Sex Ratio and Rheumatic Disease*

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Abstract

Autoimmune diseases are said to have high female/male (F/M) ratios, but these ratios are imprecise. Published definitions and classifications of autoimmune diseases differ substantially, as do the F/M ratios themselves. Imputed causality of autoimmune diseases requires better precision. Some thyroid, rheumatic and hepatic diseases consistently have high F/M ratios, but marked differences exist in the reported quantity of the ratios. Other autoimmune diseases have low F/M ratios. Because F/M ratios reflect incidence and not severity of disease, gonadal hormones, if they play a role, must do so through a threshold or permissive mechanism. Sex differences related to environmental exposure, X-inactivation, imprinting, X or Y chromosome genetic modulators, and intrauterine influences remain as alternate, theoretical, explanations for sex differences of incidence. The epidemiology of the sex-discrepant autoimmune diseases – young, female – suggests that an explanation for sex discrepancy lies in differential exposure, vulnerable periods, or thresholds, rather than in quantitative aspects of immunomodulation.

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Autoimmune (rheumatic) diseases affect more women than men. Many physicians believe that the reason for the sex differences is the immunomodulatory effects of gonadal hormones. This paper argues that alternative reasons for sex differences are more likely.

Inconsistencies of fact

Differing definitions of autoimmunity cause conflicting answers to the question: Which diseases are autoimmune? Most definitions of autoimmunity require the presence of autoantibody and autoantigen. One definition accepts cell-mediated autoreactivity as a defining characteristic, another includes immunization and passive transfer in animal models, and still another includes participation of the major histocompatibility complex [1–3]. Inconsistent definitions cause individual lists of autoimmune diseases, i.e., which diseases are considered to be autoimmune, to differ markedly. Classifications of autoimmunity also differ. One classification distinguishes organ-specific autoimmune disease from systemic [1], a second differentiates between primary autoimmune disease (autoimmunity to normal tissue) and secondary (autoimmunity to "damaged" tissue) [2], and a third distinguishes among mechanisms, e.g., cellular responses of autoimmunity [3].

Despite the inconsistencies, most contemporary texts agree that, in general, thyroid (Hashimoto, Graves), rheumatic (lupus, rheumatoid arthritis, scleroderma, Sjogren), and non-toxic, non-infectious hepatic (autoimmune hepatitis, primary biliary cirrhosis) diseases are autoimmune. Texts also agree that these diseases mostly affect women. However, some but not all authors consider ankylosing spondylitis, vasculitis, Goodpasture disease, multiple sclerosis, juvenile-onset diabetes, and inflammatory bowel disease to be autoimmune. The latter diseases are not highly female predominant.

Because most published female/male ratios derive from the epidemiologically weak sources of individual clinics, physician's practices, and voluntary agencies [4], published F/M ratios are inconsistent. Ratios also differ by age. Among rheumatic diseases, lupus, Sjogren, and scleroderma consistently have F/M ratios > 3; the rheumatoid arthritis ratio is between 2 and 3; dermatomyositis and vasculitis have a ratio close to 1; and B27 spondyloarthropathy is male predominant [Table 1]. Published F/M ratios vary tenfold for Hashimoto disease (from 10 to 50), sevenfold for multiple sclerosis (from 1.5 to 10), and fivefold (from 0.2 to 1) for Goodpasture disease. Among rheumatic diseases, cited F/M ratios vary fourfold for scleroderma (from 3 to 12) and threefold for lupus (from 7 to 20, Table 1) [5,6].

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F/M = female/male

Table 1. Female/male ratios cited by various authors and the American Autoimmune and Related Diseases Association

Disease	Beeson [6]	Rose [5]	Janeway [3]	AARDA [4]
Sjogren	19	15	-	9
Primary biliary cirrhosis	9	–	–	–
Chronic active hepatitis	8	–	–	–
Lupus erythematosus	7	9	20	9
Hashimoto thyroiditis	6	18	5	50
Graves hyperthyroidism	6	7	5	7
Scleroderma	4	12	–	3
Rheumatoid arthritis	2	3	3	4
ITP*	2	–	–	–
AIHA	2	–	–	–
Multiple sclerosis	1.5	2	10	–
Pemphigus	1	–	–	–
Myasthenia gravis	1	3	1	2
Type 1 diabetes*	1	–	–	–
Ankylosing spondylitis	0.3	–	–	–
Goodpasture	0.2	–	1	–

* Age-specific
AARDA = American Aautoimmuine and Related Diseases Association, IHA = autoimmune hemolytic anemia, ITP = idiopathic thrombocytopenic purpura

In human illness the term "female predominance" refers to sex differences of incidence, not severity. Sex discrepant severity differences among rheumatic diseases, if they exist at all, are quantitatively slight [7]. In animal models, however, "female predominance" means differences of both incidence and severity, a distinction that may invalidate imputations derived from animals.

Immunization and infection as tests of immune response

Examinations of sex-specific responses to immunization and to infection test the hypothesis that sex differences of immune response account for differences in disease frequencies. Vaccination studies inconsistently show higher antibody titers in females but few clinical differences between the sexes [Table 2]. Intriguingly, arthritic reactions to immunization may be more common in women.

Viral infections generally affect men and women equally. However, coxsackie virus myocarditis is male predominant, possibly because male hearts have more virus receptors than do female. Bacterial infections also affect the sexes equally. In acute and chronic Lyme disease – a possible infectious etiology model for rheumatoid arthritis – male and female incidence and severity are similar. Sex-specific attack rates of mycobacterial, fungal and parasitic diseases are equal; differences that do exist are mostly explained by differences in exposure to the infecting agent. Cytokines that induce autoimmune rheumatic symptoms do so for both male and female-predominant diseases [8]. Thus immunizations and infections do not support the idea that intrinsic male-female differences in immune response account for the high F/M ratios of rheumatic disease.

Table 2. Sex differences in immunization

Immungen	Finding
Pertussis	No sex difference
Measles	No sex difference (antibody response)
Measles	Girls have higher case fatality rates (due to lack of immunization)
Measles	Antibody-dependent cellular cytotoxicity lower in females; neutralizing antibody equal
Rubella	Arthritis 3.5 x more common in girls
Rubella	More vigorous recall response in males
Mumps	Vaccination meningitis, no sex difference
Influenza	More systemic adverse reactions in women
Influenza	More local adverse reactions in women
Hepatitis B	Seroconversion rates equivalent
Hepatitis B	Antibody titer higher in young women
Hepatitis A	Antibody titers higher in women
Pneumococcus	Elderly women have lower antibody

Potential causes of sex discrepancy

Environment

The possibility that environmental factors are responsible for sex discrepancy is supported by the examples of drug-induced lupus [9] and toxin-induced scleroderma-like disease. More men than women take drugs that induce lupus (male predominant), more men are exposed to silica inducers of scleroderma-like disease (male predominant), and more women were exposed to the contaminated cooking oil that caused a scleroderma-like illness in Spain (female predominant) [10]. More women than men took contaminated L-tryptophan, a putatively "natural" antidepressant; the resulting epidemic of eosinophilia-myalgia syndrome was female predominant [11].

When infection capable of producing arthritis affects both sexes equally, its autoimmune sequelae, for instance chronic Lyme disease, are not sex discrepant [12]. Different exposures, differences in processing infecting organisms, vulnerable periods, or threshold immune responses are possible explanations for differences in attack rates of infections. The high attack rate of malaria in the postpartum period is an example of a vulnerable period [13]. Incubation periods are an additional concern. Serological lupus precedes clinical lupus by decades [14,15]. If lupus has an infectious cause, exposure to a causative agent may have been very remote, and sex-discrepant exposure would be correspondingly difficult to discern.

Hormones

Case reports of change in disease activity of autoimmune disease after castration or hormone treatment suggest that gonadal hormones modulate disease severity in individuals [16]. Such reports do not, however, constitute evidence for differences of sex incidence in populations. Indeed, most population studies of the relationship of hormone therapy to autoimmune disease show little effect on either incidence or severity. Estrogen replacement therapy, oral contraceptives, and ovulation induction probably do not worsen lupus [17]. Synoviocyte estrogen receptors may be target organs in rheumatoid arthritis

[18], a possible explanation for female predominance in this illness. However, these receptors would also be present in synovium of patients with chronic Lyme disease and ankylosing spondylitis, which are not female predominant. In ankylosing spondylitis, androgens have no apparent role [19].

Studies often attribute pregnancy-associated remission or flare of the disease to the effect of hormones. Rheumatoid arthritis remits during pregnancy, as does multiple sclerosis. The rheumatoid remission may be due to HLA mismatch between mother and fetus rather than to pregnancy-associated hormones [20]. Lupus does not or only slightly worsens during pregnancy [21]. Thus pregnancy data do not in themselves establish a role for hormones in modulating autoimmune disease. A threshold mechanism, i.e., a specific level of estrogen at a vulnerable time, could explain a hormone-caused increase in disease incidence but not severity. Estrogen may play a permissive role, allowing survival of forbidden autoimmune clones [22].

Hormones might influence F/M ratios in non-immunological ways. Vascular pathology is prominent in the systemic autoimmune diseases. Hypothetically, hormone (or other sex) effects on endothelium, rather than on immunocytes, might be critical for disease initiation. An unknown sex difference related to ovulation or menstruation cytokines, to apoptosis, or to vascular rheology might be responsible for the different disease experiences of the two sexes.

Genes

Abundant evidence confirms genetic control of autoimmunity: family and twin studies, HLA associations with specific illnesses, disease susceptibility or resistance genes, and transgene experiments [23,24]. Evidence of this type is particularly strong for spondyloarthropathy, rheumatoid arthritis and lupus. HLA types by themselves do not explain sex dimorphism, but sex-discrepant HLA-associated effects are possible [25].

Ankylosing spondylitis, the only sex-discrepant rheumatic disease studied for X-chromosome markers to date, has no X-chromosome susceptibility locus [26]. Except for CD40 ligand, few putative autoimmune markers are on the X or Y chromosome. No conclusive evidence for imprinting or differential X-inactivation differences exists for autoimmune diseases. However, sex-different chromosomal markers, imprinting, and inactivation have been rarely sought in autoimmunity [27,28]. Skewed X-inactivation in the thymus may lead to inadequate thymic deletion and hence loss of T cell tolerance [29].

Non-MHC genes may be relevant to sex discrepancy. In a mouse model of diabetes, mutation of a tissue/developmental stage-specific proteasome product is sex discrepant. Sex dimorphism of T cell trafficking may be due to sex-determined cell surface markers [9]. Other chromosomal effects may be operative.

MHC = major histocompatibility complex

Whole body/life stages/life events

Most female-predominant diseases cluster in the young-adult years, while autoimmune diseases that affect younger or older patients are more evenly divided between the sexes. Characteristics of young adulthood (other than sexual intercourse or pregnancy) that may explain female predominance include chronobiologic non-hormonal effects of menstrual cycles, gonadal hormones, thresholds, vascular responses, immune responses, and as yet unknown other variables. The large quantity and long duration of circulating fetal cells in scleroderma patients [30] suggests a profound new biological difference between men and women, the implications of which are unknown.

Lessons from animal models

Experimental animal models of autoimmune disease that test causes of sex discrepancy include immunization, in-breeding, transgenic and gene knockouts. These models give mixed messages [Table 3].

Strains of mice and rats are variably susceptible to an immunization model of thyroiditis. Despite the female predominance of human thyroiditis, estrogen in rodents increases anti-thyroid antibody titer but not histologic thyroiditis. In contrast, the severity of induced mouse thyroiditis does vary with iodide content of the diet and with types of chow. Genetic and extrinsic factors, therefore, influence experimental thyroiditis incidence more than do hormones.

The (NZB x NZW)F1 mouse model of lupus shows high female incidence and severity, but the MRL lpr/lpr model is sex neutral and the BXSB model is male predominant [31]. Castration/replacement experiments, primarily in (NZB x NZW)F1, demonstrate estrogen enhancement and testosterone suppression of spontaneous disease severity and incidence. Genetic susceptibility is linked to MHC and other immune-relevant genes, such as those controlling complement and apoptosis. Like its human counterpart, lupus in mice develops in young adulthood, implying that incubation, maturation or cumulative damage is required for disease expression. At maturation, but not before, susceptible mouse strains have more numerous and more avid estrogen receptors on lymphoid and uterine tissue than do non-susceptible strains, a possible explanation for strain susceptibility differences but not necessarily for sex differences [32].

Male and female mice in germ-free environments are equally affected by lupus, but germ-free females develop higher autoantibody levels. Germ-free, antigen-free animals have less frequent disease than do germ-free or conventionally raised animals, indicating environmental contribution to illness, and leaving open the possibility that differential exposure causes sex discrepancy in humans [33]. Both the p21 knockout and the DNAse 1 knockout mouse lupus models show slightly higher autoantibody levels in females. Inexplicably, glomerulonephritis is much worse in female p21 knockouts but equals that of males in DNAse 1 knockouts [34,35]. The human HLA B27 gene

Table 3. Animal models of human autoimmune diseases, according to potential genetic, hormone, life stage, and environmental influences

Human disease	Method	Animal	F/M	Gene	Hormone	Life stage	Environment
Thyroiditis	Immunization with thyroglobulin	Mouse	F = M	Inbred strains (MHC)	**Estrogen enhances antibody level** but not clinical disease in susceptible strains	Young adults tested	Diet modifies
	Immunization with thyroglobulin	Rat	F > M	Inbred strains, polygenic (not MHC), **X chromosome**	**Castration, estrogen replacement increases severity and incidence** in males	Young adults tested	
Lupus	Spontaneous disease	Mouse	F > M	Inbred strains, MHC, complement, other immune genes relevant; **susceptible strain estrogen receptor more numerous, higher affinity at maturity**	**Castration, estrogen replacement increases severity and incidence** in males	Disease develops in young adulthood (all strains)	Diet modifies
	Spontaneous disease	Mouse	F = M	Inbred strains, MHC, complement, other immune genes relevant		Disease develops in young adulthood	Germ-free, no difference in incidence or severity between M and F or conventionally raised controls. **Germ-free, antigen-free M but not F have lower lymph node weight** than conventional controls. Glomerulonephritis less in both sexes in germ-free, antigen-free animals.
	Knockout	Mouse	F > M	**p21, antibody slightly worse in F; severe glomerulo-nephritis in F**		Disease develops in young adulthood	
	Knockout	Mouse	F = M	**Dnase 1, antibody slightly worse in F**		Disease develops in young adulthood	
Spondylopathy	Transgenic	Rat	F < M	MHC		Disease develops in young adulthood	Germ-free: intestinal bacteria required for phenotype, **M more frequent**

Data consistent with sex discrepancy in humans are indicated in boldface.

transgenically expressed in rats induces a phenotype with features of psoriasis and ankylosing spondylitis. In a germ-free environment the spondylitis does not occur. Introduction of specific gastrointestinal pathogens to the germ-free animal induces spondylitis [36]. Male predominance is true of this model, as it is of the human disease, but the reasons are unknown. In these animal models of autoimmune disease, genetic, hormone, life stage, and environmental factors are all relevant to disease causation. No consistent cause for sex discrepancy appears.

Conclusion

Table 4 shows mechanisms that account for sex differences in non-autoimmune human illnesses. The most striking differences of incidence occur when exposures to infectious agents or toxins differ between the sexes. If (unidentified) infections or toxins induce autoimmune rheumatic disease, differences in exposure remain as plausible explanations for the sex differences.

Because human autoimmune rheumatic disease is female predominant in incidence but not severity, gonadal hormones, if they play a role likely do so through a threshold or permissive mechanism rather than through the quantitative immunomodulation that *in vitro* models imply. Differences related to X-inactivation, imprinting, X or Y chromosome genetic modulators, and intrauterine influences remain as alternate theoretical explanations for sex differences of incidence.

The epidemiology of the sex-discrepant autoimmune diseases – young, female – suggests that an explanation for sex discrepancy lies in differential exposure, vulnerable periods, or thresholds, rather than in the immune response itself. These topics remain to be explored.

Table 4. Non-immunologic mechanisms by which males and females differ in disease incidence

Level of study	Mechanism	Example
In utero effect	*In utero* nutrition and hormone exposure determine adult phenotype	Sexual behavior, prostate size and adult-onset diabetes can be influenced by prenatal exposures in animals; girls with prenatal growth restriction have insulin resistance and ovarian hyporesponsiveness later in life
Imprinted gene	Maternal or paternal origin of a gene influences phenotype differently in males and females	Turner syndrome patients whose X chromosome is of paternal origin are more aggressive than those whose X chromosome is of maternal origin
X-inactivation	Because of incomplete inactivation, XX cells may produce higher levels of an X chromosome gene product than do XY cells	Gastrin-releasing peptide receptor is higher in women, causing increased risk of lung cancer in women smokers compared to men
X chromosome mosaicism	In the presence of a mutated X chromosome gene, XX individuals have one healthy allele, but an XY or XO individual does not	Females survive incontinentia pigmenti because unaffected X chromosomes exist in mosaic with affected; males have only affected Xs and die
Hormone	Estrogen affects non-hormone cell receptors	Women have a longer QTc interval than men. Cardiac ion channel sensitivity renders women more susceptible to drug-induced arrhythmia.
Organ difference	Organ function differs between the sexes	Men and women use different parts of the brain in language; gastrointestinal transit times differ in men and women
Exposure	Sexes encounter exogenous substances at different rates	Toxic-oil scleroderma affects women; procainamide-induced lupus affects men
Exogenous chemical processing	Exogenous substances are handled differently by the sexes	Kappa opioid drugs are more effective in young adult women than men
Life event	Effects of pregnancy	Fetal cells circulate longer and at higher quantity in scleroderma patients than controls; rheumatoid arthritis remits during pregnancy, and is related to HLA mismatch between mother and fetus
Behavior	Social activities have different effects in the sexes	Athleticism and diet lead to amenorrhea and osteoporosis in women but not men

* References may be found in "Exploring the Biological Contributions to Human Health – Does Sex Matter", at http://lab.nap.edu/catalog/10028.html

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