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Menopause and rheumatic disease

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Abstract/Synopsis

Menopause occurs naturally in women at about age 50. There is a wealth of data concerning the relationship of menopause to systemic lupus erythematosus, rheumatoid arthritis and osteoarthritis, while there are limited data concerning other rheumatic diseases. Age at menopause may affect the risk and course of rheumatic diseases. Osteoporosis, an integral part of inflammatory rheumatic diseases, is made worse by menopause. Hormone replacement therapy has been studied and its effects are varied depending upon the disease and even different manifestations within the same disease. Cyclophosphamide can induce early menopause but there is underlying decreased ovarian reserve in rheumatic diseases.

Keywords

Menopause; systemic lupus erythematosus; osteoarthritis; rheumatoid arthritis

Introduction

Menopause is defined as cessation of menses retrospectively for 12 months without pathophysiological cause. However, age-related changes in ovarian function begin in the middle of the fourth decade of life with decreased ovarian follicles. Resultant changes in hypothalamic and pituitary hormones to compensate for the falling reserve of ovarian follicles maintain ovulation and fertility, sometimes for decades. The transition to the menopausal state demonstrates highly variable cyclic follicle development and ovulation, along with disrupted menstrual bleeding patterns[1]. The average at menopause is about 51 with later age of menopause correlating with longevity[2–4].

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Rheumatic illnesses include diseases with evidence of autoimmunity as well as the common, near ubiquitous, osteoarthritis. These diseases are generally more common among women compared to men. There are extensive data describing the relationship of some diseases with the menopausal state, while the data are scant for other rheumatic diseases. In this review, we will consider the impact of menopause on several of these diseases, and the reverse; that is, the impact of the diseases on menopause.

Systemic Lupus Erythematosus (SLE)

SLE is the prototype systemic inflammatory rheumatic disease. There is a wide range of serological and clinical manifestations attributed to SLE with virtually every patient having a unique disease course. The disease affects women about 10 times more commonly than men with onset typically in the third or fourth decade of life[16]. Despite the usual onset well prior to the average age of menopause, there is a wealth of data concerning menopause and SLE, with multiple aspects of this relationship to consider. Among these are whether age of onset of menopause is a risk factor for SLE, and whether onset of menopause alters the course or severity of the disease or its complications, including accelerated cardiovascular disease. Hormonal therapy for menopause may also interact with the disease. Disease with onset after menopause, while uncommon, may be a distinct entity compared to pre-menopausal onset. Finally, cytotoxic therapy of SLE may induce an iatrogenic and early menopause. This review will consider these aspects of SLE and menopause.

A recent cross-sectional study examined menopause in 961 SLE patients, of whom 7.9% had natural menopause[17]. Meanwhile, 4.1% had undergone a hysterectomy and 6.3% had menopause after taking cyclophosphamide. Only a small number (0.1%) had menopause associated with end stage renal disease. The mean age at menopause was 46.4 years and the median age was 50.7 years, both similar to reported values for the general population[17]. An early age at menopause was associated with an earlier age of SLE diagnosis, however[17]. In LUMINA, a multi-ethnic SLE cohort from the USA, 37 of 316 woman had premature menopause. In a multivariable regression analysis, age at receiving cyclophosphamide, cyclophosphamide induction therapy, higher disease activity and Texas-Hispanic heritage were associated with a premature gonadal failure[18]. Older studies also show age and cumulative dose of the drug as important predictors of premature menopause[19]. Another study compared prolonged IV cyclophosphamide to 5–7 monthly doses followed by mycophenolate mofetil. In the latter group only 1 of 22 women (4%) had sustained amenorrhea, while in patients with prolonged cyclophosphamide treatedment 20 of 39 (51%) had sustained amenorrhea. Once again, older age at initiation of treatment was an important risk factor[20]. Neutrophil count suppression by pulse IV cyclophosphamide[21] as well hypothyroidism[22] may also predict premature ovarian failure. In the latter study, 11 of 71 SLE patients receiving cyclophosphamide developed ovarian failure:all 11 had hypothyroidism as evidenced by an elevated TSH[22]. Thus, treatment with cyclophosphamide can induce premature menopause in women with SLE, especially when treatment begins at an older (>32 years) age, while hypothyroidism as a risk factor is reported but not confirmed by subsequent studies.

Nonetheless, factors unrelated to cyclophosphamide can affect ovarian reserve in SLE patients. Using levels of anti-Muellerian hormone (AMH) as a measure of ovarian function in a study of 33 pre-menopausal SLE women (without past cyclophosphamide use) and 33 age and ethnicity matched healthy controls, Lawrenz and colleagues found lower mean AMH in SLE (2.15 ±1.64 versus 3.17 ±2.29); however, there was no difference in number of pregnancies or spontaneous abortions between the groups[23]. Another study confirmed this result but found AMH levels did not predict early menopause[24]. The factors intrinsic to SLE that affect ovarian function and reserve have not yet been identified. And, while anti-ovarian antibodies have been described in SLE patients[25], there is no evidence of premature menopause among SLE patients apart from the effects of cyclophosphamide[26]. Pharmacological suppression of ovarian function by GnRH agonists may protect women from premature ovarian failure caused by this drug[27,28], and there are several other strategies to preserve fertility after cyclophosphamide including oocyte preservation[29].

Whether or not menopause, natural or otherwise, affects the course of SLE has been investigated. This includes study of SLE with onset at an older, post-menopausal age. A study of SLE with average age of onset at 55 years among 20 post-menopausal and 70 premenopausal women showed the post-menopausal women were statistically less likely to have malar rash (55% versus 80%), renal disease (30% versus 69%), leukopenia (25% versus 56%) or positive ANA (70% versus 93%)[30]. Other studies find low incidence of anti-dsDNA and hypocomplementemia among post-menopausal SLE onset[31]. Thus, absence of these characteristic features, along with the older age, may make diagnosis difficult.

Menopause may also affect the course of SLE. In a study of 34 post-menopausal SLE patients with pre-menopausal onset compared to SLE patients continuing to have menstrual periods, Mok and colleagues found fewer (0.5/ year versus 0.14/ year) and less severe flares[32]. Mean and maximum disease activity were both decreased in 30 SLE patients not receiving sex hormone therapy followed for an average of 1.7 years before and 3.3 years after menopause[33].

Surgical menopause before SLE onset was associated with less renal involvement and lower anti-dsDNA seropositivity, an effect independent of ethnicity[34]. However, the Toronto Lupus Group have shown a constant rate of improvement in disease activity over time since diagnosis regardless of onset of menopause, concluding that menopause is not a proximate cause of improved SLE disease activity[35]. That is, the evidence suggests that SLE improves after menopause but a cause and effect relationship has not been established.

The relationship of menopause to disease activity in SLE begs the controversial question of whether post-menopausal sex hormone replacement is safe in SLE patients. This topic has been studied and reviewed extensively[36,37]. Evidence from the Nurses' Health Study, a large prospective cohort study, shows a 2-fold increased risk of SLE for women treated with post-menopausal hormone replacement[38]. However, these data were collected at a time when such therapy was much more common than at the present. Estrogen or combined estrogen-progesterone therapy[39] is associated with increased mild to moderate flares of SLE, but not with severe flares[37]. New data is available that may suggest possible mechanisms of SLE flares with hormonal therapy. In a recent study of 35 SLE patients and 15 controls,

investigators found increased expression of toll-like receptor (TLR)-3, -7 and 9 on peripheral blood mononuclear cells when comparing patients to controls. Post-menopausal status among the patients was associated with a higher percentage of cells expressing TLRs[40]. Another study reported decreased TNF production by estrogen-treated peripheral blood mononuclear cells from SLE patients[41].

Menopause has been studied in relationship to complications of SLE, especially premature atherosclerosis and osteoporosis. Low bone density is associated with disease activity and damage accrual: osteoporosis is an intrinsic part of SLE that is not induced purely by treatment[42]. Menopause is a risk factor for more severe osteoporosis as well as fragility fracture. Post-menopausal SLE patients were significantly more likely to have a vertebral compression fracture than pre-menopausal patients[43]. Further, the 10-year risk of osteoporotic fracture is greater among women with SLE compared to matched controls, despite comparable bone mineral density values. This risk was predicted by premature menopause as well as cumulative glucocorticoid dose[44]. Treatment with either estrogen or selective estrogen agonists such as raloxifene[45] maintain bone density in post-menopausal SLE patients. Newer data suggest that raloxifene does not worsen lupus flares, alter disease activity, or increase inflammatory markers in post-menopausal SLE patients[46]. But, the study is small (n=62) and relatively short (12 months)[45].

Women with SLE have dramatically increased rates of cardiovascular disease such that beginning about 10 years after diagnosis this is the most common cause of death[47]. Interestingly, a correlate of premature cardiovascular disease, as measured by coronary artery calcification, is low bone mineral density[48]. There are a number of studies of vascular function, which may serve as a surrogate of vascular disease, in women with SLE. Pulse wave velocity measured at peripheral large arteries determines arterial elasticity. Post-menopausal SLE patients (n=96) had worsened pulse wave velocity compared to pre-menopausal patients (n=124) but most of this difference was explained by age in a multivariate analysis. But, higher cumulative organ damage and worsened renal function were associated with stiffer arteries in the post-menopausal group[49]. A more traditional measure of arterial function is flow- mediated dilatation, usually determined at the brachial artery. A meta-analysis of these studies found that while endothelium-dependent flow mediated dilatation was impaired in SLE patients, menopause was not an important determinate in multivariate analysis[50].

Rheumatoid Arthritis

Rheumatoid arthritis affects about 1% of the worldwide population with a ratio of women to men of up to 6 to 1 in young adults[52], but the sex ratio approaches 1 as age of onset increases[53]. The onset of disease is substantially older than that seen in SLE such that initial disease among women is commonly in post-menopausal years[54]. Extra-articular disease may rarely lead to life threatening complications, but RA patients have excess mortality from several causes including cardiovascular, infectious, and hematological disease[54]. Similar to SLE and OA, there are multiple aspects of the disease potentially related to menopause.

First among these to consider is whether menopause increases risk or severity of RA. In fact, the results of observational studies of both menopause and estrogenic hormones, either post-menopausal or contraception, are variable and discrepant[55,56]. A study from Belgium showed that first symptoms of RA had a mean time from onset of menopause of zero. The authors suggested these data indicate that the average women with RA has the onset of symptoms concurrent with menopause[53]. A recent study showed that menopause prior to age 45 (early menopause) was associated with milder RA[57]. Meanwhile, another study found early menopause was associated with post-menopausal onset of RA[58]. Thus, a definite conclusion about the effects of menopause on RA cannot be made.

Some observational studies, but not all, show hormone replacement therapy (HRT) or oral contraception improves disease among post-menopausal women[56,61–69]. Similar to cardiovascular disease risk of HRT, studies of RA risk may be confounded by use of estrogen alone versus estrogen plus progesterone. A recent population-based epidemiologic study from Sweden showed a decreased risk of anti-CCP positive RA among post-menopausal women over age 50 with most of this reduction occurring in women on combination HRT, (odds Ratio 0.3)[66]. But, in a 2 year study of HRT in 88 post-menopausal women with RA, there were no changes in autoantibodies[70]. In addition, a 6-month, randomized, single-blinded, placebo-controlled trial showed no improvement in RA[71]. But, the latter trial likely has no bearing on whether or not HRT reduces the risk of developing RA.

Similar to other inflammatory rheumatic illnesses, osteoporosis is caused in part by the disease itself with specific effects on bone remodeling an not simply a result of glucocorticoid therapy[72]. In a study of 343 post-menopausal and 100 pre-menopausal women with RA, 56% of the former but only 18% of the latter had osteoporosis[73]. Of course, study of healthy women before and after menopause might find similar numbers. However, there is clearly excess osteoporosis among RA women compared to controls with post-menopausal status an important predictor[74]. Excess bone loss seen in RA occurs early in the disease[75]. Recent studies from the era of biologics (and low prevalence of post-menopausal HRT) continue to show excess osteoporosis in RA patients compared to age-matched controls (30% versus 17.4%), and an association with menopause[76]. HRT reduces bone resorption regardless of glucocorticoid therapy in post-menopausal RA patients[77,78], but there are, of course, other potential health concerns with post-menopausal HRT.

Osteoarthritis

Osteoarthritis (OA) is highly prevalent in postmenopausal women. The Women’s Health Initiative showed that 44% of the participating postmenopausal women reported OA. Risk factors in this study include higher BMI and older age. American Indian and African American women in the extreme obesity category have significant odds of OA compared to non-Hispanic white women[86].

Estrogen receptors are present in joint tissues. Estrogen has chondro-protective roles in part due to glycosaminoglycan synthesis, which is an important part of connective tissue. Estrogen also inhibits cyclooxygenase 2 mRNA expression in bovine articular chondrocytes

as well as other tissues, leading to protection against reactive oxygen species induced chondrocyte damage[92]. Estrogens decrease cartilage damage. Conincubation of chonodrocytes with IL-1b and raloxifene led to dose dependent increase in proteoglycans and reduction of MMP-3 and nitric oxide induced by IL-1B[93]. Polymorphism in the estrogen receptor (ER) alpha gene may be associated with risk of severe OA of large, lower limb joints in a sex specific manner suggesting that estrogen activity may influence the development of large joint OA[94]. The same study concluded that variation in aromatase gene CYP19A1 and ER alpha gene, are associated with risk of severe OA. Influence of the CYP19A1 single nucleotide polymorphism is more important in women than in men, and in knee OA than in hip OA[94]. Recent meta-analysis by Gong, et al. reported rs9340799 and rs2228480 polymorphisms, rather than the rs2234693 polymorphism, in estrogen receptor alpha gene are associated with the incidence of OA[95].

It has been demonstrated that CTX II, marker of collagen degradation, increases in the urine of asymptomatic postmenopausal women and ovarectomized rats, suggesting that estrogen deprivation leads to cartilage breakdown. No association has been found for urinary Helix II and estrogen deprivation leading to cartilage breakdown[96]. Study of 860 women in China noted that menopause is associated with cartilage degeneration of knee joint compared to pre and peri-menopausal women. Knee cartilage showed progressive severe degeneration on MRI in the first 2.5 years since menopause. However, while the authors reported controlling for age, the study did not achieve much overlap in age across the menopause status group. The authors concluded that estrogen deficiency is a risk factor for cartilage degeneration and further studies are needed to clarify whether age or menopause plays a more important role in progression of cartilage degeneration[97]. The study could not definitely differentiate between the effects of menopause and age in our opinion.

Chen, et al. studied endogenous estrogens and estrogen metabolites in pre and postmenopausal Chinese women with osteoarthritis. The study showed that serum concentration of free estradiol and total 2-hydroxyestrone were significantly lower in premenopausal women with OA compared to the levels in controls (RA and healthy women). In post-menopausal women, serum concentration of free and total estradiol was significantly decreased compared to controls. 2-hydroxyestradiol was significantly increased in post-menopausal women. The authors reported that apart from free and total estradiol deficiency, decreased serum level of total 2-hydroxyestrone in premenopausal women and increased total 2-hydroxyestradiol level in post-menopausal women with OA may correlate with pathogenesis of OA[100,101].

Studies on hormonal therapy in post-menopausal women with osteoarthritis have shown conflicting evidence (Table 1). Women's Health Initiative study showed that there are 29% greater odds of OA with past HRT use and 38% greater odds of OA for current HRT. American Indian women who reported current HRT use had an odds ratio of >2 for arthritis (presumably OA) than the population as a whole[86]. In contrast, an Italian study showed HRT is associated with 27% lower odd ratio of physician diagnosed OA[102]. A cohort study of 1001 post-menopausal women (mean age 71 years) examined effect of post-menopausal estrogen therapy on hand, knee and hip osteoarthritis. 638 women had used estrogen post-menopause for greater than one year, 71% were current users. Post-menopausal estrogen use

for greater than one year was associated with higher prevalence of OA compared to no use of estrogen (34.5% compared to 30.9%, p=0.02). Women using estrogen had significantly higher prevalence of hip and hand OA (15.8% vs 13.5%, p=0.02 for hip, 4.1% compared to 1.1%, p=0.002 for hand). Knee OA was slightly higher with estrogen use; however, the difference was not statistically significant. Unfortunately, this study did not report radiographic evidence of OA[103]. In contrast, a large cross sectional study evaluated 4,366 post-menopausal women for osteoporotic fractures. Women currently using estrogen had 40% lower prevalence of radiologic and symptomatic hip OA. Reduction was greater for estrogen use >10 years[104]. In the Framingham OA study, estrogen use was not associated with increased risk of radiographic osteoarthritis of the knees. In fact, estrogen use had a modest but non-significant protective effect in the study[105]. In heart and estrogen/progestin replacement study, older postmenopausal women with cardiac disease (n=969) were assessed for knee pain. There was no significant effect of 4 years of estrogen plus progestin therapy compared to placebo on knee pain and related disability, indicating that HRT is not associated with more prevalent or severe knee pain[106].The Chingford cross-sectional study demonstrated an inverse association of current post-menopausal HRT use and radiologic knee OA, suggesting protective effects. There was a non-significant protective effect for distal interphalangeal OA, but no clear effect on carpometacarpal joints, leading to the conclusion that effect was weaker in the hand joints[107]. Further studies are needed to evaluate true effect of estrogen replacement on the OA considering the current contradictory evidence. Consideration of the site of OA may be critical in any such study.

The effect of hormone therapy on risk of hip and knee joint replacement was evaluated in the Women's Health Initiative study. The population included post-menopausal women aged 50–79 who were followed for a mean of 7.1 years. Women who had had hysterectomies (n=10,272) were randomly assigned to received 0.625 mg per day of conjugated equine estrogen or placebo. Those with an intact uterus (n=16,049) were randomly assigned to receive estrogen (conjugated equine estrogen 0.625 mg) and progestin (medroxyprogesterone acetate 2.5mg/d) vs placebo. Women receiving estrogen alone had significantly lower rates of arthroplasty (HR 0.84, 95%CI: 0.70–1.00). This effect had only borderline significance for hip arthroplasty (HR 0.73, 95%CI: 0.52–1.03), and was not significant for knee arthroplasty. In the estrogen and progestin trial, there was no association for total, hip, or knee arthroplasty[108]. In a recent prospective study of 2,621 women greater estradiol concentration was associated with lower incidence of knee replacement (HR 0.70, 95%CI: 0.50–0.96). Lower androstenedione concentration and higher sex hormone binding protein concentration were associated with higher incidence of knee replacement (HR 1.7, 95% CI 1.05–2.77)[109]. Estrogen appears to have a protective effect on joint replacement, specifically on the hip more than knee; however, this effect is negated by presence of progestin. Further studies are needed to clarify the role of estrogen after menopause on mitigating OA.

Sjögren's Syndrome

Primary Sjögren's syndrome has a marked bias towards women with at least a 10:1 ratio to men, but generally has its onset late in life, frequently in post-menopausal years[110]. Nonetheless, menopause and its effects on this disease are little studied. Postmenopausal as

well as pre-menopausal women with Sjögren's syndrome have increased vaginal dryness and dyspareunia[111] as well as decreased quality of sexual life compared to controls[112]. The decrease was related to multiple factors, including dyspareunia, lubrication, desire and arousal according to the Female Sexual Function Index[112].

Sex hormone levels have been studies minimally compared other rheumatic illness. One small study of 17 Sjögren's patients and 19 healthy controls showed statistically significantly higher prolactin levels among the patients (11.4 versus 6.7 ng/ml), while there were no statistical differences of estrogen or progesterone levels[113]. There is an aspect of sex hormone metabolism that could be affected uniquely by Sjögren's syndrome among the rheumatic illnesses. Dehydroepiandrosterone-sulfate (DHEAS) is produced in the adrenal glands of estrogen-deficient women and is converted into dehydroepiandrosterone in exocrine glands. This latter metabolism may be abnormal as a result of Sjögren's pathology in these glands resulting in immune effects[114,115]. Trials of dehydroepiandrosterone in Sjögren's syndrome have failed to show benefit for fatigue or salivary flow even among patients with low serum levels[116–118]. Perhaps these negative trials were the result of failure to convert DHEAS in exocrine gland tissue.

Scleroderma

Systemic sclerosis (SSc) is a disorder characterized by vascular damage, overproduction of collagen and its deposition and other matrix constituents into skin and internal organs[119]. Estrogens have a protective role on arterial endothelium[119]. Postmenopausal SSc patients have lower level of testosterone, DHEAS and androstenedione compared to controls. There is a negative correlation between androstenedione and anti-centromere antibodies (ACA) levels. It was postulated that ACA is generally present in localized SSc and higher level of hormones suppress the autoimmune process in the skin and synthesis of ACA. Surprisingly, the same study has shown a positive correlation between Scl-70 antibodies and androgen levels[120].

Menopause has effects on skin thickening, especially in diffuse SSc patients. Postmenopausal women with diffuse SSc have lower mean modified Rodnan skin scores compared to pre-menopausal status women. The effect was smaller, but statistically significant, in limited SSc patients[121].

In contrast to the skin, post-menopausal status is a risk factor for developing pulmonary hypertension. In the study by Scorza et al., 93 patients (49.2%) were post-menopausal and 49 (31.2%) were fertile. The cumulative probability of pulmonary hypertension increased over time in post-menopausal women compared to fertile women. Mean free interval time for pulmonary hypertension was 10.6 years in post-menopausal subjects compared to 20 years in fertile subjects ($p<0.003$). Relative risk of menopause for pulmonary hypertension was 5.2 with p value of <0.0001. The mechanism underlying this effect was postulated as a lack of estrogen leading to decrease in nitrous oxide production and endothelial damage[119]. One retrospective study found that HRT soon after menopause has shown to be beneficial in preventing pulmonary hypertension in patients with limited SSc. However, the study was

retrospective and the duration of hormone therapy was not defined. Randomized controlled trials are required to draw definitive conclusions[122].

Post-menopausal women with SSc have higher prevalence of osteoporosis (42.7%) compared to controls (10.7%), with significant alteration in trabecular bone component in SSc patients. The presence of ACA was associated with lower bone mineral density in the same study. Digital ulceration was associated with lower total hip and femoral neck bone density[123]. Another study pointed out that earlier onset of menopause in SSc patients is associated with lower bone mineral density[124].

Summary

Menopause interacts with rheumatic disease in various ways. For example, SLE with onset after menopause is generally milder, while menopause is a risk factor for pulmonary hypertension in SSc. The data concerning the relationship of menopause and rheumatic diseases are incomplete or contradictory in many cases. Osteoporosis is a part of many of these diseases and risk for this complication is increased by menopause. In SLE, treatment with cyclophosphamide can cause premature menopause, especially in women over 30, who have decreased ovarian reserve. Treatment of menopause with hormone therapy has differential effects depending upon the disease and the manifestation examined.

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Key Points

1. Menopause, and its treatment, may affect rheumatic diseases; and rheumatic diseases may affect menopause.
2. Treatment with cyclophosphamide, especially at an older age, may induce menopause.
3. Decreased ovarian reserve is a feature intrinsic to disease notwithstanding treatment.
4. Osteoporosis is common in several rheumatic diseases, and menopause increases the risk of osteoporosis as well as fragility fracture.
5. The effect of menopause and its treatment is difficult to define in osteoarthritis because of contradictory results.

Table 1

Effect of post-menopausal hormone replacement on osteoarthritis

Study	Type of study	Population	Results
WHI (86)	Observational study	N=146,494 post-menopausal women	• HRT use associated with increased odds of OA. • 29% increase odds of OA with current use and 38% with past use of HRT.
Parazzini F (102)	Cross sectional study	N=42,464 Italian postmenopausal women	• Increase odds of OA with menopause • Natural menopause associated with increased OR of 1.13 for OA (95% CI 1.07, 1.21) • Surgical menopause OR of 1.18 for OA (95% CI 1.09, 1.28) • HRT: 27% lower odds of physician diagnosed OA compared to those not on HRT.
Von Muehen (103)	Cross sectional	N=1001 post-menopausal women	• Post-menopausal estrogen use: 34% higher prevalence of OA compared to non-users. • Higher prevalence of hip and hand OA I subjects using estrogen replacement therapy compared to non-users(15.8% compared to 13.5%, p=0.02 for hip, 4.1% compared to 1.1%, p=0.002).
Nevitt (104)	Cross sectional study	N=4366 post-menopausal women	• 40% lower prevalence for radiologic and symptomatic OA of hip with estrogen use.
Framingham OA study (105)	Cohort Study	N=831	• Non-significant protective effect for radiographic knee OA (OR 0.71, 95% CI 0.42, 1.20) or severe radiographic OA (OR 0.66, 95% CI 0.33,1.32) with estrogen use.
Heart Estrogen/Progestin replacement study (106)	Randomized control trial	N =969 post-menopausal women	• No difference between women on HRT vs. placebo on knee pain and related disability.
Chingford Study (107)	Cross sectional study	N=606 post-menopausal women	• Current HRT use was protective for knee OA (OR 0.31, 95% CI 0.11, 0.93) • Non-significant protective effect for OA of DIP joint with HRT use; OR 0.48 (95% CI 0.17, 1.42) • No effect on carpometacarpal joint. (OR 0.94, 95% CI 0.44, 2.03)