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Gender and autoimmunity

Gisele Zandman-Goddard [a,b,1], Elena Peeva [c,1], Yehuda Shoenfeld [b,d,e,*]

[a] Department of Medicine C, Wolfson Medical Center, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, Israel
[c] Department of Microbiology and Immunology, Albert Einstein College of Medicine, New York, USA
[d] Center for Autoimmune Diseases and the Department of Medicine B, Sheba Medical Center, Israel
[e] Incumbent of the Laura Schwartz-Kipp Chair for Autoimmunity, Israel

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Abstract

The enhanced immunoreactivity in females is a double-edged sword that provides better protection against infections, but may lead to enhanced autoreactivity and thereby contribute to the induction of autoimmunity. Autoimmune diseases demonstrate a gender bias and represent the fifth leading cause of death by disease among females of reproductive age. Clinical and murine experimental studies indicate that the gender bias in autoimmunity may be influenced by sex hormones, predominantly displayed in the development and exacerbations of the prototypical autoimmune disease lupus. The associations between sex hormones and other autoimmune diseases are less clear. Our review on the impact of gender via sex hormones and sex related genes in the pathogenesis of several autoimmune diseases suggests that a better understanding of the underlying mechanisms behind the sexual dimorphism of the immune system may lead to the development of novel therapeutic approaches to autoimmunity.

Keywords: Gender; SLE; Estrogen; Prolactin; Rheumatoid arthritis; Systemic sclerosis

Contents

* Corresponding author. Department of Medicine B, Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel.: +972 3 5302652; fax: +972 3 5352855.
E-mail address: Shoenfel@post.tau.ac.il (Y. Shoenfeld).
[1] Both authors contributed equally to this work.

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1. Introduction

The etiology of autoimmune diseases is multi-factorial where intrinsic (genetic predisposition) and extrinsic (environmental) triggers contribute to disease progression and pathogenesis. The intrinsic abnormalities are complicated, with diverse genetic polymorphisms described in different ethnic groups, strongly suggesting a mosaic of autoimmunity where the immunologic disarray might not be the same for each patient [1].

Experimental and clinical evidence suggest that autoimmunity is influenced by gender. Immune reactivity is more enhanced in females than in males and lymphocytes and monocytes from females show higher antigen presenting activity and mitogenic responses. Females have higher immunoglobulin levels than males, an enhanced antibody production to both primary and secondary antigen stimulation, and a higher homograft rejection rate. Males, on the other hand, are more prone to infections. These data indicate that the gender bias in autoimmunity may be influenced by sex hormones, portrayed by the role of female sex hormones in the induction and flares of lupus, the prototype of systemic autoimmune diseases.

The sexually dimorphic prevalence of autoimmune diseases remains one of the most intriguing clinical observations among this group of diseases. There is a wealth of clinical and laboratory data generated over the past 20 years demonstrating that sex hormones affect the immune system by modulating multiple immune functions including lymphocyte maturation and activation, synthesis of autoantibodies, and cytokines (Table 1).

Table 1
Mechanisms by which gender influences autoimmune diseases

Autoimmune disease	Gender influence	Mechanism	Ref.
SLE	Estrogen	Allows survival of autoreactive B cells and skews their maturation toward marginal zone phenotype.	[3,5,22,23]
	Prolactin	Allows survival of autoreactive B cells and skews their maturation towards follicular phenotype; leads to the production of IFN-γ,	[3,5]
	Testosterone	Suppresses anti-dsDNA antibody production	[16]
	Chromosome X	Triplication of PAR1 region Duplication of TRL7	
Myasthenia gravis	Estrogen	Promotes AChR-specific Th1 cell expansion	[26]
Rheumatoid arthritis	Estrogen	Activating effects on synovial cell proliferation, including macrophages and fibroblasts.	[32]
Systemic sclerosis	X chromosome	Increased frequency of X chromosome monosomy in peripheral T and B lymphocytes.	[40]
	Estrogen	Estrogens induce fibroblast dysfunction	[36]

2. Systemic lupus erythematosus (SLE)

The role of sex hormones on autoimmunity has been most extensively evaluated in SLE patients and the female gender represents a strong risk factor linked to both the cause and pathology of the disease. The preponderance of SLE in young woman of childbearing age with a female to male ratio of 9:1, and the tendency for lupus flares during pregnancy and remissions after menopause or cyclophosphamide induced ovarian failure, suggest that female sex hormones are crucial regulators of lupus activity [2].

The results of prospective comparative studies show that male SLE is much less common, often leading to a delay in diagnosis. Men develop the typical clinical manifestations of lupus, but some researchers hold that the prognosis of the disease is different. In one study, skin manifestations, serositis, and renal involvement were more common in men. Also, male SLE patients experienced more seizures, peripheral neuropathy, as well as more severe renal disease and cardiorespiratory involvement than female patients [3].

Hormones influence the sexual dimorphism of the immune system. They can initiate or accelerate an autoimmune process, and thereby contribute to gender-biased autoimmune disorders. The female sex hormones estrogen and prolactin are both considered immunomodulators implicated in autoimmunity. Not only endogenous estrogens, but also environmental estrogens, may act in conjunction with other factors to override immune tolerance to self-antigens [2]. There is much evidence for the role of sex hormones in the pathogenesis of SLE by molecular, experimental, and clinical studies. In the B cell compartment, both prolactin and estrogen are immunostimulators that affect maturation and selection of autoreactive B cells, as well as autoantibody secretion, while progesterone is an immunosuppressor. The impact of prolactin and estrogen may be based on their capacity to allow autoreactive B cells to escape the normal mechanisms of tolerance and mature to fully functional antibody-secreting B cells that can cause

clinically apparent lupus. However, the mechanism of action of the two hormones is different; estrogen leads to the survival and activation of autoreactive B cells with a marginal zone phenotype, whereas prolactin induces self-reactive B cells with a follicular zone phenotype [4].

In murine models of lupus, female NZBXNZW F1 lupus-prone mice develop the disease earlier and have shorter life spans than males. In female NZBXNZW F1 mice, oopharectomy postpones the disease onset and ameliorates lupus activity [5]. In contrast, castrated male NZBXNZW F1 mice have earlier onset of lupus and shorter life span than their intact littermates. In addition, treatment with estrogen or prolactin exacerbates disease activity and causes early mortality (reviewed in Ref. [3]). These observations suggest that sex hormones are implicated in the pathogenesis of murine lupus and that estrogens have lupus-stimulating effects while androgens have lupus-ameliorating effects. From these findings originated the idea that agents modulating estrogen activity or blocking estrogen synthesis may have a therapeutic effect in lupus. Treatment with the selective estrogen receptor modulator (SERM) tamoxifen, a widely used agent in breast cancer therapy, ameliorated lupus activity in NZB/W F1 female mice and the beneficial effects of the agent were associated with a specific reduction in IgG3 autoantibody titer [6]. In addition, tamoxifen prevented the development of estrogen-induced murine lupus by deterring DNA-reactive B cells from becoming marginal zone B cells [7], which are known to harbor autoreactivity in this hormone-induced model of lupus [3]. Raloxifene, a SERM extensively used in the treatment of osteoporosis, increased survival in MRL/lpr lupus-prone mice by mitigating the progression of lupus nephritis [8]. Blockade of estrogen synthesis with the aromatase inhibitor 4-hydroxyandrostendione ameliorated lupus nephritis in the Mrl/lpr lupus model [9].

Twenty to thirty percent of SLE patients exhibit mild to moderate hyperprolactinemia. Unstimulated peripheral blood monocytes (PBMs) from SLE patients produce more prolactin than the PBMs from healthy individuals, and the hormone increases the production of anti-dsDNA antibodies by PBMs [10]. In addition, prolactin leads to the production of interferon-gamma (IFN-γ), an important mediator in the pathogenesis of lupus nephritis [11]. Hyperprolactinemia accelerates the disease activity in NZB/W F1 lupus-prone mice and induces a lupus-like syndrome in mice that are not genetically predisposed to the disease [2]. Increased serum prolactin levels break tolerance by impairing negative selection of autoreactive B cells and by allowing for their maturation into fully functional B cells with follicular phenotype [12]. Moreover, treatment with bromocriptine, an inhibitor of prolactin secretion, has shown beneficial effects in prolactin-induced lupus in mice [13] as well as in SLE patients with mild-moderate disease activity [14].

In addition, there is an inter-play between estrogen and prolactin that may influence the immune cells and their functions. Androgens are also implicated in the pathogenesis of murine and human lupus. Castrated male NZB/W F1 mice have early disease onset and shorter life span than their intact male littermates. Female SLE patients have accelerated oxidation of testosterone, which may result in immunomodulatory effects since testosterone suppresses anti-dsDNA antibody production. Moreover, dehydroepiandrosterone (DHEA), a mild synthetic androgen, was shown to provide therapeutic benefit to SLE patients with mild disease activity [15].

An additional aspect of the role of sex hormones in SLE derives from an imbalance in the estrogen and androgen serum levels. Male SLE patients have elevated serum 16-hydroxyestrone and estrone concentrations leading to estrogen/androgen imbalance. Some men have functional hypoandrogenism, with low levels of testosterone and elevated luteinizing hormone (LH). Female patients with SLE have lower plasma androgen levels than their healthy counterparts. Even when the serum levels of estrogen are normal, its overall metabolism tends to favor more feminizing compounds. The sex steroid metabolism (estrone hydroxylation and testosterone oxidation) of Klinefelter's syndrome (karyotype XXY) patients with SLE was similar to that of women with SLE [16], and testosterone treatment led to clinical remission of their lupus activity.

The exposure of the immune system to estrogen may occur through endogenous production, exogenous introduction for medical reasons (estrogen replacement therapy, oral contraceptives, ovulation stimulation), or through environmental exposure to plastics (bisphenol, phthalates), surfactants, pesticides, industrial chemicals, phytoestrogens or natural plant estrogens (genistein, coumesterol), and fungal sources (mycoestrogens, zearalenone) (reviewed in Ref. [3]). The recent SELENA study indicated that estrogen replacement therapy in post-menopausal SLE patients induced a slightly increased number of mild flares [17]. Since genetic factors are involved in the pathogenesis of SLE, it is plausible that hormonal treatments will cause flares only in the subset of SLE patients with a hormone-responsive disease. Ovarian stimulation, accomplished by hormonal manipulation with gonadotropins, gonadotropin-releasing hormone agonists (GnRH), follicle-stimulating

hormone (FSH), and LH. may cause an induction of a lupus flare [18].

Not only female hormones, but also specific genetic gender factors such as chromosome X may be implicated in the development of SLE. This thesis is supported by the observation that the X chromosome includes genes that are crucial in determining sex hormone levels and in maintaining tolerance. A possible association between Klinefelter's syndrome and SLE has been reported [19]; the connection is based on the presence of triplication of 2 PAR regions in some patients with the syndrome; a case report of prepubertal SLE in a XX male patient indicates conjunction between an unusual X:Y translocation with partial triplication of PAR1 region and SLE [20].

A recent study shows that BXS mice, a murine model of male lupus, have duplication of genes from X chromosome on the Y chromosome. Yaa (Y-linked autoimmune accelerator), a major genetic feature of the BXS mice, contains a duplicated copy of a gene that makes TLR7 which is a receptor for RNA. The extra copy of the TLR7 gene leads to doubling of the RNA receptor thereby making the BXS mice more likely to mount an autoimmune response to the body's own RNA [21].

3. Myasthenia gravis (MG)

MG is an organ-specific autoimmune disease caused by autoantibodies against the nicotinic acetylcholine receptor (AChR). MG affects predominantly women and is specifically pronounced in MG patients who have muscle specific kinase (MuSK) antibodies [22].

A recent study demonstrated an increased expression of the estrogen receptor (ER) α in thymocytes and ERα and ERβ in circulating T cells of patients with MG indicating the importance of estrogen in the pathogenesis of MG and possibly, the effect of the hormone on the progression of the disease [23]. These recent findings are in concordance with a previous study that demonstrated an elevated number of estrogen-binding sites in PBMCs from MG patients, and their decrease after thymectomy [24]. The immunomodulatory effects of estrogen were also confirmed in an experimental murine model of MG. Treatment with estrogen before antigen priming was necessary to promote AChR-specific Th1 cell expansion in vivo. The time-limited exposure to estrogen enhanced the production of anti-AChR antibodies and increased the severity of the disease. The effects of estrogen were mediated via AChR-specific Th1 responses [25]. The role of female sex hormones in the pathogenesis of anti-MuSK+MG has yet to be explored.

4. Sjogren's syndrome

The NOD mouse is an accepted murine model of Sjogren's syndrome. Although gonadectomy worsens the disease in male NOD mice, treatment with a near-physiological dose of estrogen does not accelerate the disease significantly. These data lead to the speculation that the sexual dichotomy in this model is due to the protective effects of androgens and not caused by estrogens alone [26].

Recent studies elucidated specific genetic factors responsible for the development of Sjogren's-like syndrome in NOD mice. Two genetic regions derived from NOD mice, Aec1 region on chromosome 1 and Aec2 region on chromosome 3, confer Sjogren's-like features in wild type C57BL/6 mice. C57BL/6.NOD-Aec1R1Aec2 is a novel strain with the Aec1 region reduced to less than 20 cM from 48.5 cM. Profiling of this recombinant inbred strain showed that male mice maintain a full spectrum of Sjogren's syndrome, while female counterparts display only stomatitis sicca. These data indicate that autosomal genes are responsible for gender-specific regulation of Sjogren's-like phenotype in the NOD mice [27].

5. Rheumatoid arthritis (RA)

Significant gender dimorphism is also observed in patients with RA. Several studies confirm that there are reduced levels of androgens and progesterone in RA patients. Men with RA have low levels of testosterone, DHEA and estrone while estradiol, the most potent naturally occurring estrogen, is increased and correlates with the inflammatory indices [28].

Synovial fluid levels of estrogens relative to androgens are significantly elevated in both male and female patients with RA, which is most probably due to increased local enzymatic aromatase activity mediated by TNF-α [29]. TNF blockers seem to affect the level of sex hormones in the RA synovial tissue before they have any influence on the hormonal serum levels. The beneficial effects of restoring synovial androgens might be clinically more important for male patients with RA since they suffer more from the decreased androgen levels caused by the increased TNF-α levels. Locally increased estrogens may exert activating effects on synovial cell proliferation, including macrophages and fibroblasts. Not only the increased estrogen level, but also the differential expression of estrogen receptors on immune cells might be implicated in the pathologic

changes seen in the RA joints. Since the synovium in active RA is diffusely infiltrated with lymphocytes, ERβ on these cells along with the increased estradiol levels in the synovial fluid might be a contributory factor to the development of RA pathology.

The possible role of prolactin in the development and disease activity of RA is controversial. There are observations suggesting that breast-feeding through the actions of prolactin may lead to RA flares [30].

Although sex hormones might be implicated in the pathogenesis of RA, their role seems much less critical for the disease development and flares than in SLE. This notion is supported by the fact that RA develops predominantly in patients at age 40 and above, and that female patients experience remissions during pregnancy when estrogenic hormones reach their peak. In addition, in collagen induced arthritis (CIA), a murine model of RA, the male mice have accelerated and a much more severe disease course than their female counterparts [31]. In addition, treatment with estradiol decreases inflammatory cytokines TNF-α and IL-1 and thereby ameliorates disease activity in CIA. However, in contrast to the CIA mice, in the KBxN murine model of RA, all offspring develop erosive arthritis [32]. The data from CIA and KBxN mice suggest that there may be RA subsets characterized by variant association with gender.

6. Systemic sclerosis (SSc)

SSc shows gender bias with an overall ratio (women to men) of approximately 3:1.6 and a ratio of 5:17 for limited SSc. Although the difference can reach a ratio of 15:1 in women during childbearing years, the published data on the implications of female sex hormones in the pathogenesis of SSc are rather limited. Some studies have shown that estrogens induce fibroblast dysfunction [33] and thereby contribute to the pathogenesis of SSc. The SERM tamoxifen was reported to have beneficial effect in limited SSc, but an open label trial of tamoxifen in patients with diffuse SSc did not demonstrate therapeutic effect [34]. High prolactin and low DHEA levels have been observed in patients with SSc [35] and in most cases altered levels of the hormones were related to the duration and activity of the disease [36]. However, studies of the mechanisms by which prolactin and DHEA may affect the immune system in patients with scleroderma are lacking. A fraction of the gender gap in SSc may be attributable to genetic factors involving the X chromosome. Skewed chromosome X inactivation was observed in DNA from peripheral blood cells in 64% of patients with SSc, as compared with 8% in the controls [37]. Also, the rate of monosomy X in white blood cell subpopulations was significantly higher in patients with SSc and autoimmune thyroid disease when compared with healthy female individuals. The X chromosome monosomy rate was most frequent in peripheral T and B lymphocytes, without evidence for the presence of male fetal microchimerism. These data provide evidence for chromosome instability in women with SSc and that haplo-insuffficiency for X-linked genes may be a critical factor for female preponderance of this disease [38].

The tight skin 2 mouse displays cutaneous fibrosis and mononuclear cell infiltration resembling those seen in patients with SSc [39]. The mutation that leads to increased collagen content and expression of type I collagen genes has been mapped to a 15.3 cM region on mouse chromosome 1, but no association with X or Y chromosome has been made. MRL/lpr mice lacking IFÑ-γ receptor develop disease resembling human SSc. Skin disease appears earlier in female than male mice, but no further distinction of gender was made in this murine scleroderma model [40]. Possible hormonal disturbances and implications of sex hormones in the pathogenesis of experimental SSc models have yet to be explored. Hormonal studies in mice and humans in Wegener's granulomatosis, polyarteritis nodosum, Churg–Strauss syndrome and cryoglobulinemia are lacking.

7. Conclusions

Female predominance in autoimmunity is very prominent, and may be related to sex hormones and / or sex related genes. As suggested by animal models and clinical studies, in some autoimmune diseases such as SLE, endogenous estrogen and prolactin, as well as exogenous endocrine disruptors may break tolerance and induce a development of autoimmunity. In other autoimmune diseases, such as MG and RA, the pathogenesis of the disease does not seem to be heavily influenced by the sex hormones, which points to the possible role of other gender-related factors. The X chromosome and its alterations may be involved in the development of autoimmunity, but its role requires clarification and further investigation.

Bulletins

- As suggested by animal models and clinical studies, in some autoimmune diseases such as SLE, endogenous estrogen and prolactin, as well as exogenous endocrine disruptors may break tolerance and induce the development of autoimmunity.
- In the B cell compartment, both prolactin and estrogen are immunostimulators that affect maturation and

selection of autoreactive B cells, as well as autoantibody secretion, while progesterone is an immunosuppressor.

- Treatment with bromocriptine, an inhibitor of prolactin secretion, has shown beneficial effects in murine models of lupus as well as in SLE patients with mild-moderate disease activity.
- Tamoxifen prevents the development of estrogen-induced murine lupus by deterring DNA-reactive B cells from becoming marginal zone B cells, which are known to harbor autoreactivity in this hormone-induced model of lupus. Raloxifene increased survival in MRL/lpr lupus-prone mice by mitigating the progression of lupus nephritis.
- Female SLE patients have accelerated oxidation of testosterone, which may result in immunomodulatory effects since testosterone suppresses anti-dsDNA antibody production. DHEA, a mild synthetic androgen, was shown to provide minor therapeutic benefit to SLE patients with mild disease activity or in conjunction with other medications in treatment of patients with severe lupus.
- Sex related genes may be implicated in the development of SLE.
- A recent study demonstrated an increased expression of the estrogen receptor (ER) α in thymocytes and ERα and ERβ in circulating T cells of patients with MG indicating the importance of estrogen in the pathogenesis of MG.
- Since the synovium in active RA is diffusely infiltrated with lymphocytes, ERβ on these cells along with the increased estradiol levels in the synovial fluid might be a contributory factor to the development of RA pathology.
- The X chromosome and its alterations may be involved in the development of autoimmunity such as in systemic sclerosis and autoimmune thyroid disease.

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High prevalence of anti-C1q antibodies in biopsy-proven active lupus nephritis

Anti-C1q antibodies (anti-C1q) have been shown to correlate positively with systemic lupus erythematosus (SLE) nephritis. However, the true prevalence of anti-C1q at the time of active lupus nephritis has not been well established. The aim of this study, Trendelenburg M. et. al. (Nephrology Dialysis Transplantation 2006; 21: 3115-21) was to determine prospectively the prevalence of anti-C1q in proven active lupus nephritis at the time of renal biopsy. A total of 38 patients fulfilling at least 4/11 ACR criteria for the diagnosis of SLE were included. Out of this, 36 patients had proliferative (class II, III or IV) and two had class V lupus nephritis. All but one patient with proliferative lupus nephritis were positive for anti-C1q (97.2%) compared with the 35% of control SLE patients with inactive lupus nephritis and 25% of SLE patients without lupus nephritis ever. All patients were positive for glomerular C1q (36/36) and 37/38 patients had glomerular IgG deposits. Anti-C1q strongly decreased during successful treatment. Thus, anti-C1q have a very high prevalence in biopsy-proven active lupus nephritis, thus a negative test result almost exclude active nephritis. This data support the hypothesis of a pathogenic role of anti-C1q in lupus nephritis.