Autoimmune diseases and reproductive aging

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Abstract

As the population ages, more individuals with autoimmune diseases are experiencing reproductive senescence. Understanding the impact of menopause and age-related androgen decline on disease onset and course, as well as the potential for hormonal interventions, is critically important. In men, lupus erythematosis (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS) are associated with lower androgen levels. However, the impact of age-related declines in testosterone, as well as of testosterone replacement, on disease course remains underexplored. In women, the course of all three diseases with onset after the age of menopause differs from that with onset before menopause. Early age at menopause is associated with increased disease risk, and after menopause, disease course changes in SLE and RA. Less is known about MS. This article summarizes what is known about the relationship between reproductive aging and autoimmune diseases in men and women, and highlights areas for further investigation.

Keywords

Multiple sclerosis; Systemic lupus erythematosus; Rheumatoid arthritis; Menopause; Andropause; Hormone replacement therapy

1. Introduction

Studies of autoimmune disease onset and course during reproductive transitions such as puberty and pregnancy have highlighted the modulatory role of gonadal hormones. Less is known about the impact of reproductive senescence (menopause and age-related androgen decline) on autoimmune diseases. This article reviews what is known about the effect of reproductive aging, first in men and then in women, on systemic lupus erythematosis (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS). Data are obtained from a Pubmed search, until November 30 2012, without language restrictions, for all papers combining one of the terms "menopause", "andropause", "hormone" "estrogen" or "testosterone" with one of the terms "lupus", "rheumatoid arthritis", "multiple sclerosis" or "autoimmune". Where comprehensive reviews are available, these are included rather than individual studies. The aim is to highlight relatively unexplored questions, and central avenues for further research.

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2. Age-related androgen decline in men and autoimmunity

2.1. Protective effects of testosterone

Testosterone's impact on the immune system is, on aggregate, anti-inflammatory. Specific mechanisms include: (1) lower secretion of IL-1 , IL-6, TNF, and other pro-inflammatory mediators by monocytes and macrophages; (2) increased production of anti-inflammatory IL-10 by T cells and (3) inhibition of the NF -mediated activation of the IL-6 gene promoter in human fibroblasts, and of T cell proliferation in animal models.

MS is a chronic demyelinating disease that in addition to an inflammatory component as is the case for SLE and RA, is also characterized by neurodegeneration. Testosterone has been shown to be not only inflammatory but also neuroprotective in animal models of MS, through mechanisms including regulation of gliosis, protection of spinal cord neurons in culture from glutamate-mediated toxicity and of cultured neurons against beta amyloid toxicityinduced cell death, induction of neuronal differentiation and neurite outgrowth, and increased cell survival in the dentate gyrus promoting hippocampal neurogenesis (Reviewed in [5]).

2.2. Hypoandrogenism and inflammatory diseases

In animal models of SLE, RA and MS, androgen deficiency following castration has resulted in a more inflammatory milieu and increased disease activity [6–9]. Treatment of castrated animals with testosterone, particularly DHT (which cannot be aromatized to estrogens, thus demonstrating androgen-specific effects) has resulted in alleviation of symptoms and inflammation [7,10–12].

In men, a higher prevalence of autoimmune diseases has been suggested in patients with hypogonadism [13]. In fact, relative androgen deficiency has been noted in some, but not all, studies of men with SL [14–23], RA [24–34] and MS [35–38] (Table 1). Limitations of some of these studies include low numbers of subjects, variable definitions of androgen deficiency, and lack of control for marked diurnal cyclicity of testosterone levels. Additionally, some failed to account for the effects of corticosteroid use, which even in low doses may suppress the hypothalamic–pituitary–testicular axis [27], as well as of disease duration and disease status; a negative correlation has been noted between androgen levels and disease activity in RA [24]. In SLE and RA, these findings are not attributable to increased renal clearance [39]. Nonetheless, altogether existing studies do point to both hypogonadotropic as well as testicular patterns of hypogonadism in men with SLE, RA and MS. It is mostly not possible to establish causality, i.e. to determine whether low testosterone levels are risk factors for autoimmunity, or rather, sequelae of chronic illness. Notably, one study of subjects with RA noted low testosterone levels very early in the course of RA, with increases observed over a 2-year period in patients who responded to disease modifying treatments [33].

2.3. Age-related androgen decline and autoimmune diseases

In humans, a gradual decline in function of the male hypothalamic–pituitary–gonadal axis occurs with age. This is marked by decreased central regulation by the hypothalamus and pituitary, as well as by decreased testicular function, including decreased number and function of testosteroneproducing Leydig cells, and decreased number and secretory function of sperm-producing testicular Sertoli cells [40]. Thus, average total testosterone levels in healthy men decrease from 617 ng/dL in men aged 25–34 years to 606 ng/dL in men aged 45–54 years, and to 471 ng/dL in men aged 75–84 years, without any abrupt cutoff [41]. Given the gradual changes that occur in men, there is likely not a clear period of symptomatic change, or "andropause", that would be analogous to the menopausal transition

in women [42,43]. Thus, while men may over time experience decreases in androgen levels, these levels may not necessarily correlate with specific symptoms such as muscle mass or libido, or with response to androgen therapies.

Epidemiologically, it has been hypothesized that the later age of onset of MS in men relative to women, and the peak presentation of SLE and RA in older men [44], may be secondary to an age-related decline in protective testosterone levels in men. Most studies summarized in Table 1 linking low androgen levels and inflammatory diseases focused on younger male populations, and hence did not explicitly assess for any effect of age-related declines in testosterone levels. To our knowledge, no studies have specifically assessed the impact of ARAD on autoimmune diseases. Furthermore, there is limited literature regarding the interaction between androgen deficiency and clinical course, in terms of either outcomes or comorbidities [45].

2.4. Limited clinical trials of androgen therapy in men with autoimmune diseases

2.4.1. SLE

2.4.1.1. Testosterone: No trials of testosterone have been reported in men with SLE.

In 34 women with mild to moderate SLE, a 150 μg testosterone patch administered for 12 weeks in a randomized, double-blind, single-centre placebo-controlled trial did not result in increased adverse events or laboratory safety parameters (e.g. full blood count, erythrocyte sedimentation rate, creatinine, liver function tests, cholesterol) but nor was it effective in affecting disease [46].

2.4.1.2. DHEA: The oral adrenal androgen DHEA has been administered in women with SLE, with three prospective studies demonstrating increases in testosterone levels after treatment, as well as decreasing disease activity [47,48] and flares [49]. Main side effects were mild acne and hirsutism. However, a Cochrane review of seven randomized controlled trials found that DHEA offered little clinical benefit in patients with mild or moderate SLE, but did yield some modest increases in health-related quality of life measures [50].

2.4.2. RA

2.4.2.1. Testosterone: Two trials of testosterone therapy have been reported in men. In an open-label study, oral testosterone undecanoate administered daily for 6 months to 7 male RA patients of mean age 57.9 years (+/−9) led to a significant increase in testosterone levels and in the number of CD8+ T cells, and to a decrease in the CD4 + (helper): CD8+ T-cell ratio and in the IgM rheumatoid factor. There was also a decrease in the number of affected joints and daily intake of NSAIDS [51]. However, in a placebo-controlled trial of 30 men aged 34–79 years with RA, randomized to receive monthly injections of testosterone enanthate 250 mg or placebo as an adjunct therapy for 9 months, there were significant rises in serum testosterone, dihydrotestosterone and estradiol in the treatment group but no effect of treatment on disease activity [52].

In women, early studies suggested that testosterone propionate treatment led to significant improvement or remission in RA, but treatment was limited by masculinizing side effects [53]. More recently, a double-blind placebo-controlled study of testosterone administration in 57 postmenopausal women revealed clinically relevant improvement in 21% patients [54]. Furthermore, testosterone therapy has been shown to increase DHEA-s levels in RA patients.

Synergistic interactions in RA between androgens and both immunosuppressive agents (cyclosporin A (CSA) [1–3], methotrexate [4]) and anti-IL-6 receptor antibody [55],

including androgenizing effects, have also been explored. These associations should be confirmed, as they may provide a rationale for androgen therapy as an adjuvant to disease modifying treatments.

2.4.3. MS

2.4.3.1. Testosterone: In a pilot clinical trial of 10men with MS (age < 65 years), treatment with testosterone gel for 12 months was associated with significant improvement in cognitive performance, slowing of the rate of brain atrophy [56], reduced delayed type hypersensitivity (DTH) skin recall responses, and immunologic shift in peripheral lymphocyte composition, with fewer CD4+ T cells and more NK cells [57]).

3. Menopause and changes in endocrine and immune function

3.1. Menopause

The menopausal transition involves a much more defined and time-limited series of physiological changes associated with reproductive senescence, divided into a series of stages [58]. Operationally, menopause is defined as the final menstrual period (FMP), after which no further menses occur during a 12-month interval. The mean age at menopause in Western societies is 49–52 [59,60].

3.2. Endocrine changes at menopause

The endocrine changes associated with menopause have historically been thought to arise from ovarian follicular depletion and degradation, with compensatory hypothalam-ic and pituitary changes. As follicles become exhausted, the ability of the ovary to produce estradiol is compromised, and hence the ability of estradiol to stimulate ovulation and endometrial buildup [61]. As ovarian production of estradiol and estrone declines premenopausally, FSH production by the pituitary is stimulated and can rise or fluctuate in an attempt to drive increased estrogen production [62].

Decreases in estradiol may occur only very late perimenopausally, in the last six months before menopause ([58], Fig. 1). However, starting in the fourth decade, or early perimenopause, there is gradual decline in progesterone, leading to luteal phase defects. As estradiol and progesterone levels become more erratic, cycle length may fluctuate and even accelerate premenopausally, before the eventual spacing and cessation of cycles [61,63–66]. After menopause, the primary endogenous source of estrogen is estrone, which is synthesized in adipocytes from androstenedione (progesterone derivative), via aromatase. In contrast to the sudden fall in estradiol during menopause, the levels of total and free testosterone, as well as dehydroepiandrosterone sulfate (DHEA-s) and androstenedione appear to decline more or less steadily with age. An effect of natural menopause on circulating androgen levels has not been observed [67].

However, more recently, a more central role for hypothalamic–pituitary–gonadal axis (HPG axis) dysfunction in triggering menopause, independently of its compensatory role in response to follicular depletion, has been implicated in rodent, primate and human studies (first rodent studies [68], reviewed in [69]). There is impaired hypothalamic response in middle-aged females to the positive feedback that E2 typically exertson GnRH neurons, and on the balance between excitatory and inhibitory signals leading to the LH surge; this impaired response can lead to an LH surge induction ranging from normal to failed. In humans these changes accelerate in the years closer to menopause [70]. This aberrant HPG responsiveness likely leads to ovarian dysregulation, including luteal phase abnormalities due to aberrant E2 secretion, variable cycle length, and increasing ovarian folliculogenesis in turn accelerating follicular depletion [71,72].

Altogether then, menopause is characterized by a complex interaction between central endocrine regulation and peripheral follicular responsiveness, leading to fluctuating cycle length and E2 levels, and ultimately to lower E2 and P levels, peaking of FSH levels, follicular depletion, and irreversible cessation of menses.

3.3. Immune changes at menopause

During periods of endocrine change, such as menses and pregnancy and with exogenous use (HRT, OCP), immune changes have been observed [73–75]. The endocrine changes occurring at menopause induce changes in immune function,

in addition to those associated with immunosenescence [76]. Thus, declining levels of estrogen and DHEA sulfate may be associated with increased production of proinflammatory cytokines (IL1, IL6, TNF-alpha), and increased physiologic response to these cytokines, decreased secretion of antiinflammatory cytokines (INF-gamma), decreased lymphocyte levels (CD4+ T cells, B cells), and decreased cytotoxic activity of NK cells. Conversely, immune changes may also lead to endocrine changes associated with menopause. For example, changes in lymphocyte composition and continuous rather than cyclical secretion of cytokines may accelerate ovarian follicular atresia (See [77,78] for review). Postmenopausal hormone therapy may mitigate these changes in the cellular immune response [79–81].

3.4. Associations between menopause and autoimmune diseases

Investigations into the association between menopause and autoimmune disease onset and course have centered around four main areas of inquiry: (1) effect of age at menopause on disease onset and course; (2) subject and disease characteristics in individuals with "late onset", typically after 50; (3) impact of menopause on disease course and (4) modulatory effects of HRTs (Table 2).

3.4.1. SLE

3.4.1.1. Age at menopause: In the Nurses Health Study I and II, two landmark longitudinal epidemiological studies following 121,700 female registered nurses since 1976 (NHS I) and 116,000 female nurses since 1989 (NHS II) to assess risk factors for major chronic diseases in women, an early age at menopause, especially surgical, was associated with an increased risk of developing SLE [82].

3.4.1.2. Age of disease onset: Approximately 16% patients experience disease onset after the age of 50 [83]. In this group with later onset, the F:M ratio is usually lower than in individuals with earlier onset [84] (3:1 vs. 13:1 [85]). The median time to diagnosis is also longer than in subjects in addition to those associated with earlier presentation (5 years vs. 3 years), and there is a lower incidence of high titer anti-ds DNA and anti-Ro antibodies [83–85]. Finally, in subjects with later onset there may be a different distribution of specific symptoms; for example, a lower incidence of nephritis, malar rash, and photosensitivity has been observed. Women undergoing hysterectomy before disease onset were noted to have similar characteristics as individuals with onset of disease after age 50, suggesting a role for gonadal hormones in these observed differences [86].

3.4.1.3. Menopausal transition: Several longitudinal studies following female subjects through the menopausal transition have noted decreased frequency of flares after menopause, modestly decreased SLE Disease Activity Index (SLEDAI), but greater damage accrual in affected organs from individual flares in the postmenopausal period [87–90]. Cohort studies comparing pre- and post-menopausal subjects yielded similar findings [89]. It should be noted that the disease trajectories in these subjects were not compared with those

of age-matched males to control for the effect of advancing age. Fewer flares were also observed among younger women experiencing cyclophosphamide-induced ovarian failure than age-matched controls, suggesting a causative role for estrogen decline associated with menopause and not just age per se [91].

3.4.1.4. HRT

3.4.1.4.1. Disease risk: An increased risk of developing SLE has been associated with HRT use for 2 or more years in the Nurses Health Studies [82,92,93] as well as others [82,92,93], but this may be biased by misattribution of SLE symptoms to menopause, hence prompting HRT use.

3.4.1.4.2. Disease course: While there have been case reports of worsening flares after initiation of HRT, the randomized prospective placebo-controlled multicenter SELENA (Safety of Estrogens in Lupus Erythematosus-National Assessment) trial of HRT revealed no increase in severe, and a modest increase in mild-moderate flares in women taking combined estrogen-progestin replacement [94]. In contrast to the SELENA, other studies did not sub-stratify flares by disease severity, and found no increased rate of flares with HRT relative to placebo [95,96]. These results cannot be generalized to women with certain severe co-morbidities, such as severe disease activity at baseline, ischemic heart disease, prior history of thrombosis, or positive antiphospholipid antibody and lupus anticoagulant.

3.4.1.4.3. Disease sequelae: Increased risk of venous thrombosis or thromboembolism was noted in one large randomized controlled trial [97], but risk did not reach significance in SELENA (which excluded women with prior thrombosis and/or history of anticardiolipin antibody) [94]. Bone mineral density was better preserved in women with SLE taking 50 mg transdermal 17beta-estradiol than in women taking placebo, in one small study (N = 32, p < 0.005) [98].

3.4.2. RA

3.4.2.1. Age at menopause: It has been estimated that an average woman develops RA at the time of her menopause [99]. Later age at menopause has been associated with a decreased risk of RA (adjusted risk ratio of 0.64 with menopause after age 51 years vs. prior to age 45 [100]). This is true both for seronegative, and perhaps seropositive, RA [101]. These findings suggest that exposure to estrogen may be protective against the onset of disease. Interestingly, earlier age at menopause has also been associated with a greater proportion of patients presenting with a milder disease course [102], pointing to more complex interactions between hormone levels and disease subtypes.

3.4.2.2. Age of disease onset: Because median age of first symptoms of RA occurs later than in other inflammatory diseases (45 in women and 50 in men), late onset disease is usually considered after age 60. Late Onset RA is associated with a F:M ratio of 1 (vs. 3.7:1 in individuals younger than 30 [99]), as well as with higher frequency of acute onset, greater disease activity and functional decline, more systemic manifestations, proximal large joint involvement, similarity with polymyalgia rheumatica [103–105].

3.4.2.3. Menopausal transition: A cohort study following individuals early in disease course over 6 years found higher Radiographic Joint Damage s vcores and higher physical disability scores as reported in a Health Assessment Questionnaire in postmenopausal women than in premenopausal women or in male subjects [106].

3.4.2.4. HRT

3.4.2.4.1. Disease risk: The Women's Health Initiative (WHI), a landmark longitudinal study that included randomized controlled trials evaluating the effects of (1) unopposed estrogen and (2) estrogen plus progestin compared with placebo on a diverse set of health outcomes, noted no significant reduction in the risk of RA [107].

3.4.2.4.2. Disease course: While previous studies suggested decreased both risk of RA and disease activity with HRT [108], The Women's Health Initiative (WHI) noted only a non-significant improvement in joint pain scores among HRT users [107], and additional studies have yielded no significant association (e.g.[109]).

3.4.2.4.3. Disease sequelae: HRT has protective effects on bone density in women with RA [110–113].

3.4.3. MS—Less is known about the association between menopause and MS.

3.4.3.1. Age at menopause: The peak age of MS onset in women is 24 [114], i.e. before the menopausal transition.

3.4.3.2. Age of disease onset: In subjects with disease onset after age 50, F:M ratios are lower (1.9:1 vs. 2.8:1), disease type at onset is less frequently relapsing remitting (80% vs. 95% for females) and more frequently primary progressive, course is more rapidly progressive with fewer relapses or new gadolinium enhancing lesions, and symptoms more often involve motor and coordination symptoms and less often visual symptoms, than in individuals with disease onset between ages 18–49 [115–120]

Further, time to progression to an Expanded Disability Severity Scale (EDSS) of 6 (Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting) in women with late onset MS is more rapid than in women with earlier onset MS, and in contrast to the latter group, is as fast as that of men.

3.4.3.3. Menopausal: transition. In MS, advanced age is associated with worsening disability and accelerated conversion to progressive forms [116,117,121]. There are no objective data regarding the effect of menopause on MS disease outcomes. Menopause has been associated with patient-reported worsening of symptoms in 40–54% of women in two small studies [122,123] but not in a third study [124].

3.4.3.4. HRT: No objective data exist on the impact of HRTs on disease course. Patient reports differ vastly in the reported effectiveness of HRT, from limited utility to improvement in 75% patients [122–124].

3.5. Potential mechanisms

While epidemiologic data summarized in the previous sections point to an association between estrogen decline and disease onset or activity, the pathophysiological mechanisms are likely to be complex. Typically, high levels of estrogens (such as seen during pregnancy) are felt to shift T helper cell ratios from 1 to 2, leading to improved disease activity in RA but worsened in SLE. It would follow that the low levels of estrogens postmenopausally would lead to a decrease in the progression and severity of disease activity in SLE and worsened activity in RA, which has been observed.

However as summarized above, early age at menopause seems to increase risk of both SLE and RA. Furthermore, F:M ratios in later onset disease are decreased for SLE, RA and MS, relative to sex ratios in earlier-onset disease.

This points to complex interactions between estrogen levels and inflammation, and to immune changes regulated not only by changing estrogen levels but also by changes in androgens, progesterone, and estrogen/androgen ratios. Furthermore, some effects are likely mediated by hormonal changes on end organs affected by AIDs. Finally, in MS, decreasing estrogen levels postmenopausally are likely to affect not only inflammation but also neurodegeneration, yielding varying aggregate effects on disease course.

3.6. Non-immunological associations between menopause and autoimmune diseases

Other important aspects of menopause in autoimmune disease include but are not limited to: impact of inflammatory disease and its treatments (e.g. cyclophosphamide) on premature ovarian failure and age of menopause; additive effects of estrogen decline and inflammatory disease on other systems, e.g. cardiovascular; and exacerbation of postmenopausal bone loss in patients subjected to long-term glucocorticoid use (reviewed in [125]) (Fig. 2).

4. Conclusion

In summary, the endocrine changes occurring during the menopausal transition are associated with changes in disease risk, onset and course in women with SLE and RA. The effects of HRT on these outcomes, if any, are likely modest. In women with MS, the potential impact of menopause on disease course is unknown, and may be more complex given that both the inflammatory and neurodegenerative aspects of MS are under estrogenic regulation. Longitudinal assessment of disease course and of HRT effects through the menopausal transition and into the later postmenopausal years, is required. Comparison should be performed with men, to control for changes attributable to age itself. For MS, SLE and RA, exploring the synergistic effects of menopause and diseasespecific pathophysiology on function is important in evaluating the potential impact of HRT. In men, more longitudinal investigations are needed to determine a potential causal link between age-related hypoandrogenism and disease risk and progression, as well as the potential for intervention with androgen therapies.

Understanding this complex interplay between reproductive senescence and the course of autoimmune diseases is of critical importance to address the needs of, and minimize the progression of disability in, affected patients in our aging population.

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(1) **Clarification of the association between hypogonadism and disease.**
- **In MS particularly, studies with larger numbers, close to onset of disease to distinguish risk factors from sequelae of disease, using morning samples and controlling for prior/current steroid use, that assess for central vs. peripheral etiology of low testosterone levels.**

(2) **Clarification of causal link between hypoandrogenism and increased risk and severity of autoimmune disease**
- **Comparison of hormone levels from stored serum samples of presymptomatic subjects and healthy controls**
- **Prospective assessment of longitudinal effects of age-related androgen decline on disease susceptibility and course.**

(3) **Clinical trials: Efficacy of replacement therapy**
- **Pilot investigations in SLE**
- **Replication of potential effect in RA and MS, assessing effect of testosterone replacement on both testosterone levels and clinical response.**

(4) **Consideration of interactive effects**
- **Between genetic polymorphisms potentially associated with androgen decline, and both hormonal levels, HLA status and risk of AID [1-3]**
- **Between androgens and disease modifying treatments) [4-7]**

Figure 1.
Key areas required to clarify association between autoimmune diseases and male reproductive aging.

- **Impact of Menopause:**
  - **Longitudinal assessment of disease course from premenopausal through postmenopausal period**
  - **Inclusion of male cohort as a comparison group, to distinguish the effect of age from female sexual aging**
  - **Outcomes: include both clinical and patient-reported outcomes, given potential disconnect between clinical measures and subjective symptoms**
- **Efficacy of HRT:**
  - **Longitudinal analysis**
  - **Adjust for timing of initiation of HRT to assess for the "window of opportunity" phenomenon, during which HRT may be helpful but beyond which, due to estrogen receptor downregulation, HRT may no longer be effective**
  - **Consideration of symptoms prompting HRT, to distinguish menopause from disease-specific symptoms**
- **Distinguishing disease progression from menopausal symptoms**
  - **Synergistic effects of menopause and autoimmune disease (e.g. worsening of sexual function in women with MS)**
- **Additional Foci of Inquiry**
  - **Altered pharmacokinetics in therapies postmenopausally**

Figure 2.
Key areas required to clarify association between autoimmune diseases and female reproductive aging.

Table 1

Summary of investigations of androgen levels in male patients with SLE, RA and MS.

Only studies including 5 or more male patients are presented.

Unless noted, HC's refers to male age-matched healthy controls.

Unless noted, specimens were drawn in the am.

Ref	Study design	N	Age (years)	Androgen levels	Limitations/notes
SLE					
[14]	Cross-sectional descriptive	8 SLE cases,		4 had elevated plasma estradiol and estrone; 1 with low T and high LH; 1 with high LH and FSH	No mention of time of day No patients on corticosteroids
[15]	Cross-sectional descriptive	49 SLE cases	Mean 45(20–74)	25/49 cases with T below assay range (of these, 24 on corticosteroids, which suppress LH and only 1 of these 24 had elevated LH)	35 cases on corticosteroids
		49 HCs (for E assesment only)		36/49 with androstenedione and/or DHEAs levels below normal (of these, 31 on corticosteroids). Cases with higher mean E2 (p < 0.05); Elevated E1 in 10/49 cases vs. 0% HCS (p < 0.01); elevated E2 in 18/49 cases vs 3/49 HCs (p < 0.001).	No mention of time of day
[16]	Case control	10 SLE cases	Mean 39.6 (25–60)	No differences in T or E2 between cases and HCs (and no effect of steroid use on T or E2 in cases)	5 cases on corticosteroids
		10 HCs		Cases with lower T/E2 ratio (p < 0.05). Lower mean T increase after HCG stimulation in cases (p < 0.05)	
[17]	Case control	6 SLE cases		Cases with decreased androgen and increased estrogen.	Cases without prior steroid exposure
		4 HCs		Tendency toward an increase in aromatase activity in cases (skin and SC tissue); aromatase activity varied inversely with disease activity, and significant direct correlation with estrogen levels.	? Time of day
[18]	Case control	14 SLE cases 17 HCs		At least one abnormal level (FSH, LH or T) in 43% cases, 0 controls (p < 0.01); 35% cases with functional hypoandrogenism (high LH and/or low T). Cases with higher E2/T (lower T/E2) ratio (p < 0.03).	Excluded an additional 3 SLE cases with prior cyclophosphamide therapy or pre-puberty
[19]	Case control	7 SLE cases		No significant difference in basal T, FreeT.	Did not account for steroid use
		10 HCs		Significantly lower DHEAS androstenedione and E2; higher FSH levels; as well as E2 Impaired testicular (FreeT) response after HCG stimulation	
[20]	Case control	16 SLE cases 20 HCs	Mean 26 (19–46)	No significant differences in FSH, LH, testosterone, oestradiol, and beta-HCG levels in cases vs. HCs	All cases newly diagnosed and untreated

Ref	Study design	N	Age (years)	Androgen levels	Limitations/notes
				Higher prolactin in cases (p = 0.012)	
[21]	Case control	35 SLE cases 33 HCs	Mean40.1 (17–71)	No difference in T, E2, PRL and E2/T ratio; Significantly higher FSH (p = 0.004) and LH (p = 0.01); 14% cases and 0% HCs with low T and high LH. Higher PRL/T ratio in cases (p = 0.04); and ratio correlated with SLEDAI	Excluded prior cyclophosphamide, and renal failure, from study
[22]	Case control	23 SLE cases	Mean 46, median45 (24–69)	Lower mean DHEAS (1.9 nmol/L) and total T (8.9 nmol/L) levels than normal reference range. 2.5% with T levels below reference range.	Could not disentangle effects of steroid use; However, DHEAs but not T significantly negatively associated with daily and cumu-lative corticosteroid doses Did not control for prior steroid or chemotherapy use
[23]	Case control	25 SLE cases	Mean 27 (15–45)	No difference in total T; low T levels in 24% cases vs. 0% HCs (p = 0.022);	
		25 HCs		Higher mean FSH and LH levels (p <0.01)	Also found lower penile and testicular measurements incases than HCs
RA					
[24]	Longitudinal observational	10 RA cases		During hospital admission for flares, significantly lower total and free T levels than in post-hospitalization follow-up (p < 0.01)	Excluded 1 case with progressive testicular failure ? Steroids ? Time of day
[25]	Case control	14 RA cases OA controls		Lower T in cases than OA controls (p < 0.01)	?Steroids ?Time of day
[25]	Case control	8 RA cases 8 HCs		Failure of serum T to achieve nomral levels in response to hCG stimulation, vs HC's (p < 0.05)	?Steroids ?Time of day
[26]	Case control	87 RA cases 141 HC	Cases mean 58 (SD 11) HCs mean 35 (SD 9.4)	Significantly lower total and free T in cases vs. HCs (p < 0.001). Difference persisted after controlling for age differences.	Samples taken from 9 am-5 pm Only excluded current cortticosteroid users
[27]	Case control	12 RA cases off prednisone	62 (38–75)	Non-steroid users: Normal T, elevated LH and FSH (p < 0.01) vs. HCs	No prior steroid treatment
		24 RA cases on 5–10 mg/d prednisone 70 HCs		Steroid users: low T (p < 0.05), only slightly elevated LH and FSH vs. HCs; lower T, FSH and LH vs. non steroid cases	
[28,29]	Case control	14 RA cases 8 HCs		Lower mean T in cases (p < 0.001)	?Steroids ?Time of day
[30]	Case control	13 cases with new onset synovitis (<1 yr), fitting criteria for RA 32 HCs		Lower mean free T in cases vs. HCs aged 45+ (p < 0.03)	No prior steroid treatment

Ref	Study design	N	Age (years)	Androgen levels	Limitations/notes
				Similar levels of ACTH, cortisol, DHEA, DHEA-s, and total T.	
				A steeper age-associated decline in DHEA in cases than HCs	Morning samples
[31]	Case control	36 RA and eRA Cases 40s 55 HCs	Mean Early (15–80)	No difference in DHEAs levels	No prior steroids
[32]	Longitudinal observation	18 RA cases treated with TNF antago-nists for 2Y	Median 59 Decrease in DHEAs after 1 and (44–74) 2Y of TNF antagonists, but no changes in LH, E2 or T.		
[33,34]	Cross-sectional case control;	41 RA cases with joint symptoms b1Y	Mean 53	At baseline, lower mean T than HCs for cases significant for cases <50Y (p < 0.001, p = 0.004) and not for cases <50 (p = 0.06, p = 0.07); lower LH in cases <50 years (p b 0.001)	Did not control for corticosteroid use
	Longitudinal observation	131 HCs		At 2 years, in clinical responders to disease modifying therapies (improved DAS28 score), significant increase in T and SHBG. LH levels were low and stable Decrease in DAS28 score during 2Y correlated with increased T (r = –0.46, p = 0.006)	
MS [35]	Case control	25 MS cases (mean EDSS 5.3)	Mean 40.8 (25–57)	Serum T below lower limit of normal in 24% cases, 0% HCs; LH and FSH were not appropriately elevated.	Patients were inpatients, within 4 weeks of a clinical relapse
		6 HCs	HC mean 34.7	Only 2 cases responded inappropriately to the GnRH test: 1 with delayed response, another with exaggerated response	No discussion of steroid use
[37]	Case control	25 MS cases, mean disease duration 6.1 years (1–26) 18 HCs	Mean 32.3 (but mean includes F cases)	Non-significant lower FSH in cases (p = 0.06)	No mention of time of day No steroids in prior 2 months Positive correlation between E2 levels and MRI features: T2 lesion load (r = 0.47, p = 0.02) and T1 leion load (r = 0.43, p = 0.04).
[38]	Case control	66 MS cases, mean disease duration 9.5 years	Mean 40.6 (28–55)	Significantly lower mean serum T, LH, FSH (p = 0.01), FAI (androgen index) (p = 0.003) and higher SHBG (p = 0.02) in cases. PRL non-significantly elevated in cases (p = 0.06).	Morning samples
		48 HCs		GnRHa response inadequate in 67% cases, and lower LH and FSH levels relative to HCs (p = 0.001)	All cases medication free for 6 months

Ref	Study design	N	Age (years)	Androgen levels	Limitations/notes
					Decreased total sperm count, sperm motility and % normal sperm morphology lower in cases than HCs Pituitary- and testicular-level impairments Progressive disease with more HPT abnormalities than relapsing remitting disease

DHEA-s = dihydroepiandrosterone sulphate E1 = estrone E2 = estradiol FSH = follicle stimulating hormone HC = healthy control (age-matched) LH = luteinizing hormone PRL = prolactin T = testosterone

Table 2

Menopause and autoimmunity.

	SLE	RA	MS
Age at menopause	Nurses Health Study: Increased risk of SLE with earlier menopause, esp surgical [82]	Increased risk of RA with earlier menopause, <45Y vs. <51Y [100]. Menopause <45Y vs. <45Y: increased risk of seronegative RA, and trend towards increased risk of seropositive RA [101]. Earlier menopause associated with milder disease course [102].	MS onset typically in 3rd-5th decades
Late onset disease	16% patients with onset <50Y F:M ratio: lower (3.2:1 vs. 13.3:1)	Late Onset RA typically <60Y F:M ratio: lower (1:1 vs. 3.7:1 in individuals younger than 30 [99])	3–12% individuals with onset <50Y F:M ratio: lower (1.9:1 vs. 2.8:1)
	More insidious presentation	More acute onset	Disease type at onset: less frequently relapsing remitting (80% vs. 95% for females) and more frequently primary progressive
	Symptoms: lower incidence nephritis, malar rash and photosensitivity Serology: lower incidence anti ds DNA and anti-Ro antibodies [83–85].	Symptoms: Greater disease activity and functional decline, more systemic manifestations, proximal large joint involvement, similarity with polymyalgia rheumatica [103–105].	Symptoms: more motor and coordination symptoms, fewer visual symptoms. Shorter time to progression to EDSS 6.
Menopausal Transition	Decreased frequency of flares after menopause Decrease SLEDAI Greater damage accrual in affected organs from individual flares	A cohort study following individuals early in disease course over 6 years found higher Radiographic Joint Damage scores and higher physical disability scores as reported in a Health Assessment Questionnaire in postmenopausal women than in premenopausal women or in male subjects [106].	Unknown
Hormone	Disease risk: increased risk of SLE in NHS [82,92,93] as well as others [82,92,93], but this may be biased by misattribution of SLE symptoms to menopause, prompting HRT use.	Disease risk: WHI: no significant reduction in RA risk [107].	Unknown
Replacement Therapies	Disease course: SELENA trial: no increase in severe, and a modest increase in mild-moderate flares in women taking HRT [94].	Disease course: WHI: non-significant improvement in joint pain scores [107], additional studies have yielded no significant association (e.g.[109]).	
	Disease sequelae: Increased risk of venous thrombosis or thromboembolism [94,97]. Protective effects on bone density in one small study [98].	Disease sequelae: Protective effects on bone density [110–113].	