

Invited review

Menopause, oestrogens and arthritis

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Abstract

The menopause coincides with the appearance of many of the common arthritic conditions and with the lessening of severity of others such as SLE. The hormonal changes that occur may modulate these diseases. Thus, hormonal manipulation may have either beneficial or detrimental effects on the incidence and activity of a number of common joint diseases. We review the evidence regarding the effect of the menopause and oestrogen replacement therapy on the pathogenesis, incidence and prevalence and disease activity of osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus and carpal tunnel syndrome. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

There is no doubt that the hormonal changes occurring around the menopause modulate disease. It has been postulated that they may act as a trigger for the emergence of some diseases (e.g. breast carcinoma), or that the resultant oestrogen deficiency may modulate the activity of diseases already present (e.g. ischaemic heart disease).

Joint symptoms, one of the principal components of the menopause [1], are experienced by up to 50% of women with menopausal symptoms [2]. These are often non-specific or common problems such as back pain which may only be related by chance, or musculoskeletal pain syndromes such as fibromyalgia which are associated with depression.

The role of oestrogens in the pathogenesis of common rheumatologic conditions is controversial. Little evidence exists, and much of that which is present is conflicting. In most studies, no distinction is made between the level of oestrogen in hormone replacement or whether the use of progesterone modulates the effect of oestrogen. In

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this review we will examine recent developments in our understanding of the role of menopause and hormonal factors on the rheumatological conditions osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus and carpal tunnel syndrome.

2. Osteoarthritis (OA)

2.1. Epidemiological evidence for association between hormonal factors and OA

Osteoarthritis (OA) is a group of clinically heterogeneous disorders unified by the pathological features of hyaline cartilage loss and subchondral bone reaction. The prevalence of OA in women and men is similar until about age 50, but thereafter the disease becomes more prevalent, severe and generalised in women [3–5]. Kellgren and Moore described a form of ‘menopausal arthritis’ in a group of women with Heberden’s nodes characterised by a rapid onset of symptoms and multiple joint involvement (hands, spine and knees) which they renamed ‘primary generalised osteoarthritis’ [6]. In a further population-based study of middle aged women, clustering between joint sites in OA was shown to be more common in peri and postmenopausal women than would be expected simply from the rising prevalence of the disorder with age [7]. The apparent increase in women presenting with polyarticular symptoms in middle age suggests that there may be a relationship between the onset of OA and the menopause [8].

Further support for a hormonal effect on OA comes from some, but not all studies, which have shown that women who had a previous hysterectomy had significantly higher rates of clinical signs of knee OA and first carpometacarpal OA than control women without hysterectomy [9,10]. An inverse association between premenopausal status and patellofemoral OA has also been observed [11].

The trigger for the appearance of OA in middle aged women is unknown but it has been suggested that it may be related to the hormonal changes occurring at the menopause. Whether these are

active in all cases of OA in women, or are restricted to the so-called subtypes of OA (‘menopausal OA’ or ‘generalised OA’) is unclear.

2.2. Hormonal factors and animal models of OA

The possible link between oestrogens and OA has come from the suggestion that excess or unopposed oestrogens might predispose cartilage and bone to OA.

In some animal models of OA, subjects treated with oestrogen show reduced changes of OA [12]. In ovariectomised sheep, changes in the mechanical properties of the knee cartilage were seen that resembled the effect seen after the transection of the anterior cruciate ligament in dogs [13]. These changes were not seen in those sheep, which had not been ovariectomised or received oestrogen replacement following surgery. Male OA prone mice, treated with oestrogen early in life, had less OA than those who did not receive oestrogen [14]. Those treated later in life had less changes of OA than the control group, but their life span was less, confounding this result. Thus the age of the animal and state of articular cartilage at the time of oestrogen replacement or induced deficiency were important factors in the response of cartilage to oestrogen, suggesting it may play a modulating role in the development of OA.

However, in other animal models, exogenous oestrogen, administered parenterally and intra-articularly in suprapharmacological doses has been shown to adversely affect OA [12,15]. The anti-oestrogen drug, tamoxifen, has been reported to be beneficial in these same animal models, reducing the effect of oestrogen on cartilage destruction [16,17].

Oestrogen may affect tissues directly because oestrogen receptors have been found on human articular chondrocytes, or indirectly using secondary messengers [4]. Oestrogen has been shown to affect cytokine levels both in vitro and in vivo. The production of IL-6 by human chondrocytes is affected by oestradiol, suggesting a possible mechanism whereby it may affect cartilage metabolism [18]. HRT in ovariectomised monkeys treated with unopposed oestrogen increased synovial levels of IGF-1, IGF-2 and IGF binding proteins-1

and 3 [19]. This effect was reduced in those treated with combined therapy, and absent in the control group. A dose response to oestrogen was demonstrated. Thus systemic oestrogen replacement therapy, unopposed and combined with progestogen, in pharmacological doses, appears to affect the IGF system, intra-articularly.

Genetic studies have shown the IGF-1 locus to be associated with the presence of radiographic OA [20]. It is possible that changes in oestrogen level may trigger OA via their effect on IGF-1; the success of the trigger dependent on genetic make-up of the individual.

2.3. Endogenous sex steroid levels in women with generalised OA

There are no known definite features of prior endogenous oestrogen exposure which predict the development of OA. Case control studies have shown no effect of the duration of exposure to endogenous oestrogens, measured by the age at menarche, menopause and parity with occurrence of OA [10,21]. Whether absolute hormone concentrations affect the risk of developing OA, or alter disease progression in women has not been determined.

In premenopausal women, no association between testosterone or oestradiol levels and knee OA has been found, although lower testosterone scores were seen in women with hand OA [22].

Studies of urinary and serum sex-hormone levels in peri-menopausal and post-menopausal women with OA have yielded inconsistent results [23,24]. Middle-aged women with generalised OA have been shown to have lower circulating sex hormone binding globulin levels, implying that higher circulating free oestrogens and androgens are present [23]. However, no association between endogenous hormone levels and severity of hand OA was observed when the age and obesity adjusted sex hormone concentrations were compared by the worst Kellgren-Lawrence (X-ray) score or by the worst score of the individual radiological features of OA [24].

2.4. HRT and prevalence and incidence of OA

A number of studies in the last decade have examined the effect HRT on hip and knee OA. Most suggested that HRT has a protective effect on the prevalence of OA (Table 1) [10,21,25–30]. A meta-analysis of four of these studies, which used a combined end point of knee and hip OA showed a pooled odds ratio of 0.76 (95% confidence interval 0.63–0.91) [31]. Some studies were also able to demonstrate a dose-response effect [21,25]. Other studies suggested a reduction in severity of OA associated with HRT [21,32].

One study suggested that HRT had a detrimental effect on knee OA [30]. This study defined cases as being on the waiting list for knee arthroplasty. This study is flawed by an imprecise definition of exposure, with HRT use being defined if used after age 50, regardless of whether it preceded or postdated symptoms of OA or surgery, and used less than 0.65 controls per case. In addition to this, survivor bias may also have been present with women undergoing knee arthroplasty constituting a healthy woman effect, because this surgery is generally only offered to well patients.

There have been three studies of incident knee radiographic OA (Table 2): two cohort studies suggested HRT to have a protective effect on the risk of developing knee OA, and one retrospective nested case-control study suggested an increase in risk of incident symptomatic OA at any site [32–34]. However, all confidence intervals included unity. The Framingham study suggested a trend of HRT to reduce radiographic progression of OA [32].

2.5. Study limitations

All studies of women on HRT have a number of limitations. Despite attempting to adjust for confounders, women who use, and remain on HRT, differ from women who do not. These differences may be associated with the risk of OA also, such as age, weight, socio-economic status and bone mineral density. For example, HRT is often used to protect against osteoporosis, and there is some evidence for an inverse relationship between osteoporosis and OA [22,35]. Women

Table 1
Studies examining the relationship between postmenopausal HRT and prevalence of OA^a

Study	Year	Design	N	Joint/s	OA definition	Outcome (95% CI)
Hannan [25]	1990	Cohort, cross-sectional	615	Knee	Radiographic	Ever estrogen use, reduced any knee OA, OR 0.93 (0.62–1.4); Estrogen use > 4 years, reduced bilateral knee OA, OR 0.52 (0.25–1.09)
Samanta [10]	1993	Case-control	690	Hip, knee	Symptoms + X-ray	Ever HRT use: large joint OA, OR* 0.31 (0.07–1.35); large joint + hand OA, OR* 0.59 (0.19–1.89)
Wolfe [26]	1994	Case-control	1129	Knee, hip	Symptoms + X-ray	Ever HRT use: reduced radiological abnormalities
Nevitt [27]	1996	Cohort, cross-sectional	4366	Hip	Radiographic ± symptoms	Current HRT; reduced risk of OA, OR 0.62 (0.46–0.86)
Spector [28]	1997	Cohort, cross-sectional	606	Knee, hand	Radiographic (osteophytes, knee, DIP, CMC)	Current HRT: reduced risk of: knee osteophytes, OR 0.31 (0.11–0.93); hand DIP, OR 0.48 (0.17–1.42)
Vingard [29]	1997	Case-control	503	Hip	Hip arthroplasty	HRT > 1 year reduced end-stage hip OA, OR 0.7 (0.5–1.0)
Dennison [21]	1998	Case control	826	Hip	Hip arthroplasty	HRT < 5 years Prior to OA, reduced disease OR 0.5 (0.2–1.2); HRT ≥ 5 years; prior to OA, reduced disease OR 0.5 (0.2–1.5)
Sandmark [30]	1999	Case control	153	Knee	Knee arthroplasty	Oestrogen exposure after age 50, before and/or after surgery, OR 1.8 (1.2–2.6)

^a OR: adjusted odds ratio (OR*: crude OR), DIP: distal interphalangeal joint.

Table 2
Studies examining the relationship between incident radiographic OA and HRT

	Year	Study design	Cases	Outcome	HRT	Adjusted OR (95% CI) ^a	Comments
Fallon CHP [34] ^b	1996	Nested case control	60 cases (29 knees)	Incident hand, hip or knee OA	Ever use: ongoing use; past use; long-term use	1.5 (0.7–3.4); 1.4 (0.6–1.9); 0.7 (0.3–1.9); 1.0 (0.4–2.8)	Confounders: weight, CHP visits; low % oestrogen use
Framingham [32]	1998	Cohort-8 year follow up	112 knees	Incident knee OA	Past use: current use	0.8 (0.5–1.4); 0.4 (0.1–3.0)	Trend to reducing X-ray progression
Chingford [33]	1999	Cohort-4 year follow up	95 women	Incident knee OA	Ever use: current use	0.7 (0.3–1.7); 0.4 (0.1–1.4)	

^a Adjusted for body mass index, and other confounding factors in the study.

^b CHP: community health plan, cases identified by radiographic and symptomatic incident hand, hip and knee OA.

taking HRT have higher bone mineral density than those who do not. With increasing bone mineral density, bone stiffness may be increased. This may place increased mechanical stress on the overlying articular cartilage, which results in cartilage damage [36]. Alternatively, 'bone forming' women have higher bone mineral density and are more likely to develop the hallmarks of OA [31]. Despite some studies attempting to adjust for such differences (i.e. bone density), residual confounding may remain.

2.6. Conclusion: HRT and OA

The hormonal changes occurring around the menopause appear to modulate the changes of OA. Oestrogens may have a role in triggering the initial changes in proteoglycan in cartilage, either directly or indirectly via cytokines [31,37]. The efficacy of this trigger may be modulated by the state of the articular cartilage and the individual's genetic make-up. However, the response to HRT is somewhat paradoxical to the menopause relationship, suggesting we do not yet understand the mechanisms involved.

In post-menopausal women, the use of HRT reduces radiological disease progression and may prevent incident disease. Although the evidence supporting this is mounting, strong evidence from randomised controlled trials is lacking.

3. Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a multi-factorial disease in which both environmental and genetic factors play a role in disease initiation. Many observations suggest a possible effect of changes in sex hormone levels on the pathogenesis of RA, especially the strong age and sex distribution of disease [38]. In a population of 564 patients with RA, the onset of symptoms was studied in relation to age, sex and last menstrual period for women [39]. The median age of first symptoms was 45 years in women and 50 in men, with the average woman developing the first symptoms at the time of her menopause. The female to male (F:M) ratio of all patients was 2.3; with increasing

age the F:M ratio decreased from 3.7 before 30 years of age to 1 after the 6th decade of life, with a peak at the age of 40–44 years. Some epidemiological studies suggested the risk of developing RA to be decreased in those women who used oral contraceptive [40–42].

4. Relationship of RA with fluctuations of sex hormone levels

The age of menarche, parity and menopause bear no relationship to the age of onset of RA. This has been demonstrated in many large, methodologically different studies [43–45].

Many observations, made in both the clinical and laboratory settings, suggest that RA disease activity is sensitive to sex hormone level fluctuations. For example, disease activity in women with RA has long been recognised to remit during pregnancy [46]. In premenstrual women, disease activity may fluctuate with menstrual cycle [47]. Additional evidence for a role of oestrogen in disease modulation comes from experimental models, where changes in hormonal status have been shown to affect disease activity. In collagen induced arthritis, oophorectomy will exacerbate disease, whereas oestrogens suppress disease activity [48,49].

It has been suggested that prolactin, not oestrogen, may account for the observations relating to RA and the peri-partum period. The risk of RA developing within the 1st year following a live birth is significantly increased [50]. High prolactin levels during this period have been proposed as the mechanism. Breast-feeding and infertility, two factors associated with increased prolactin levels, have both been shown to increase the risk of developing RA [51–55]. Prolactin has been shown to have proinflammatory immunomodulatory properties [56,57]. A connection between the prolactin gene, is found on the short arm of chromosome 6, near the HLA region, and susceptibility to RA has been proposed. In women who had developed RA within the first 12 months after a live birth, breast-feeding was more common in women who were HLA-DR4 positive [58]. In those women, the most common allele was

DRB1*0401. The same group demonstrated that in women with RA, this allele associates with microsatellite markers close to the prolactin gene, suggesting either a possible biologic interaction between the prolactin gene and HLA status, or linkage disequilibrium [59].

4.1. Abnormalities in sex hormones in patients with RA

A number of studies have examined the association between sex hormones and RA. The concentrations of sex hormones were studied in women with RA, including 19 who were postmenopausal [60]. These women were compared with 20 postmenopausal controls. Androgen levels were higher in the postmenopausal women with RA compared to their controls. However, this may be age related, with others having shown reduced DHEA in premenopausal women with RA [61]. Other studies examining testosterone levels found no difference between RA patients, not treated with corticosteroids, compared with controls, although those so treated had lower total testosterone and sex hormone binding globulin [62].

Certainly in men with RA, a hypogonadic condition, characterised by low total serum testosterone, seems associated with active disease. In an open trial of testosterone therapy in men with RA, correction of this deficiency normalised the CD4:CD8 ratio and reduced NSAID use and tender joint count [63]. Disease flared in two of three men on withdrawal, suggesting a role for androgens in maintaining immunosuppression in this disease.

4.2. The role of dehydroepiandrosterone in RA

Dehydroepiandrosterone (DHEA), an adrenal product, is the major androgen in women. DHEA has immunomodulatory properties: in vitro it affects IL2 secretion by activated T lymphocytes and reduces IL4, IL5 and IL6 production and in vivo an inverse correlation exists between elevated levels of IL12 in premenopausal women with RA and reduced levels of DHEA [64,65]. Thus any changes in the level of DHEA may affect the activity of RA.

DHEA levels are low in both men and premenopausal women with RA [66–68]. Recent data have suggested that levels of this hormone may be depressed before the onset of disease in premenopausal women [69]. However, another study, albeit with limited power to refute this, found no change [70].

However, the role of DHEA in the postmenopausal woman with RA remains controversial, with early studies of postmenopausal women with RA finding an increase in DHEAS, others describing no difference, and recent studies consistently finding a reduction [66,67,71–73]. Postulated reasons for these discrepancies include differing disease durations and differences in the definitions of control groups [74].

Whether low DHEA is a primary or a secondary phenomenon, related either to the chronic disease state or an abnormality of adrenal function in RA, is unknown. In postmenopausal women with RA, a weak inverse correlation exists between DHEA levels and disease duration, measurements of damage as a result of disease and duration of morning stiffness [67]. No consistent correlation between markers of disease activity and DHEA levels has been found, suggesting only a relationship with the chronic disease state. An alternative hypothesis suggested that low levels of DHEA may relate to dysfunction of the hypothalamic-pituitary-adrenal axis in patients with RA, with reduced levels seen in these subjects despite otherwise normal adrenocortical function [75].

Concerns regarding cardiovascular disease may preclude long-term androgen therapy in women, especially if the benefit of such therapy is marginal. A double blind randomised placebo controlled study of testosterone therapy in postmenopausal women with RA showed minimal efficacy [76]. This study also had a high drop out rate, mainly for inefficacy.

4.3. Mechanisms by which oestrogens may affect RA

It has been suggested that polymorphism of the oestrogen receptor may be integral to the triggering of RA, especially in premenopausal women. Indeed the age of developing RA in women was

associated with different oestrogen receptor genes [77]. This suggests that the combination of perimenopausal hormonal changes and the differing morphology of the oestrogen receptor act in combination to affect the age of onset of RA, although other groups have yet to confirm this finding.

The tendency of RA disease activity to be sensitive to hormone level fluctuations may be as a result of the role of Th1 lymphocytes in driving this disease [64]. The reduction in disease activity seen in pregnancy may be related to the increase in Th2-type anti-inflammatory cytokines (IL10) [64]. This effect reverses in the post-partum period associated with a fall in IL10 [64].

4.4. Does HRT affect the risk of developing RA? (Table 3)[45,78–82]

Most case control studies have shown no effect of HRT on the risk of developing RA [78,79,82]. One of these showed a reduction in risk among women who had ever used non-contraceptive oestrogens with a progestin component of 34% (OR 0.66, 95% CI: 0.40–1.08) [82]. However, no dose-response relationship was seen.

Only one case control study found that use of non-contraceptive HRT provided a fourfold risk reduction of developing RA (OR 0.22, 95% CI 0.07–0.66) [45]. No duration-response association was found. This study is flawed by a failure to

confirm the temporal association between the onset of symptoms and the use of oestrogen therapy.

Cohort studies have shown no effect of HRT on the risk of developing RA. The largest excluded a twofold increase or reduction in the risk of developing RA in post-menopausal women who were current, past or ever users of HRT [80].

4.5. Does HRT have an effect on disease activity in RA?

A small, prospective, double blind cross over study of HRT in pre- and post-menopausal women with RA showed a tendency towards general improvement in the treatment group [83]. However, no distinction was made between the pre and post-menopausal women.

No effect of HRT on RA disease activity has been found in subsequent randomised double blind, placebo controlled trials [84,85]. Although no effect on disease activity has been observed, one study found an increase in pain in the HRT treated group, and the other, a larger study showed an improvement in well being. Both studies had high withdrawal rates and the authors noted a high probability of poor-compliance.

4.6. Conclusions: HRT and RA

Although sex hormone changes appear to play a role in RA, current evidence suggests that HRT

Table 3
Studies examining the effect of HRT on incidence of RA

Author	Year	Method	Subjects	Definition of HRT use	Result ^a
Linos [78]	1983	Case-control	687	Postmenopausal oestrogen \pm progestin	OR 0.9–1.2 (0.2–4.7)
Vandenbroucke [45]	1986	Case-control	663	Any non-contraceptive hormone use	OR 0.35 (0.18–0.68)
Carrette [79]	1989	Case-control	416	Ever users of HRT versus never users	OR 0.9 (0.56–1.44)
Hernandez-Avila [80]	1990	Prospective cohort	906 851 person years	Ever use of post-menopausal hormone	RR 1.0 (0.7–1.4)
Spector [81]	1991	Retrospective cohort	4326	HRT current users versus never users	RR 1.08 (0.3–6.75)
Koepsell [82]	1994	Case-control	727	Ever non-contraceptive oestrogen use \pm progestin	OR 1.04 (0.7–1.55)

^a Adjusted OR (95% confidence intervals); RR: relative risk.

use by post-menopausal women does not affect the risk of developing RA. Neither has a major consistent effect of HRT has been noted on RA disease activity, as measured by laboratory or clinical parameters. However, the beneficial effect on bone mineral density, and possibly improved well being, justifies its use in this clinical setting.

5. Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a multifactorial disease with both genetic and environmental aetiology. It is markedly more prevalent in women than in men. Its incidence is highest in pre-menopausal women, with increasing incidence after puberty.

There is observational evidence to suggest that SLE disease activity is affected by the sex hormone status of the individual, and that SLE may cause abnormalities in hormonal metabolism. Symptoms of SLE may vary during the menstrual cycle, and a hypoestrogenic state and abnormal oestrogen metabolism have been described in this disease [86]. The effect of pregnancy on the activity of SLE is controversial, with some studies showing no effect and others exacerbation of disease [87–89]. Oral contraceptives can induce antinuclear antibodies [90]. Cyclophosphamide induced premature ovarian failure has been associated with a reduction in disease flares, suggesting that a hypoestrogenic state is protective of disease flares [91].

5.1. Sex hormone levels in SLE

Abnormal levels of sex hormones have been demonstrated in patients with SLE, including elevated 16α -hydroxyestrone and oestriol and reduced levels of circulating androgens [92,93]. Whether these changes are primary or secondary to the disease process has not been elucidated — studies directly measuring sex hormone status prior to disease onset are unlikely to be performed.

5.2. Mechanisms by which oestrogen may affect SLE

Oestrogen has been suspected of causing changes in the lupus disease process, possibly by alterations in cytokine production and function. It has been suggested that the depression of cell mediated immunity, natural killer cell function and T suppressor cell function, theoretically combining to promote T helper function and promotion of immunoglobulin production, may be involved [94,95]. Other suggested factors include demonstrations in mice with experimental SLE of significant elevations in IL-1 and TNF- α and reductions in IL-2, IL-4 and IF- γ levels compared with the levels seen in healthy controls [96]. These abnormalities normalised with treatment by either the anti-oestradiol antibody or with tamoxifen, suggesting a role for oestrogen in cytokine modulation. In vitro, 17- β -estradiol has been shown to augment pokeweed mitogen induced B cell differentiation in normal human peripheral blood mononuclear cells [97].

Animal model evidence suggesting sex hormone differences affect SLE comes from the differential survival and disease outcome in male and female NZB \times NZW F1 (B/W) mice. These differences are reduced by the castration of male mice [98]. Androgens, also shown to be immunosuppressive, have been shown to ameliorate disease in experimental studies in mice [99].

Oestrogens have been shown to affect immunoglobulin function and production. A proposed mechanism for the conversion of photosensitivity to subacute cutaneous lupus erythematosus relates to the ability of oestradiol to facilitate the binding of anti-SS-A/Ro and anti-SS-B/La to human keratinocytes [100]. Other in vitro studies have shown that oestrogen increases production of anti-double stranded DNA antibody and immunoglobulin production by mononuclear cells from patients with SLE [101]. Thus there are many levels of the immune system upon which oestrogens appear to have an effect, which may affect disease activity in SLE: by affecting cytokine level, immune cell function (directly or indirectly), antibody binding or anti-body production.

5.3. Dehydroepiandrosterone (DHEA) in SLE

DHEA levels have been shown to be low in subjects with SLE, regardless of age, sex, or disease activity [93,102,103]. Levels tend to be lower in those patients receiving steroid therapy [103]. DHEA has been shown to have immunomodulatory functions in vitro, and to correlate with soluble IL-2 receptor levels in female SLE patients [103–106].

In open trials of DHEA in female SLE patients with mild to moderate disease activity, a significant effect was seen on disease activity and prednisolone dose in follow up of up to 12 months [107,108]. Randomised placebo-controlled, double-blind controlled trials of DHEA in severe SLE have also been performed. In the larger, DHEA enabled steroid reduction [109]. In the smaller, DHEA treated subjects failed to show statistically significant improvement although the authors felt improvement did occur [110].

5.4. Potential benefits and risks of HRT in women with SLE

Women with SLE have the potential to benefit greatly from HRT because they are at increased risk of osteoporosis and IHD [89,111]. These elevated risks may be attributable to prolonged corticosteroid use, ovarian dysfunction, an increased incidence of premature menopause, longstanding disease and medication use [112].

The concern regarding the use of HRT in these women stems from clinical and laboratory evidence which suggests that elevated oestrogen levels may affect both the risk of developing SLE and the degree of disease activity. In some animal models, an oestrogenic state has been shown to accelerate disease [113]. Abnormal oestrogen metabolism has been described in women with SLE. Onset or aggravation of symptoms by use of the oral contraceptive and high dose oestrogens used in ovarian induction therapy have been described in case reports and small retrospective series of women with SLE [113–115].

Also, there is concern regarding the increased potential for thrombosis related to HRT, espe-

cially patients who also have an anti-phospholipid antibody who may already have a thrombotic tendency.

5.5. Does HRT affect the risk of developing SLE?

Weak evidence from a case-control study using the UK General Practice Research Data base suggested that unopposed oestrogens may increase the risk of developing SLE and discoid LE, over and above the risk of combined oestrogen and progestogen therapy [116]. This study showed current but short term oestrogen exposure was not associated with increased risk of developing SLE. However, the risk of developing SLE (adjusted OR 2.8; 95% CI 0.9–9.0) or discoid lupus (adjusted OR 2.8; 95% CI 1.0–8.3) was significantly increased among current users, exposed for 2 or more years, suggesting a dose response effect.

An investigation of the Nurses' Health Study, a prospective cohort, has suggested that postmenopausal hormone therapy is associated with a small increased risk of developing SLE [117]. This study used 631 551 women years (69 435 women) of follow up. Subjects without SLE or connective tissue disease, aged 30–55 years in 1976, entered the study upon entering menopause. All were followed every 2 years from 1976 to 1990. With never-users of postmenopausal hormones as the reference group, age-adjusted relative risks for SLE ($n = 45$ women) were 2.1 (95% CI, 1.1–4.0) for ever-users, 2.5 (CI, 1.2–5.0) for current users, and 1.8 (CI, 0.8–4.1) for past users. A proportional increase in the risk for SLE was observed that was related to the duration of use of postmenopausal hormones (test for trend, $P = 0.011$).

5.6. Does HRT affect disease activity of SLE?

Despite concerns regarding the safety of HRT in post-menopausal women with SLE, there is experience suggesting that its use is safe in many cases (Table 4) [118–121]. These mainly observational studies are limited in that they tend to be studies of patients with mild disease. Nevertheless,

Table 4
Studies of the safety of HRT in SLE

Study	Year	Method	Subjects	Flare	Results	Adverse events
Arden [118]	1994	Retrospective case control	60 (30 on HRT)	Clinical	No difference over 12 months in disease activity	One TIA 6 weeks after HRT stop
Buyon [119]	1995	Retrospective observation	48	Clinical	No control group, four subjects flared	
Kreidstein [120]	1997	Prospective case control	48 (16 on HRT)	Change in SLEDAI ^a	No difference in rates of disease flares	One DVT; one migraine
Mok [121]	1998	Prospective cohort	34 (11 on HRT)	Change in medication, serological	No difference in flares or disease activity	None

^a SLEDAI: systemic lupus disease activity index, utilises clinical and serological markers of disease.

the incidence of documented flares of disease activity and generalised increase in disease activity is low, although the durations of therapy studied were relatively brief. Also, small numbers of subjects with positive screens for anti-phospholipid antibodies were included, only two subjects experienced thrombotic events possibly related to HRT (TIA, DVT). One patient discontinued for an increase in frequency of migraines, attributed to HRT.

A randomised placebo controlled trial studying the safety of HRT in SLE, the safety of estrogens in lupus erythematosus-national assessment (SELENA) Trial, is currently in progress. It is a randomised placebo-controlled multi-centre American study of 600 postmenopausal women with SLE; 300 receiving 0.625 mg conjugated oestrogens daily for 12 months and 0.5 mg medroxyprogesterone acetate for 12 days each month, and 300 receiving placebo. It is to be hoped that when the results of SELENA become available, definitive guidelines regarding the use of HRT in postmenopausal women with SLE will be made [122].

5.7. SLE recommendations

Counselling of women on the use postmenopausal hormones should include a discussion of these risks and benefits in addition to the risks of cardiovascular disease, uterine and breast cancer, and osteoporosis. Although HRT may increase the risk of developing SLE by a factor of 2, this information must be taken in the context of SLE being a rare disease, with low incidence in the post-menopausal woman. It is still unclear as to which women are at increased risk, or whether different schedules of HRT affect this risk.

HRT is useful and safe in patients with stable SLE, provided there is close follow-up, particularly during the first 6 months of treatment. Treatment with oestrogen is contraindicated in SLE patients with a history of thromboembolism, positivity for phospholipid antibodies, and in the presence of severe organ involvement, such as renal disease.

6. Carpal tunnel syndrome

It has been suggested that carpal tunnel syndrome is also sensitive to sex hormones, although the evidence here is weak. It is more common in women than men [123]. It often occurs in women associated with pregnancy, menopause and obesity, but its pathophysiology is not well understood. Carpal tunnel syndrome has been reported to have been precipitated by iatrogenic menopause [124,125]. Additional evidence supporting steroid hormones playing an aetiological role in this condition comes from a study of megestrol acetate, in which symptoms of carpal tunnel occurred in 4% of subjects [126].

The role of HRT in carpal tunnel syndrome is most unclear. HRT has been associated with improvement of symptoms in some postmenopausal women [2,127]. However, a case-control study found evidence to the contrary: women who underwent carpal tunnel release were more likely to be users of HRT than controls (who did not have carpal tunnel syndrome) [128]. This study was unable to relate symptoms to prescription of HRT or the menopause.

6.1. Conclusions: carpal tunnel syndrome and HRT

Although carpal tunnel syndrome appears to be affected by sex hormone status, the role of HRT in its aetiology or modulation of symptomatology is currently undefined.

7. Conclusion

The menopause coincides with the appearance of many of the common arthritic conditions, including OA and RA, and with the lessening of severity of others such as SLE. There is an increasing body of evidence suggesting that these diseases may be hormonally sensitive. Thus, use of HRT may modulate both the risk and the expression and disease activity of these common rheumatologic diseases. However, as yet, we know little of the mechanisms involved.

Indeed, there is an increasing body of evidence to suggest that oestrogen replacement therapy prevents OA, and reduces the risk of severe disease. Most RA patients would benefit from osteoprotection with HRT, despite little disease modifying effect having been demonstrated. Stronger evidence supports minor increase in incidence of SLE in users of HRT, although this should be taken in context of SLE being a rare disease, especially in the post-menopausal woman. However, HRT is a useful and safe drug for women with stable SLE, but we need to be cautious for those with renal involvement or severe disease. Nevertheless, many questions remain unanswered, but studies are proceeding to resolve these issues.

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