Reproductive history and osteoarthritis**

Menstrual cycling and pregnancy are physiological phenomena affecting endogenous sex hormone levels during the reproductive period. Both menstrual cycling and pregnancy involve alterations in exposure to endogenous sex hormones\textsuperscript{27}, inflammatory responses\textsuperscript{28} and body weight\textsuperscript{29,30} which might expose women to the risk of developing OA.

**Menstrual cycle and osteoarthritis**

Three studies examining the association between age of menarche and knee OA reported conflicting results. Similar findings were reported in two cohort studies: one showed that early onset of menarche (earlier than 11 years) was associated with increased risk of knee arthroplasty for OA\textsuperscript{29}, and the other showed that increasing age of menarche was associated with decreased risk of total knee arthroplasty for OA\textsuperscript{31}. One cross-sectional study reported no association between age of menarche and knee cartilage defect, cartilage volume or joint space narrowing\textsuperscript{32}. Two cohort studies examined the association between age of menarche and hip OA. While one study reported onset of menarche earlier than 11 years was associated with increased risk of hip arthroplasty for OA\textsuperscript{29}, the other found no association between age at menarche and the risk of total hip arthroplasty for OA\textsuperscript{31}. Two cross-sectional studies examined the association between age of menarche and hand OA. One study showed that increasing age of menarche was associated with reduced radiographic hand OA score\textsuperscript{33}, while the other study found no association between age of menarche and hand OA\textsuperscript{34}. The three studies examining the age of menarche and knee OA have also examined the age of menopause and knee OA and found no associations. Age of menopause was not associated with risk of knee arthroplasty for OA\textsuperscript{29,33}, knee cartilage defect, cartilage volume loss or joint space narrowing\textsuperscript{32}. Similarly, age of menopause was not associated with
risk of hip arthroplasty for OA\textsuperscript{29,31}. In contrast, increasing age at menopause was associated with symptomatic hand OA and a more severe distal interphalangeal joint (DIP) score but not with the presence of radiographic OA\textsuperscript{34}, and years of menstruation were associated with both symptomatic hand OA and a more severe DIP score\textsuperscript{34}.

**Parity and osteoarthritis**

A number of studies have reported that parity is associated with a mild to moderate increase in the risk of radiographic knee OA\textsuperscript{30,35,36} and knee arthroplasty for OA\textsuperscript{29,30}. Increasing parity was found to be associated with greater magnitude of increase in knee arthroplasty risk\textsuperscript{29}. One cross-sectional study found that parity was associated with greater knee cartilage defects and lower cartilage volume, but not joint space narrowing\textsuperscript{32}. Another cohort study reported no association between parity and knee arthroplasty due to OA\textsuperscript{31}. Four studies examined the association between parity and hip OA and showed conflicting results: one showed that parity was associated with increased risk of hip arthroplasty for OA\textsuperscript{29}, whereas the other three failed to show any association\textsuperscript{31,35,37}. The only study showing pregnancy as a risk factor of hip arthroplasty for OA reported a dose–response relationship in a way that the risk of hip arthroplasty increases with increasing parity\textsuperscript{29}. One study showed that parity was associated with symptomatic hand OA and a more severe DIP score but not with presence of radiographic disease\textsuperscript{34}.

**Other reproductive factors and osteoarthritis**

Three studies examining the association between hysterectomy and varied degree of knee OA yielded different results. While two studies showed that hysterectomy was not associated with progression of knee joint space narrowing or osteophytes\textsuperscript{38}, knee cartilage defect or cartilage volume\textsuperscript{32}, the other study showed that women having a hysterectomy had a higher risk of clinical knee OA\textsuperscript{39}. No association between hysterectomy and hip arthroplasty due to OA was observed\textsuperscript{37}. While one study found no association between hysterectomy and hand OA\textsuperscript{34}, the other showed that women with a previous hysterectomy had a higher rate of clinical OA at the first carpometacarpal joint\textsuperscript{39}. Oophorectomy was not associated with the risk of hip arthroplasty for OA\textsuperscript{37} or hand OA\textsuperscript{38,40}. While breastfeeding was not associated with knee cartilage defect or cartilage volume\textsuperscript{32}, DIP OA, or Heberden’s nodes\textsuperscript{34}, it was associated with reduced prevalence of carpometacarpal OA\textsuperscript{34}.

While age at menarche and age at menopause were examined separately as risk factors for OA, a prolonged menstrual cycle as a risk factor has not been well examined. A prolonged menstrual cycle is a marker of prolonged reproductive life and active ovarian function\textsuperscript{61}, which means the availability of adequate endogenous hormones including estrogen. Hormonal depletion including less availability of estrogen might make the women prone to OA. Age at menarche earlier than 11 years has been found to be a risk factor of knee OA\textsuperscript{29}. This paradoxical association is hard to explain. Several studies have shown a U-shaped relationship between age at menarche and the rate of the general aging process and other chronic conditions such as cardiovascular disease\textsuperscript{42}, coronary heart disease\textsuperscript{43}, elevated blood pressure and glucose intolerance\textsuperscript{44}, and mortality\textsuperscript{45}. This might be similar for the case of OA onset and progression. Pregnancy and other reproductive factors influence the sex hormone availability. The results from longitudinal studies are consistent in showing increasing numbers of pregnancies as a risk factor of OA, especially for knee OA. It is hard to comment on the effect of other reproductive factors, e.g. hysterectomy, on OA risk based on the limited number of studies. Furthermore, oophorectomy and premature ovarian failure will cause prolonged estrogen deficiency, but how and to what extent this will affect OA risk are yet to be determined.

**Exogenous hormones and osteoarthritis**

Hormonal supplementation such as CHC/HC and postmenopausal HRT may influence the development and/or progression of OA. Menopause is associated with an increase in the prevalence of OA\textsuperscript{46,47}. Although HRT is the most effective method for the treatment of postmenopausal vasomotor changes, large population-based studies, such as the Heart and Estrogen/progestin Replacement Study\textsuperscript{48} and the Women’s Health Initiative\textsuperscript{49}, have shown an increased health risk after HRT.

**Hormonal contraception and osteoarthritis**

The data for the association between CHC/HC and the risk of OA are consistent, with no association observed between CHC/HC and risk of knee\textsuperscript{29,31,50}, hip\textsuperscript{29,31,51}, or hand\textsuperscript{34} OA.

**Hormone replacement therapy and osteoarthritis**

A large number of studies have examined the association between HRT and OA (Table 1). While some of these studies have specified the type of HRT used, others have not.

Knee osteoarthritis

Nine studies examined the use of estrogen-alone HRT and the risk of knee OA. Estrogen replacement therapy was associated with greater tibial cartilage volume\textsuperscript{54}, but not longitudinal change in tibial cartilage volume over 2 years\textsuperscript{56}. Four studies showed no association between estrogen replacement therapy and the presence of radiographic\textsuperscript{3} or clinical knee OA\textsuperscript{45}, incidence or progression of radiographic knee OA\textsuperscript{53}, or incidence of joint space narrowing or osteophytes\textsuperscript{38}. There was no association between postmenopausal estrogen use or its duration and radiographic knee OA\textsuperscript{52}. Two studies examined the association between postmenopausal estrogen use and risk of knee arthroplasty for OA, with one study showing an increased risk\textsuperscript{50} but the other reporting no association\textsuperscript{57}. Two randomized, double-blind, placebo-controlled trials examined combined estrogen and
Table 1. Relationship between hormone replacement therapy and osteoarthritis of the knee, hip and hand.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>n</th>
<th>Duration of follow-up</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee osteoarthritis</strong></td>
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<tr>
<td><strong>Estrogen only</strong></td>
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</tr>
<tr>
<td>Hannan (1990)</td>
<td>615</td>
<td>9 years</td>
<td>Radiographic knee OA</td>
<td>Ever used: OR 0.93 (0.62, 1.40)</td>
</tr>
<tr>
<td>Sowers (1996)</td>
<td>573</td>
<td>N/A</td>
<td>Joint score ≥2</td>
<td>HRT use vs. no, OR 2.56 (0.68, 9.5)</td>
</tr>
<tr>
<td>Zhang (1998)</td>
<td>551</td>
<td>8 years</td>
<td>Radiographic knee OA</td>
<td>Incident radiographic knee OA: never use, referent; past use, OR 0.8 (0.5, 1.4); current use, OR 0.4 (0.1, 3.0)</td>
</tr>
<tr>
<td>Hart (1999)</td>
<td>715 (osteophytes), 644 (joint space narrowing)</td>
<td>4 years</td>
<td>Knee osteophytes; knee joint space narrowing</td>
<td>Knee osteophytes: ever use, OR 0.73 (0.32, 1.67); current use, OR 0.41 (0.12, 1.42)</td>
</tr>
<tr>
<td>Sandmark (1999)</td>
<td>153</td>
<td>N/A</td>
<td>Knee replacement</td>
<td>User vs. non-user: RR 1.8 (1.2, 2.6)</td>
</tr>
<tr>
<td>Wluka (2001)</td>
<td>97</td>
<td>N/A</td>
<td>Tibial cartilage volume</td>
<td>User vs. non-user: mean difference in total cartilage, 0.30 (0.08, 0.52); mean difference in medial cartilage, 0.073 (0.01, 0.15); mean difference in lateral cartilage, 0.23 (0.06, 0.40)</td>
</tr>
<tr>
<td>Von Mühlen (2002)</td>
<td>1001</td>
<td>5.7–7.1 years</td>
<td>Knee replacement</td>
<td>Use ≥1 year vs. use 0–1 year, OR 1.30 (0.93, 1.81)</td>
</tr>
<tr>
<td>Wluka (2004)</td>
<td>81</td>
<td>2.5 years</td>
<td>Tibial cartilage volume loss</td>
<td>User vs. non-user: mean difference in total cartilage volume loss, 0.006 (−0.05, 0.06); medial cartilage volume loss, 0.013 (−0.02, 0.04); lateral cartilage volume loss, 0.008 (−0.05, 0.03)</td>
</tr>
<tr>
<td>Cirillo (2006)</td>
<td>10 272</td>
<td>5.7–7.1 years</td>
<td>Knee replacement</td>
<td>User vs. non-user, HR 0.80 (0.61, 1.05)</td>
</tr>
<tr>
<td><strong>Estrogen and progestin</strong></td>
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<tr>
<td>Nevitt (2001)</td>
<td>969</td>
<td>4 years</td>
<td>Knee symptoms: Western Ontario and McMaster Universities Osteoarthritis Index</td>
<td>User vs. non-user: difference in frequent knee pain, −2.0% (−7.4%, 3.5%); difference in knee pain severity, −0.2 (−1.2, 0.8); difference in disability, −0.7 (−3.8, 2.4)</td>
</tr>
<tr>
<td>Cirillo (2006)</td>
<td>16 049</td>
<td>5.7–7.1 years</td>
<td>Knee replacement</td>
<td>User vs. non-user: HR 0.95 (0.71, 1.27)</td>
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<tr>
<td><strong>Non-specified HRT</strong></td>
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<tr>
<td>Spector (1997)</td>
<td>606</td>
<td>N/A</td>
<td>Radiographic OA</td>
<td>Knee osteophytes: current use, OR 0.31 (0.11, 0.93); ever use, OR 0.80 (0.43, 1.49)</td>
</tr>
<tr>
<td>Szeoeke (2006)</td>
<td>224</td>
<td>11 years</td>
<td>Radiographic OA</td>
<td>Knee joint space narrowing: current use, OR 0.41 (0.05, 3.15); ever use, OR 1.00 (0.34, 2.96)</td>
</tr>
<tr>
<td>Liu (2009)</td>
<td>1010 914</td>
<td>6.1 person-years</td>
<td>Knee replacement</td>
<td>Never use: RR 2.9 (0.8, 11.6) Past use: RR 1.39 (1.29, 1.49); current use: RR 1.58 (1.48, 1.69) Years of use: &lt; 5 years, RR 1.52 (1.37, 1.68); 5–9 years, RR 1.52 (1.39, 1.66); ≥ 10 years, RR 1.72 (1.56, 1.89)</td>
</tr>
<tr>
<td>Hellevic (2017)</td>
<td>26 742</td>
<td>8.3 years</td>
<td>Knee replacement</td>
<td>Past use, HR 1.42 (1.06, 1.90); current use, HR 1.25 (0.90, 1.73); years of use, HR 1.03 (1.00, 1.06)</td>
</tr>
<tr>
<td><strong>Hip osteoarthritis</strong></td>
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<tr>
<td>Vingård (1997)</td>
<td>503</td>
<td>Cannot be determined</td>
<td>Hip replacement</td>
<td>User vs. non-user: RR 0.7 (0.5, 1.0)</td>
</tr>
<tr>
<td>Cirillo (2006)</td>
<td>1001</td>
<td>N/A</td>
<td>Hip replacement</td>
<td>Use ≥1 year vs. use 0–1 year: OR 5.03 (1.70, 14.84)</td>
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<td>User vs. non-user: HR 0.55 (0.35, 0.88)</td>
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<td><strong>Non-specified HRT</strong></td>
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<td>Dennison (1998)</td>
<td>16 049</td>
<td>1.5 years</td>
<td>Hip replacement</td>
<td>Ever use: RR 1.5 (0.9, 2.5) Years of use: &lt; 5 years, RR 1.8 (1.0, 3.3); ≥ 5 years, RR 0.7 (0.3, 1.9)</td>
</tr>
<tr>
<td>Karlson (2003)</td>
<td>93 442</td>
<td>N/A</td>
<td>Hip replacement</td>
<td>Ever use: RR 1.2 (1.0, 1.5) Past use, RR 1.13 (1.06, 1.21); current use, RR 1.38 (1.30, 1.46) Years of use: &lt; 5 years, RR 1.49 (1.36, 1.62); 5–9 years, RR 1.36 (1.25, 1.47); ≥ 10 years, RR 1.26 (1.14, 1.39)</td>
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<td>6.1 person-years</td>
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<td>Past use, HR 1.03 (0.80, 1.33); current use, HR 1.19 (0.92, 1.53); years of use, HR 1.04 (1.01, 1.07)</td>
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<td>26 742</td>
<td>8.3 years</td>
<td>Hip replacement</td>
<td>User vs. non-user, OR 0.54 (0.07, 4.2) Use ≥1 year vs. use 0–1 year, OR 1.57 (1.05, 2.33)</td>
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<td><strong>Hand osteoarthritis</strong></td>
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<td>ACR standard criteria</td>
<td>Use ≥1 year vs. use 0–1 year, OR 1.30 (1.20, 1.41)</td>
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</table>

(continued)
progestin therapy, with no association observed between combined estrogen and progestin therapy and knee arthroplasty\textsuperscript{57} or knee pain and disability\textsuperscript{58}. Four studies did not specify which type of HRT women were using. One study showed that HRT use was protective for knee osteophytes but not for joint space narrowing\textsuperscript{59}. Another study found no association between HRT use and radiographic knee OA\textsuperscript{60}. A large cohort study showed both past and current HRT use were predictive of incident knee arthroplasty for OA, and duration of HRT use was associated with increased risk of knee arthroplasty\textsuperscript{29}. Another cohort study reported that past but not current HRT use increased the risk of knee arthroplasty, with no association observed for the duration of HRT use\textsuperscript{31}.

### Hip osteoarthritis

Three studies examined the association between estrogen replacement therapy and hip OA with conflicting results: no association between estrogen replacement therapy and hip arthroplasty for OA\textsuperscript{59}, a protective effect of estrogen on hip arthroplasty\textsuperscript{57}, and a risk factor for clinical hip OA\textsuperscript{55}. Only one randomized, double-blind, placebo-controlled trial examined the association between combined estrogen and progestin therapy and hip arthroplasty and showed no association\textsuperscript{57}. Four studies examined the association between non-specified HRT use and hip arthroplasty for OA. One study showed that past and current HRT use were associated with increased incidence of hip arthroplasty\textsuperscript{29}, while the other three studies found no association between current, past, or ever HRT use and risk of hip arthroplasty\textsuperscript{31,37,61}.

### Hand osteoarthritis

Three studies examined the association between estrogen replacement therapy and hand OA. One study showed increased risk of clinical hand OA in relation to estrogen replacement therapy\textsuperscript{55}, while the other study found no association between estrogen replacement therapy and radiographic hand OA\textsuperscript{15}. In terms of non-specified HRT, both current and ever HRT use were associated with increased prevalence of Heberden’s nodes and severity of Heberden’s nodes and DIP OA\textsuperscript{34}. HRT usage for less than 5 years was associated with increased severity of both DIP disease and Heberden’s nodes\textsuperscript{34}. In contrast, another study showed never having used HRT was a risk factor for radiological hand OA\textsuperscript{60}, and two studies found no association between HRT and radiographic or clinical hand OA\textsuperscript{59,62}.

### Overview on hormone replacement therapy and osteoarthritis

To summarize, CHC/HC is not associated with OA risk. While a large number of studies have evaluated the association between HRT and OA risk, no conclusion can be drawn based on the available data. This is because not a single study has comprehensively examined the following: (1) whether HRT changes the circulating sex hormone levels significantly which can affect joint structure; (2) whether there is a true

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<tr>
<td>Spector (1997)\textsuperscript{59}</td>
<td>606</td>
<td>N/A</td>
<td>Radiographic OA</td>
<td>Distal interphalangeal joint OA: current use, OR 0.48 (0.17, 1.42); ever use, OR 0.67 (0.34, 1.35)</td>
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<td></td>
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<td>Carpometacarpal joint OA: current use, OR 0.94 (0.44, 2.03); ever use, OR 0.65 (0.34, 1.23)</td>
</tr>
<tr>
<td>Maheu (2000)\textsuperscript{62}</td>
<td>711 women: 238 'painful' hand OA patients, 240 'quiescent' hand OA patients and 233 controls</td>
<td>N/A</td>
<td>ACR clinical criteria and X-ray features</td>
<td>No differences between HRT + and HRT- patients on the characteristics of hand OA: Dreiser's index scores were 11.3 ± 3.8 vs. 12.3 ± 4.5 in ‘painful’ patients, and 3.6 ± 2.5 vs. 3.7 ± 2.7 in ‘quiescent’ patients</td>
</tr>
<tr>
<td>Cooley (2003)\textsuperscript{34}</td>
<td>348</td>
<td>N/A</td>
<td>Radiographic hand OA</td>
<td>Distal interphalangeal joint OA: current use, OR 2.21 (0.88, 5.51); ever use, OR 2.10 (0.94, 4.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carpometacarpal joint OA: current use, OR 1.60 (0.76, 3.39); ever use, OR 1.41 (0.72, 2.79)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Heberden’s nodes: current use, OR 3.02 (1.42, 6.44); ever use, OR 2.46 (1.34, 4.49)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Distal interphalangeal OA severity: current use, B 2.82 (0.13, 5.51); ever use, B 2.70 (0.32, 5.07)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Carpometacarpal OA severity: current use, B = 0.06 (−0.08, 0.69); ever use, B 0.65 (−0.01, 1.31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heberden’s nodes’ severity: current use, B 1.27 (0.60, 1.93); ever use, B 1.20 (0.62, 1.78)</td>
</tr>
<tr>
<td>Szeoke (2006)\textsuperscript{60}</td>
<td>224</td>
<td>11 years</td>
<td>Radiographic OA</td>
<td>Never use: hand OA, RR 2.33 (1.0, 1.1)</td>
</tr>
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<td></td>
<td>Carpometacarpal narrowing: RR 1.4 (0.6, 3.2)</td>
</tr>
<tr>
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<td></td>
<td>Carpometacarpal osteophytes: RR 1.2 (0.5, 2.8)</td>
</tr>
<tr>
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<td></td>
<td>Proximal interphalangeal OA narrowing: RR 0.7 (0.2, 2.7)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Proximal interphalangeal osteophytes: RR 2.0 (1.0, 4.1)</td>
</tr>
</tbody>
</table>

B, regression coefficient; HR, hazard ratio; HRT, hormone replacement therapy; OA, osteoarthritis; OR, odds ratio; RR, relative risk; ACR, American College of Rheumatology.
difference in OA outcomes between combination estrogen plus progestin therapy and estrogen therapy alone; and (3) whether there is difference in OA outcomes based on the timing and duration of HRT. These factors should be considered while evaluating this association in further studies. This is important to improve the understanding of the OA-related risks and benefits of hormone therapy, an important issue for women around the world.

**Antihormones and osteoarthritis**

Postmenopausal women maintain low levels of circulating estrogen as a result of androgen aromatization in adipose tissue and muscles. Aromatase inhibitors (AIs), which are the commonly used therapy for postmenopausal women with breast cancer, systemically block non-ovarian estrogen production, resulting in profound estrogen depletion. AI use has been associated with bone loss, increased risk of fracture, joint pain and stiffness. There are no data specifically examining the association between AI and OA. A prospective study showed greater expansion of the tibial plateau in AI-treated women compared with healthy age-matched controls. There has been an increased appreciation of the role of subchondral bone in OA pathogenesis, but whether this translates into increased prevalence of knee OA in women on AI is still unclear. Another receptor blocker, selective estrogen receptor modulator (SERM), is currently being used in treating breast cancer and osteoporosis and has shown a consistent agonist activity in joint tissues of animals. In animal studies, SERMs reduce articular cartilage turnover, regulate bone growth and remodeling, promote matrix production and mineralization, and regulate osteoblast and osteoclast development and function. However, the effect of SERMs on OA cannot be determined as there is no human study conducted in this area. Further research is needed to examine the associations of AIs and SERMs with joint-specific OA.

**Discussion**

The findings from previous studies suggest that endogenous hormones and reproductive factors have a role in the pathogenesis of OA, especially knee OA, although uncertainty surrounds any potential effect of exogenous hormones. It is plausible that greater exposure to estrogens may protect against osteoarthritic changes by preserving articular cartilage and subchondral bone. In animal studies, estrogen helps preserve healthy joints by maintaining articular cartilage and subchondral bone, supporting the notion that estrogen depletion may directly increase cartilage damage and subchondral bone loss or increase susceptibility for an osteoarthritis trigger. There is also evidence that estrogen exerts either direct or indirect effects on the maintenance and wellbeing of skeletal muscle and cartilage through ERα and ERβ via several pathways, such as transforming growth factor β and the insulin-like growth factor I and II pathways, and that estrogen plays an important role in fibroblast metabolism. Furthermore, women gain weight during menarche, menopause, and pregnancy (pregnancy-related weight gain and postpartum weight retention). Obesity and increasing body weight are unprecedented risk factors for OA. Reproductive factors, by changing body weight, may contribute to the underlying mechanism and may mediate the relationship between endogenous sex hormones and joint-specific OA. Low-grade systemic inflammation is observed in OA patients. Systemic inflammation might contribute to OA development and progression by triggering cartilage degeneration and stimulating apoptosis of osteocytes.

Endogenous hormones and reproductive factors through obesity may create an inflammatory environment and thus nurture OA development and progression. Alternatively, a low level of estradiol can create an inflammatory environment in the joint by inducing inflammatory stressors through the anti-inflammatory properties of ERβ. Systemic inflammation has been associated with sex hormone availability. For example, in vascular tissue during late menopause, estrogen becomes inflammatory due to interaction with Toll like receptors (TLRs) that boost inflammation. Similarly, mature chondrocytes express TLRs that may react to cartilage matrix/chondrocyte-derived degradation products leading to synthesis of pro-inflammatory cytokines.

Studies examining the relationship of endogenous sex hormones, reproductive factors and hormone supplementation with OA are heterogeneous in terms of the characteristics of study population, definition of OA, and measurement of the exposures. Although all the sex hormones are interrelated, only one study has examined all the sex hormones and SHBG, while others have examined only estradiol or estradiol and estrone or SHBG. While most of the studies have adjusted for body mass index or body weight or obesity, no study has investigated the mediation effect of obesity or inflammation in this relationship. Furthermore, a number of studies examining the effect of HRT have not specified whether it was an estrogen-based or combined estrogen–progestin-based HRT. When HRT was started after menopause and for how long HRT was continued would contribute to the conflicting results for the association between HRT and risk of OA.

**Conclusion**

The available data suggest that the role of endogenous sex hormones, reproductive factors and hormone supplementation in the pathogenesis and progression of OA is complex. Further studies are needed comprehensively to evaluate the effect of sex hormones, reproductive factors and hormone supplementation on OA pathogenesis, especially initiation and progression. These studies should consider (1) the mediation effect of body weight and inflammation; (2) the effect of changing body weight through the life course; (3) the circulatory levels of all endogenous hormones and SHBG; (4) the circulatory levels of hormones after HRT in this complex relationship; and (5) the route of administration of HRT as well as the various doses and the different progestin preparations. The results of such studies may provide clarification of
the clinical questions regarding the role of these factors in the prevention and treatment of OA.

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References


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