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Male SLE: A Review of Sex Disparities in this Disease

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Introduction:

Accompanying increasing evidence for sex-specific health issues, many clear-cut differences between men and women have been highlighted in a wide range of diseases, including ischemic heart diseases, some autoimmune diseases, hypertension, Parkinson's disease, acquired immunodeficiency syndrome, and depression (1,2). However, sex differences are still far from being generally recognized with regards to clinical manifestations and outcome in many other conditions resulting in delays diagnosis and potentially inappropriate treatment in some patients. Thus, it seems necessary to refine diagnostic criteria and treatment guidelines for these diseases germane to either sex (2). In addition, sex differences affect drug action, and it has been suggested that therapy specifically tailored to men and women should be developed; some pharmaceutical companies have begun stratifying clinical trial subjects according to sex for pharmacodynamic purposes (2,3). Nevertheless, although there is a large amount of emerging truth in these suppositions, there remain major challenges with regard to how to meet the call for better scientific inquiry into sex differences that may have clinical significance.

One of these challenges is male lupus. Systemic lupus erythematosus (SLE) is often called a “woman's disease” because of the striking differences in prevalence related to sex. As a distinct minority, males with SLE have been subordinated to females with SLE in terms of

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AUTHOR CONTRIBUTIONS

Dr. Weisman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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most health related issues (including clinical trials where males with SLE are sometimes excluded) which would be inappropriate if male SLE has its own distinguishing characteristics in terms of etiology, clinical manifestations, outcome, and drug management. Over the past few decades, rheumatologists and lupus experts have studied male lupus to try to determine whether there are distinctive, unique features. Some new research has emerged that makes a review of sex disparities in SLE especially pertinent to our understanding of the genetic and environmental aspects of SLE disease susceptibility, clinical features, and outcome.

Epidemiology

Although SLE predominantly affects females in childbearing years, it can also occur in males and at any age. According to the data accumulated in the medical literature, approximately 4% to 22% of SLE patients in reported lupus series or lupus populations are male, even reaching 30% in studies considering familial aggregations of SLE (4–19). SLE is 8 to 15 times more common in reproductive age women compared with age-matched men. Before puberty, this ratio is much lower at 2-6:1. After menopause, this ratio again decreases to 3-8:1 (20–24). A study from the UK reported the age-standardized SLE incidence as 7.89 per 100 000 for females and 1.53 per 100 000 for males during the 1990s (25). In other recent studies, a Caucasian Spanish population had an annual incidence rate of 0.54 per 100 000 inhabitants for men, and the male incidence was thought to be greater at 0.7 for every 100,000 among an Afro-American population (26,27). The female predominance in SLE is clearly evident in spite of a lower ratio in prepuberal children and after menopause.

Potential clinical characteristics in male lupus and the current dilemma

Since 1975 there have been 26 articles published addressing male SLE in an attempt to identify the distinguishing clinical characteristics of these lupus subjects. In general, the results of these studies reveal that male patients develop the typical clinical manifestations of lupus as in female subjects, yet certain key clinical manifestations may be different. To demonstrate the potential clinical characteristics in male SLE, we have displayed all clinical characteristics involved with male lupus followed by references offering evidence in 26 articles in table 1.

We observed that renal involvement was frequently found to be more common among male SLE patients. Many studies demonstrated a higher prevalence of renal disease in male patients compared to female patients, in both adult and pediatric SLE populations (7,8,14,16–18,28–33). In some studies, diffuse proliferative glomerulonephritis was observed as the dominant histological finding on renal biopsy in males(33–36). Some authors even observed an increased risk of renal failure in males (32,33,36). Among these, a study from Germany showed end-stage renal disease to develop in 5 of the 21 men (24%), but only in 6 of the 82 women (7%) (32).

Most results displayed a significantly higher prevalence of skin involvement in males as opposed to females (31,33,37). Several authors claimed that discoid lesions and/or subacute lesions were more common in male SLE patients, but malar rash was much less common

(10,16,30). However, the results from Chang et al did not support this conclusion (29) since in the latter's study, malar rash was found more commonly in males.

In addition, hematological involvement may exist more frequently in male SLE. Male dominance in hemolytic anemia, lymphopenia, and thrombocytopenia were reported in several studies (7,8,17,30,39). With regard to arthritis, there remains a significant controversy (10,12,18,29,31,34,38). Several additional clinical manifestations of SLE have been found to be more common among males with lupus. Among these are serositis (10–12,16,30,38), neurological involvement (6,7,30,40), vascular thrombosis (14,40,32), cardiovascular damage (28,32), hepatosplenomegaly (7,38), fever and weight loss at onset (17), hypertension (17), Caucasian ethnicity (18), vasculitis (7), and older mean age at diagnosis (6). Serositis has been noted as the presenting manifestation of the disease among men compared to women in several studies (4,10) but this finding has not been replicated by others. Meanwhile, Raynaud phenomenon (14,16,28,30,38), photosensitivity (16,38), mucosal ulcers (15,16) as well as lymphadenopathy (29) had been found less often in male SLE. .

With respect to serological findings (Table 2), decreased prevalence for anti-Ro (or SSA) (15,16,34) and anti-La (or SSB) (16,28) antibodies were reported in some studies. As the hallmarks for SLE, anti-dsDNA and anti-Sm antibodies shown to be more prevalent among males (14,30,37). Men more frequently had anticardiolipin antibodies, and the lupus anticoagulant was observed to occur more commonly in some studies (17,18,32). Although vascular thrombosis was observed to take place frequently in male SLE, the correlation between antiphospholipid antibodies and thrombosis in males remains unproven (32). Anti-U1RNP antibodies, low C3, low CH50 were also noted more commonly in males with SLE in several studies (17,30).

Of extreme current interest with regard to serologic findings, male and female first-degree relatives of SLE subjects in a unique population of African Americans with minimal genetic admixture had similar rates of antinuclear antibody (ANA) seropositivity. However, none of the male first-degree relatives who had significant titers of ANAs, had developed the lupus disease-specific autoantibodies (anti-dsDNA, anti-Sm, or anti-RNP), whereas 6% of the female first-degree relatives were found at least 1 positive result for these antibodies (19). This provides an interesting insight into sex differences in a study of potential progression from serologic autoimmunity to overt clinical disease in SLE (19).

However, it is well worth emphasizing that definitive distinguishing characteristics of male lupus are far from established. As displayed in Tables 1 and 2, most of these characteristics, even renal disease, were found in less than half of existing clinical studies. Since many paradoxical results have been observed, it is entirely possible that these differences are more apparent than real and reflect multiple biases among the existing clinical studies. Differing ethnic origins, variable duration of follow-up, and selective ascertainment of clinical features have been proposed as possible causes for the marked discrepancies in the prevalence of male SLE clinical features (41). In addition, the low incidence and prevalence of SLE and its female predominance lead to relatively small sample size of males with SLE in the some

studies (23); this makes a type II error affecting the results from these studies difficult to exclude completely.

Also, reliance on ACR classification criteria may be part of the problem because these proposed distinctive features are difficult to confirm, and ACR classification criteria lack sensitivity and are very limited in scope and depth. Further, a “real world” population based registry (including suspected pre-lupus patients) under the active surveillance, which would be the optimum method to capture the full spectrum of SLE and including a more accurate definition of the female-male ratio across age groups, is absent at the present time (42, 43). An example of the ideal cohort would be the ongoing Centers for Disease Control and Prevention (CDC)–sponsored SLE registry directed by McCune and Lim (44), which follows a large lupus population based on several million inhabitants in Michigan and Georgia.

Based on incomplete datasets, often biased and less than optimally controlled, we can conclude that male lupus has some potential distinguishing clinical characteristics yet possesses the same spectrum of the disease compared to female lupus.

Outcome in male SLE

Disease activity.—In spite of the impression or suspicion that males with SLE possess more severe disease activity, both sex groups have been shown to have similar average disease activity scores throughout the course of the disease in recent cohort studies (17,18). These results reflect indirectly the resemblance of clinical expression of SLE for both sexes (18). To observe the effects of active disease events over time in male lupus more accurately, Aranow et al (40) used a validated Lupus Severity of Disease Index (SDI) to assess disease severity in a retrospective multicenter case-control study. Her results revealed there was no significant difference in lupus disease severity between men and women (SDI 4.8 men vs 3.9 women). However, the conclusions of these investigators are limited because the study was hindered by both its retrospective nature and the small number of male patients (18 subjects).

Damage.—Damage, as measured in SLE cohorts, reflects total disease burden caused by the irreversible effects of both active disease and the complications of its treatment over time. As noted above, renal damage is of prime concern for severe and important organ damage in male lupus. A higher risk of developing chronic renal failure in male SLE has been reported in several studies (32,33,36). In a recent report from the LUMINA (Lupus in Minorities: NAture vs. nurture) study group, damage (quantified by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index-SLICCC) was found more common and of higher magnitude in male patients (18). Furthermore, these investigators noted male sex was not only a strong predictor of baseline damage, but also accelerated accrual of damage particularly early in the course of the disease (18). Similar to LUMINA cohort, male patients from the SLEIGH (SLE in Gullah Health) cohort had significantly higher damage scores compared with female patients (19). In another large lupus cohort-GLADEL(Grupo Latino Americano de Estudio del Lupus or Latin American Group for the Study of Lupus), males achieved a 38% greater chance of

having a SLICC score greater than 0 compared to females, but the increase was not statistically significant (17). These findings hint towards a poorer long-term prognosis among men with SLE.

Mortality.—In 1981, Wallace et al (45) reported survival data for 609 lupus patients (including 63 males) followed for a mean of ten years. The comparative 5, 10, 15-year survival rates for males and females with SLE were 77% vs 89%, 75% vs 80% and 58% vs 75%. Thereafter, a decreased survival in male SLE was observed by many additional investigators (8,17,29,46–50). These findings are consistent with a recent retrospective study of 338 patients suffering from SLE where male sex was confirmed as a risk factor for mortality (51). However, and conversely, survival rates of men were shown to better (7,52) or comparable (53–56) compared to survival rates of women in some other studies. The differences in survival rates may be ascribed to variable duration of follow-up, ethnic population differences, modes of management or treatment, and even era of investigation in these studies (29,36). Regarding causes of death, the majority of were shown to be infection, neurologic disease and end-stage renal failure in these studies and did not differ from female patients (17,29).

Quality of life.—At present, although without published studies focused on quality of life (QOL) in males with SLE, QOL in male patients might be significantly different because of potential negative feelings about suffering from a “woman’s disease” and hence different and perhaps more emotional, economical, social stresses. An assessment directed to the sex differences of QOL in patients with SLE needs to be performed to scientifically address this important question.

Male lupus and gonadal function

As early as 1978 at the National Institute of Health, a presumption was questioned that males with SLE may be less masculine than males without SLE (57). This hypothesis was attributed to the female predominance and the protective effects of androgens in the murine lupus model; Stahl et al (57) studied 12 men with the disease and observed that there was no evidence for hypogonadism or androgen deficiency in male SLE. Men with lupus are fertile, sexually active and potent, and have normal reproductive histories. Until now, only a minority of male SLE patients are observed to have clinical hypogonadism or a feminizing tendency, and some of them might be complicated by Klinefelter’s syndrome (karyotype 47,XXY) (58). Recently, Scofield et al (59) analyzed 213 men with SLE by genotype analysis with X and Y chromosome polymorphism screening. The results revealed that the frequency of Klinefelter’s syndrome is increased in men with SLE (235/10000), a 14-fold increase over the known prevalence of Klinefelter’s syndrome in an unselected male population (17 per 10,000).

In other recent studies, Soares et al (60) performed a global gonad assessment in 35 male SLE patients. They observed all male SLE patients had lower median testicular volumes and a high frequency of sperm abnormalities even if no hypogonadism was clinically manifest; however, the reasons for this were mainly attributed to intravenous cyclophosphamide therapy. This finding indicates that gonad damage secondary to cyclophosphamide treatment

in males with SLE should be given the same attention as in females with SLE. Also, glucocorticoid therapy appears to reduce sex steroids such that androgens are low among men so treated (61). Altogether these studies do suggest that mild gonadal dysfunction in men with SLE does occur for a variety of reasons that are a result of the disease and its treatment.

What makes male lupus different?

Based on clinical data generated over the past several decades, there are likely to be at least some specific features of male SLE (Table 3) but until we can address underlying causes of the disease there remains no simple explanation. Although various reasons for sex discrepancies in SLE are proposed, there are no compelling data to explain them and a satisfactory hypothesis is desired (42).

Sex hormone hypothesis.

The majority of females with lupus cluster in the reproductive ages, whilst younger or older patients are more evenly divided between the sexes. Thus, sex discrepancies in SLE certainly have been ascribed to the differences between males and females in the reproductive period. It is well known that the disparity of sex hormones between males and females greatly affects phenotypic sexual differences in this period of life as well as reproduction. Not surprisingly, research involving hormones achieved prominence in investigating the causes behind sex differences of lupus.

The possible relationship among various sex hormones and SLE has been discussed in several reviews (42,62–66). Evidence for the role of estrogen and progesterone in sex differences of SLE are derived from murine models and clinical studies even though these hormones levels are normal in most SLE patients of either sex (67). Estrogen induces autoantibodies in the non-autoimmune C5-BL16 mouse and worsens immune-complex glomerulonephritis in the MRL/lpr mouse (68). There are data in humans that support a role of these hormones in SLE risk. Oral contraceptives and hormone replacement therapy, both slightly increase the risk of later SLE (69–71). Recently, an unusual case of a transgender male who developed SLE with cardio-respiratory and renal involvement following use of exogenous female sex hormones was reported (72). The case offers additional support for the influence of sex hormones on the phenotypic expression of SLE.

Androgen metabolism is also found to have importance in SLE. Castrated male NZB/W F1 mice display earlier disease onset and a shorter life span compared to their intact male littermates (1). Lower testosterone levels have been observed in male and female patients with SLE in some studies (65,73–75), though one study of male SLE patients at diagnosis prior to treatment found no abnormalities in testosterone (67). Female SLE patients have accelerated oxidation of testosterone that might influence the immunomodulatory effects of testosterone (76). In several clinical trials, dehydroepiandrosterone (DHEA) was shown to provide therapeutic benefit to SLE patients with mild disease activity, including improvement in such outcomes as ability to taper prednisone and maintenance of stable disease with fewer flares (62).

Other hormones besides testosterone or estrogen may be important. Follicle-stimulating hormone (FSH), and luteinizing hormone (LH) have caused an induction of a lupus flare (77). In addition, prolactin accelerates the disease activity in NZB/W F1 mice and induces a lupus-like syndrome in common mice (78,79). Hyperprolactinemia occurs in 20-30% of patients with SLE including both sexes notwithstanding absence of evidence that women in lactation have a higher incidence of SLE (1).

The central core of the sex hormone hypothesis pre-supposes that differing levels of sex hormones between men and women are strongly implicated in mediating sexual dimorphism existing within the immune system producing or enhancing greater risk for SLE predilection in women. There are abundant data to prove that sex hormones have multiple effects on the immune system (62–66). For example, in the B cell compartment, both estrogen and prolactin are considered to be immunostimulators that affect maturation and selection of autoreactive B cells, as well as autoantibody secretion (80–82), while testosterone suppresses anti-dsDNA antibody production. Progesterone appears to have immunosuppressant properties (83). Interestingly, 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 (1,84). Recent data (published in abstract form) has revealed that estrogen could suppress the T regulatory compartment in healthy females. However, in established SLE, this differential effect on T-cells is not observed (85). Further, sex hormones have also been verified to modulate other immune functions including T cells maturation and activation as well as dendritic cell and cytokine networks (62,63). It has become common thought that female sex hormones, particularly estrogens, cause the enhanced autoimmune reactivity and contribute to the skewed immune milieu prone to SLE, while male hormones produce the contrary or opposite effect.

Can a sex hormone theory explain all of the differences observed in male compared with female SLE? The sex hormone hypothesis seems more conformable in murine models of SLE. Lupus is more prevalent and of greater severity in female mice compared with male mice, and the course of the disease can be modulated by changes in levels of sex steroids (1,86). However, the problem is not as straightforward in human males with SLE where their disease is equally severe or possibly worse compared to females, quite in contrast to animal models. Although case reports note individuals in whom castration has altered the severity of a lupus clinical course (87), hormone therapy shows either no or very small increases of incidence of lupus or increase in disease severity. In the SELENA trial, only a slightly increased number of mild flares were shown in the estrogen replacement therapy group with SLE (88). Further, Sánchez-Guerrero et al found no increase in flares in SLE women randomized to combined oral contraceptives, intrauterine device or progestin-only pill (89). Hence, the sex hormone hypothesis, alone, appears to be insufficient to explain sex differences in SLE incidence or severity.

Sex chromosome hypothesis.

From a fundamental standpoint, sex determination is genetic: females have two of the same kind of sex chromosome (XX), while males have two distinct sex chromosomes (XY). Not only does the X chromosome include genes that are crucial in determining sex hormone

levels (3), but also some immunologically relevant genes (such as CD40 ligand and some interferon-related genes) (87) are located on the X or Y chromosome. Obviously, sex chromosomes influence the sexual dimorphism of the immune system as well; genes on sex chromosomes are possible causes of sex discrepancy in SLE.

There is newly obtained strong evidence to support a sex chromosome theory behind the difference in incidence between males and females. The striking association between Klinefelter's syndrome and SLE had been reported recently (59). The authors inferred that two X chromosomes (whether 46,XX or 47,XXY) might confer a 10-fold higher lupus risk than only one X chromosome (46,XY) in the study. More directly, Smith-Bouvier et al (90) created a transgenic SJL mice model to permit a comparison between XX and XY within a common gonadal type. They found mice of the XX sex chromosomes, as compared with XY, regardless of phenotypic sex, demonstrated greater susceptibility to lupus. Thus both these studies, one in humans and one in mice, suggest that risk of lupus is related to the presence of more than one X chromosome but not necessarily the risk of phenotypic sex. The murine study also demonstrated increased expression of interleukin (IL)13ra2 among mice with two X chromosomes compared to those with only one X chromosome. The gene for IL13ra2 resides on the q arm of the X chromosome. The receptor itself is a decoy receptor and increased expression likely produces immune deviation towards the Th2 T helper cell phenotype (90).

In addition, Chagnon et al (91) discovered an Xp22.33;Yp11.2 translocation causing a triplication of several genes of the pseudoautosomal region 1 (PAR1) in an XX male patient with SLE. This finding points to a possible relationship between the distal end of the X chromosome short arm and SLE, in whom the testes determining factor, or sry gene, was translocated to one of his X chromosomes (91). Also, some data reveal a sex-dependent pathway of TLR7(located on Xp12.8) -induced IFN-alpha with higher production in females than males (92). A comparative gene expression analysis was then used to identify candidate genes potentially responsible for gender-dependent differences in lupus susceptibility, and seven genes encoded on the sex chromosomes were identified as differentially expressed in male versus female mice splenocytes prior to disease onset (93).

Certainly, the male-predominant BXSB murine lupus model, which has Y chromosome related SLE susceptibility (94), is a proof of principle that over-expression of a sex chromosome gene may be an etiological factor for SLE. Contemporary evidence revealed that Yaa (Y-linked autoimmune accelerator), a major genetic feature of the BXSB mice, contains a duplicated copy of TLR7, thereby increasing the BXSB mice immune response to autologous RNA (95). However, a result from the recently reported study in humans could not show there is an increase in the number of TLR7 gene copies in SLE patients or gene amplification influences the autoantibody profiles(96).

Finally, sex chromosomes carry unequal weights on a scale of biologic impact per se. For instance, a male X chromosome produces less gene product than does a female X chromosome, a maternal gene diminishes the activity of a paternal gene in females, and X inactivation may be skewed to the paternal or maternal X (42,97,98). All these foregoing

examples point to the potential pivotal role for the sex chromosomes in disease susceptibility.

An interesting hypothesis along the same lines points to skewed X-chromosome inactivation as a risk factor for SLE in women. The proposed mechanism involves skewed X inactivation in the thymus that may lead to inadequate thymic deletion and loss of T cell tolerance (82,99,100). However, the results from a study comparing the pattern of X-inactivation between SLE females and normal females argued against this hypothesis(101). Notably, this study also found no X inactivation skewing among patients with autoimmune thyroid disease as well as systemic sclerosis, both of which have had skewed X inactivation found by others (102).

Another proposed potential explanation relates to the sequences on inactive X chromosomes that may reactivate by demethylation and thereby cause gene overexpression uniquely in women, predisposing them to lupus. The study conducted by Lu et al (103) demonstrated that regulatory sequences on the inactive X chromosome demethylates T cells from women with lupus, contributing to CD40LG overexpression uniquely in women. Hence, demethylation of genes on the inactive X may contribute to the striking female predilection of this disease.

However, it remains possible that non-sex linked genes also play a role. In a differential analyses performed using MBN2 mice, two loci located on chromosomes 4 (41-72 cM, MRL/lpr allele) and 7 (4-21 cM, B6/lpr allele) were male specific and suppressed autoimmune phenotypes (104). Another comparative gene expression study in BWF1 mice revealed that 77 genes encoded on the autosomal chromosomes were identified as differentially expressed in males versus females (93). In human SLE, Xing et al (105) confirmed the linkage of SLE to 13q32 specific to predisposition of African Americans to a specific form of SLE, with males at high risk. Later, this group (106) evaluated the association between SPP1 polymorphisms and SLE in a large cohort of 1141 patients. The results suggest that the SPP1 gene might be associated with the development of SLE in general and especially in males. The findings of gender-specific human lupus candidate autosomal loci hint towards the complexity of mechanisms by which other genetic factors, not just sex linked, influence the sex discrepancy of lupus.

Intrauterine selection hypothesis.

As early as 1969, Oleinick (107) observed family histories of 191 patients with SLE and found there was a significant decrease in the ratio of liveborn males to total liveborn siblings among 581 siblings. He considered that the phenomenon could provide a partial explanation for the female preponderance in SLE. Similar observations created the theory that negative selection of male fetuses bearing factors predisposing to SLE happens early in the course of conception and pregnancy. Recently, a chart review of patients with childhood onset SLE revealed a greater number of female children in these families (108). These later studies with a small number of subjects and without precise counting of miscarriages and abortions cannot be definitive. Why male fetuses are selected against remains unresolved. It has been suggested (109) that the Y chromosome possibly contains a “lethal gene” leading to miscarriage of a male fetus who would be at a very high risk for developing SLE. Male

fetuses predisposed to SLE may be more antigenic to their mothers; the details of many of these hypotheses need further testing.

Other hypotheses.

It is an intriguing observation that male and female mice in germ-free environments are equally affected by lupus (110). This suggests a plausible explanation for female predominance in SLE in that women maybe exposed earlier or have vulnerable periods to some triggering microorganism (87). Another plausible hypothesis is that male patients with mild disease rarely consult with physicians thus leading to a statistical bias (17). This theory is supported by the observation that women, regardless of the socioeconomic or cultural situation, are more likely to seek medical care (111).

Besides sex hormones, there may be many factors in sex biology that are different between males and females in the reproductive period, and these can potentially contribute to sex discrepancy in SLE. These factors include sex-specific exposure to sperm, pregnancy created chimerism, menstrual cycles, anatomical differences, chronobiology, and as yet unknown other variables (86,87,112). It is important to emphasize that the reasons for sex discrepancy in lupus require more clarification and further investigation. Nevertheless, although the underlying mechanisms for sex differences in SLE remain largely unclear, a complex interaction of sex hormones, genetics, and environment are likely to be involved.

Summary

The striking sex difference in the occurrence of SLE indicates that sex factors (including genetic and hormonal influences) may be important in the etiology and pathology of this illness. However, the same expression of the disease in both sexes observed in existing clinical studies hint that males and females with SLE possess the same disease entity. Accordingly, it can be deduced that sex factors are probably not sufficient to ascertain the origin of lupus. Instead, sex factors merely have an important permissive impact on the development of SLE. The sex-chromosome theory brought forth via the Klinefelter's data and companion observations is currently the most appealing explanation for the differences observed in prevalence. Nevertheless, it is still uncertain whether male SLE has a set of distinctive clinical features. It is possible that sex factors in lupus more likely represent a threshold effect that could be permissive for the emergence of disease rather than producing a different disease. However, male SLE appears to have different outcomes compared to female SLE and some male specific non-sex linked genes may exist. There still is a lot of work left to be done to solve the puzzle of male SLE and potentially provide additional insights into the disease and new pathways for therapeutic interventions.

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Table 1.

The potential differing clinical characteristics of male SLE from 26 papers reporting differences in comparison between men versus women with SLE*

Characteristics	References differentially reporting the characteristic listed by type of study design in each column			
	Cohort study	Case-control analysis (matched)	Case-control analysis (non-matched)	Cases analysis without controls
Renal involvement				
Renal disease ↑	14,16-18	28	29-31	7,8
Renal disease ↑ Severe renal impairment ↑			32	
Renal disease ↑ Diffuse proliferative lupus nephritis ↑				33
Severe renal impairment ↑				
Diffuse proliferative lupus nephritis ↑			34	35
Diffuse proliferative lupus nephritis ↑ Severe renal impairment ↑			36	
Skin involvement				
Skin involvement ↑			31,37	33
Discoid lesions and/or Subacute lesions ↑, Malar rash ↓	10,16		30	
Malar rash ↑			29	
Skin involvement ↓			38	
Hematological involvement				
Hemolytic anemia ↑	17			
Lymphopenia ↑			30	
Thrombocytopenia ↑			30	7,8,39
Leucopenia ↓			34	
Joints involvement				
Arthritis ↓	10,12,18		29,34	
Arthritis ↑			31,38	
Serositis ↑	10-12, 16		30,38	
Raynaud Phenomenon ↓	14,16	28	30,38	
Neurological involvement ↑	6	40	21	7
Vascular thrombosis ↑	14	40	32	
Photosensitivity				
Photosensitivity ↓	16		38	
Photosensitivity ↑			29	
Mucosal ulcers ↓	15,16			
Cardiovascular damage ↑		28	32	
Hepatosplenomegaly ↑			38	7

Characteristics	References differentially reporting the characteristic listed by type of study design in each column			
	Cohort study	Case-control analysis (matched)	Case-control analysis (non-matched)	Cases analysis without controls
Fever at onset [↑]	17			
Weight loss at onset [↑]	17			
Hypertension [↑]	17			
Caucasian ethnicity [↑]	18			
Older mean age at diagnosis	6			
Lymphadenopathy [↓]			29	
Vasculitis [↑]				7

* SLE =systemic lupus erythematosus

[↑] = more common in males with SLE than females

[↓] =less common in males with SLE than females.

Table 2.

The potential differing serological characteristics of male SLE from 26 papers reporting differences between men versus women with SLE*

Characteristic	References differentially reporting the characteristic listed by type of study design in each column			
	Cohort study	Case-control analysis (matched)	Case-control analysis (non-matched)	Cases analysis without controls
Anti-Ro ↓	15,16		34	
Anti-La ↓	16	28		
Anti-dsDNA ↑	14		37	
IgG-ACL ↑	17		32	
LA ↑	18			
Anti-Sm ↑			30	
Anti-U1RNP ↑			30	
Low C3 ↑	17			
Low CH50 ↑			30	

* SLE =systemic lupus erythematosus; dsDNA=double stranded DNA; ACL=anti-cardiolipin antibody; LA=lupus anticoagulant; U1RNP=U1 nuclear ribonucleoprotein protein; C3=complement component 3; CH50=total complement activity;

↑ =more common in males with SLE than females;

↓ =less common in males with SLE than females.

Table 3.

Some proposed conclusions reflecting on the characteristics of male SLE obtained from the existing clinical studies^{*}

- The prevalence of SLE is far lower in males than in females, especially after puberty.
- Male SLE has the same disease spectrum as female.
- Male SLE might have some distinguishing clinical characteristics.
- Male SLE has either worse or the same disease severity than female.
- Male SLE might have a less favorable long-term outcome.
- Most men with lupus have normal gonad function.

^{*} SLE =systemic lupus erythematosus.