



## Review article

## Osteoarthritis: The importance of hormonal status in midlife women

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## ABSTRACT

Osteoarthritis (OA) is the commonest joint condition globally, affecting 18 % of women over the age of 60 years, although the prevalence varies according to the definition used. Although it may develop in any joint, it most commonly affects joints of the knee, hip, hand, spine and foot. Because OA often emerges in women in midlife, there has been longstanding interest in the association between hormonal status and the development and progression of OA. Researchers have variably suggested that estrogen exposure may be a risk factor for OA development, or that, conversely, it may be used as a therapy to treat OA. This review considers the historical development of this question, first described in the literature in 1805, and highlights the need for future research in this area.

## 1. Introduction

Osteoarthritis (OA) is the commonest joint condition globally, affecting 18 % of women over the age of 60 [1]. It represents a group of overlapping disease processes of differing aetiologies, all of which cause a pattern of degenerative disorder of the synovial joints. Radiological findings associated with an OA diagnosis include destruction of articular cartilage with associated joint space loss, osteophyte formation, subchondral bone sclerosis and cyst formation. The order in which each of these changes happens remains disputed [2,3] but they are usually associated with increasing pain and joint stiffness. Importantly, the level of radiological change [4] does not always correspond to the level of symptoms, and not all women who develop OA will go on to have joint replacement surgery, and many will be managed conservatively [5].

Development of OA is multifactorial including presence of susceptibility genes, estrogen status and bone density; these systemic factors combine with joint specific biomechanical factors such as obesity on lower limb joints, or previous injury [6]. As discussed above, this review will focus on development and progression of OA around the time of the menopause. A radiographic case definition of OA results in the highest reported prevalence [4]. The recognition of an association between joint symptoms and the menopause is not new – there are many historical accounts of observations regarding this [7]. For example, in 1805 Haygarth noted ‘the nodosities of the joints are almost peculiar to women and begin when the menses naturally cease’ while in 1925 Cecil and Archer reported a form of OA occurring just after the start of the

menopause in middle aged women. By 1937 the term menopausal arthritis which had first been introduced by Cecil and Archer had appeared in the British classification of chronic arthritis. Typically, researchers reported women developing joint stiffness soon after they underwent hysterectomy or went through menopause, with Heberden node development prominent and many reporting an almost explosive onset of symptoms [7]. Estrogen may impact all aspects of synovial joint health in midlife (Fig. 1), but epidemiological studies are often impaired by confounding factors which may lead women to modify behaviours as symptoms of OA develop.

## 2. Methods

A literature search was performed on PubMed to identify relevant manuscripts and scope the related literature. Although a formal systematic review was not performed, the structure of the literature search is described here. Searches on PubMed included the following terms (“osteoarthritis” OR “arthroplasty”) AND/OR (“menopause” OR “estrogen” OR ‘oestrogen’ OR ‘hormone’ OR ‘epidemiology’). After reviewing titles and abstracts full manuscript reviews were performed and relevant information and data collected. References were examined for further relevant titles and literature which were then reviewed.

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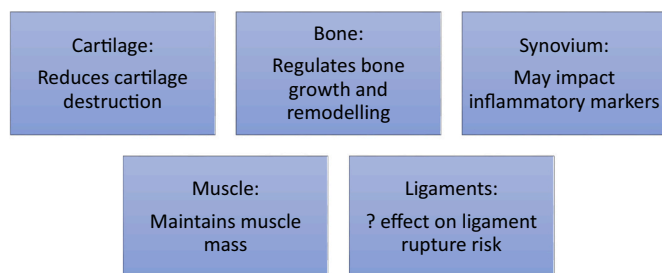


Fig. 1. Potential effects of estrogen on the joints of women in midlife.

## 2.1. Studies of association between clinical and radiographic OA and reproductive factors

### 2.1.1. Association of natural estrogen exposure and OA

In some of the first work on this topic [7], Spector highlighted the high prevalence of OA in women with fibroids and dysfunctional uterine bleeding, or in the presence of obesity. Since these conditions are often associated with relative estrogen excess, he suggested that OA may be linked to high estrogen levels, and even that tamoxifen may be a potential therapeutic option.

In follow up work [8], Spector and colleagues continued their investigation of relationships between sex steroids and OA development, where they studied 112 women (mean age 64) with generalised OA against controls (mean age 54) from the general population without clinical evidence of hand or knee OA. All women were postmenopausal. Sex hormone binding globulin level was lower in the generalised OA group, and significantly lower in the group aged 53–61 years while testosterone levels were slightly higher in women with generalised OA aged under 53. No consistent differences were seen in the older age group or for the other sex steroids. The limitations of the study, specifically around sample size and differences in age groups being considered, must of course be acknowledged.

The controversy continued in a paper by Sowers and colleagues, who reported OA prevalence in 573 Caucasian women aged 24–45 years from the Michigan Bone Health Study [9]. They found older age, increasing bone mineral density, and decreasing testosterone levels to be significantly associated with hand OA while increasing knee OA was associated with older age, increasing bone density, increasing body mass index, and current use of hormone replacement therapy. A radiographic knee grade of 2 or higher was associated with increasing estradiol levels, knee injury, and higher blood pressure.

Cooley and colleagues described the association of reproductive and hormonal factors with the presence and severity of hand osteoarthritis (OA) in 348 Tasmanian women from 76 families [10]. They reported that the prevalence of hand OA was 65–70%. Parity, increasing age at menopause and years of menstruation were associated with both symptomatic hand OA and more severe clinical arthritis in the distal interphalangeal joints (but not presence of radiographic disease) while both current and ever use of hormone replacement therapy (HRT) were significantly associated with increased prevalence of nodal arthritis in the hands. Using HRT for less than 5 years was associated with increased severity of Heberdens nodes and arthritis in distal interphalangeal joints.

### 2.1.2. Exogenous HRT and OA – friend or foe?

Although it is possible that women are turning to HRT to treat OA symptoms, or the relationship is coincidental, one might speculate that, based on the studies above, use of HRT may be associated with an excess risk of OA development. This was tested in a study by Hannan and colleagues, who studied 831 participants of the Framingham Osteoarthritis Study (mean age 73) and found no positive association of estrogen use with radiographic knee OA after controlling for age, body mass index, age at menopause, physical activity, history of knee injury, and

smoking [11]. In fact, a modest but nonsignificant protective effect for both radiographic OA and severe radiographic OA was seen in women who reported estrogen use at 2 or more follow up visits. We do not know the indication for estrogen therapy, but it is likely to be conjugated estrogen that was used in participants in this study given their age.

In 1997 Spector and colleagues published a study that considered whether HRT use was actually protective against OA [12]. 606 postmenopausal women aged 45–64 (mean age 54.2) from the Chingford Study were studied. Radiographs of hands, and knees were taken. Of 72 current HRT users there was a significant protective effect of HRT for some features of radiographic knee OA, namely overall K & L score and osteophytes but not joint space narrowing, and no relationships were seen with radiographic hand OA. Benefits appeared to be reduced after stopping HRT.

Regarding studies that have considered the prevalence of OA in women using long-term estrogen therapy found that it did reduce the risk of radiographic hip OA in the study of osteoporotic fractures [13]. Of 4366 Caucasian women aged 65 years or older, women who were currently using oral estrogen at the time of the assessment had a significantly reduced risk of hip OA of the hip. Duration of treatment appeared important as current users who had taken estrogen for 10 years or longer had a greater reduction in risk compared with women who had used estrogen for a shorter time.

However, subsequent studies failed to show that estrogen therapy protected against either the development or the progression of radiographic knee OA; of 551 women mean age 71 years in the Framingham Study followed up for 7 years, after adjusting for age and other confounders, the relative risk of incident radiographic knee OA in comparison with never users of estrogen was 0.8 (95% confidence interval [95% CI] 0.5–1.4) in past users and 0.4 (95% CI 0.1–3.0) in current users. Current use of estrogen also appeared protective against progressive radiographic knee OA [14].

In other work Maheu and colleagues considered whether HRT was associated with symptomatic hand OA [15]. They studied 711 women: 238 with ‘painful’ hand OA, 240 with ‘quiescent’ arthritis and 233 controls. Baseline characteristics were similar for patients and controls except for age (patients were older). Patients using HRT were younger, and more likely to be current cigarette smokers. In this study pain score was not different between the two groups.

Von Muhlen and colleagues examined postmenopausal estrogen therapy and prevalence of clinical OA at the hand, knee, and hip in 1001 community-dwelling postmenopausal women aged 43–97 years, mean age 72 years [16]. They reported that a significantly larger proportion of women who used ET for at least 1 year had hip and hand OA compared with women not using estrogen therapy and after adjustment for age, body mass index, smoking, exercise, and type of menopause, women who used estrogen therapy were still more likely to have hip OA and hand OA.

Two linked systematic reviews were published in 2009 and looked at relationships between OA and HRT [17,18]. The authors identified nineteen studies for inclusion and reported a protective trend for HRT use and incident radiological knee OA. They found conflicting evidence in available prevalence studies but limited evidence for a significantly increased risk of clinical hip OA with HRT but a significant protective effect of long-term unopposed estrogen use for radiographic hip OA. Taken together, these observations underline the complexities of comparison of these different studies (meta-analysis was not possible for this reason) and reinforce the need for more work in this area.

Many of the trials previously performed are now quite old. In two of the few recent papers, Wang and colleagues studied the association between self-reported OA and reproductive factors in the WHI Observational Study and Clinical Trial cohorts of 145,965 postmenopausal women, [19]. They observed relationships between, among others, OA and history of hysterectomy, history of unilateral oophorectomy, and evidence of a protective effect of current use of hormonal therapy while a recent paper from Korea [20] reported a study of 4766

**Table 1**

Summary of findings from studies that have considered relationships between estrogen exposure and OA.

Clinical outcome	Studies where endogenous estrogen exposure positively associated with outcome	Studies where endogenous estrogen exposure negatively associated with outcome	Studies where endogenous estrogen exposure inconclusively associated with outcome	Studies where exogenous estrogen exposure positively associated with outcome	Studies where exogenous estrogen exposure negatively associated with outcome	Studies where exogenous estrogen exposure inconclusively associated with outcome
Clinical and radiographic OA – presence or progression	[7,9,10]	[12]	[8]	[9,10,16]	[13,14,19,20]	[11,15,17,18]
Joint replacement surgery			[22,23,25]	[21,23–25]	[26,27]	[22]

postmenopausal women from the Korea National Health and Nutrition Examination Survey. Here knee OA (radiographic and symptomatic) was less common in women currently using HRT (Table 1).

## 2.2. Studies of association between OA joint replacement surgery and estrogen exposure

As discussed above, only a proportion of women who have OA will go on to joint arthroplasty – the decision is affected by several factors including personal choice, comorbidity, site of osteoarthritis and access to orthopedic surgeons [5]. The relationship between HRT use and severe OA was considered in a cohort study of women having arthroplasty surgery, the ULM advanced OA study, where of 475 women mean aged 67 years researchers found that, after adjustment for potential confounding factors, the odds ratios (95 % confidence intervals) of bilateral knee OA and generalised OA among HRT users compared with non-users was 1.21 (0.48, 3.03) and 1.21 (0.53, 2.74), respectively [21].

Eun and colleagues [22] also explored relationships between reproductive factors and joint replacement arthroplasty of the knee and hip in a cohort of 1,134,680 postmenopausal Korean women. Over a mean follow-up of 8.2 years, 1610 hip arthroplasty cases and 60,670 knee arthroplasty cases were studied. Later age at menarche, longer duration of breastfeeding, HRT and oral contraceptive use were associated with an increased risk of knee replacement surgery, while later age at menopause and longer reproductive span were associated with a decreased risk. For patients undergoing total hip replacement, later menarche, longer duration of breastfeeding, HRT use for more than 5 years, and oral contraceptive use for more than 1 year were associated with a higher risk of surgery. The associations between reproductive factors and severe OA were more pronounced in underweight and younger subjects. In this study stronger relationships were seen at the knee than the hip.

By contrast, in a prospective cohort study of 30,289 women from the second and third surveys of the Nord-Trøndelag Health Study, past and current users of systemic HRT were at higher risk of knee replacement surgery compared to never users (HR 1.42 (95 % confidence interval (CI) 1.06–1.90) and HR 1.40 (95 % CI 1.03–1.90), respectively) while no association was found between parity, age at menarche, menopausal status, age at menopause, oral contraceptive use or HRT use and THR [23].

In other work in a study that included 22,289 women in the Melbourne Collaborative Cohort Study, a 1-year increase in duration of menstruation was associated with a 1 % decrease in risk of total knee replacement (HR 0.99 [95 % CI 0.97–0.99]). These associations remained significant only in women of normal weight at early reproductive age. Current HRT users had an increased risk of total knee arthroplasty compared with non-users (HR 1.37 [95 % CI 1.14–1.64]); the association was significant only in non-obese women at midlife. Taken together, these data highlight that the situation is complex, and considerations include type of HRT used, and possible confounding by indication as women with an earlier menopause may be more likely to use HRT [24].

Many researchers have made use of national registries and data bases to investigate the relationship between hormonal status and surgical management of OA. A prospective study of 1.3 million women mean age 56 years at recruitment and followed up for 6 years through linkage to routinely collected hospital admission records revealed that while menopausal status and age at menopause were not clearly associated with TKR risk, current use of postmenopausal hormone therapy was associated with a significant increase in the incidence of hip and knee replacement [25]. Use of HRT may also reduce the need for revision after joint replacement. Prieto-Alhambra and colleagues studied records in the General Practice Research Database for women undergoing a primary knee or hip arthroplasty from 1986 to 2006 [26] who were then followed up for joint revision surgery. In this study higher HRT adherence and therapy duration post joint replacement were associated with further reductions in arthroplasty revision rates. Preoperative HRT appeared unrelated to implant survival.

Type of hormonal supplementation may also be important. For example in the Women's Health Initiative study [27], Caucasian women who received unopposed estrogen were less likely to undergo arthroplasties, particularly at the hip (less so in the knee) and women in the combined hormone therapy arm reported lower rates of joint pain and stiffness [8]. Researchers have speculated that the effects of estrogen may be as a result of effects of estrogen on opioid pathways, as well as direct effects on bone and cartilage, with other studies reporting that women receiving estrogen or alendronate had less OA-related subchondral bone attrition and fewer bone marrow edema-like abnormalities seen on MRI scans than women not receiving these medications [28,29].

## 3. Concluding remarks

There is a longstanding interest in the relationship between hormonal status in midlife and the emergence and progression of OA in women. In addition to epidemiological studies that have reported associations between natural menopause and joint symptoms, there are also many reports of the associations between use of hormonal therapy and OA. This is clearly a complex landscape. Differences between relationships at different sites of OA, complexities of observational versus trial data for hormone replacement, lack of recent data regarding menopausal hormonal status and joint health make comparisons and conclusions difficult. New data are now urgently required.

## Contributors

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