Effect of gender on clinical presentation in systemic lupus erythematosus

Grainne Murphy¹ and David Isenberg¹

Abstract

The incidence of SLE is markedly increased in females of child-bearing age. Although males are protected in terms of incidence of disease, it is unclear whether a distinct phenotype of male lupus exists in those who do develop SLE. We sought to explore through a detailed literature review whether gender exerts an influence on the clinical presentation and outcome of SLE. We found that males experience less of the typical mucocutaneous and musculoskeletal symptoms commonly present at diagnosis in women. On the other hand, there is limited evidence to support a negative prognostic association between male gender and disease activity or mortality.

Key words: SLE, outcome measures, lupus nephritis, male gender.

Introduction

SLE is a multisystem autoimmune condition with diverse clinical and immunological features [1]. It is characterized serologically by autoantibodies targeting self-proteins, notably ANAs, which are present in virtually all affected individuals.

The pathogenesis of SLE remains incompletely understood but most likely involves the interaction of genetic, hormonal and environmental factors [2, 3]. It is substantially more common in females of child-bearing age, where the reported female: male ratio is 8–15:1 [4]. Pre-pubertal and post-menopausal ratios are much lower at 2–6:1 and 3–8:1, respectively [5–10]. This striking predominance in females probably relates to the effect of endogenous sex hormones, which have complex effects on the immune system [11, 12]. However, a full explanation for why the disease is so uncommon in men remains elusive.

Another linked debate is whether there is a particular type of lupus among males. Opinions have varied. One of us has likened the existence of a distinct male lupus syndrome to the Loch Ness monster, i.e. often reported but not proven [13]. Others have seemed more convinced that lupus in males may take a more severe course [14], in particular with an increased incidence of renal disease, serositis, thromboses and discoid skin disease. These reports have been inconsistent and, like many studies of SLE, are complicated by disparities in ethnicity, duration of follow-up and selection bias.

We sought to explore this question through a critical appraisal of the literature in an effort to clarify whether there are true gender discrepancies in the presentation and course of SLE and if this might be reflected by an impact on survival and mortality. In particular, we also focus on the issue of a disparity in the prevalence or prognosis of LN, a particularly contentious issue in the course of lupus in men.

Clinical features

Presentation

One of the interesting issues to consider in studying gender disparities in SLE is the nature of its initial presentation in male and female patients. The greater awareness of SLE as a potential diagnosis, particularly in fertile females, may lead to a greater delay in diagnosis in men with similar symptoms. Alternatively, if men displayed an atypical phenotype at presentation, a delay in diagnosis, and thus treatment, might result. The consequence would be a greater burden of inflammation and subsequent damage over time.

Demographically it has been reported that male SLE patients are older at disease onset [15]. However, this is not strongly supported by the literature. In fact, there is little evidence to support a discrepancy in either disease onset (time of first SLE symptoms) or diagnosis (fulfilment
Interestingly, the overall trend was to a shorter delay in onset of SLE in males compared with females in the ties. Specifically, two studies have reported an older age of onset in male subjects, one of which was a study of army veterans, which seems likely to be biased by its recruitment policy [16, 20]. There is some suggestion that the age of onset in males and females may differ in certain ethnicities. Specifically, two studies have reported an older onset of SLE in males compared with females in the Caucasian subpopulation of their cohorts [14, 22]. Interestingly, the overall trend was to a shorter delay in diagnosis of male patients, with a range of 6–46 months between symptom onset and diagnosis in males and 8–58 years in females [21].

To address the clinical phenotype at presentation, a number of groups have specifically assessed organ involvement at disease onset. Although significant heterogeneity exists, the most consistent findings are a lower incidence of musculoskeletal symptoms, RP, alopecia and photosensitivity in men at diagnosis, with the suggestion of more prevalent serositis and discoid lupus. Reduced arthralgia/arthritis has been reported in Chinese (P = 0.02) [23], Greek (P = 0.004) [24] and Caucasian (P < 0.03) [25] populations. Serologically only anti-Ro antibodies have been shown to have a gender-specific association at diagnosis, being more frequently positive in females (P = 0.049) [23]. Only one study has found a greater incidence in nephropathy in men at disease onset [24], inconsistent with findings from an earlier Greek cohort [26]. Stefanidou et al. [24] also found higher frequencies of thromboses (P < 0.01) and gastrointestinal symptoms (P < 0.01) in men. Similarly, no difference in renal biopsy frequency at diagnosis or the resultant histology was shown in a Chinese SLE cohort [23]. Interestingly, a study from Latin America suggested that males may display more constitutional symptoms at diagnosis [17]; this, however, has not been reported in other geographic regions. Overall therefore, despite the suggestion that men less frequently display the typical mucocutaneous features of SLE at disease onset, this has not been reflected by a delay in diagnosis as outlined above.

Follow-up

The relative paucity of male patients with SLE has contributed to the difficulty in analysing the disease course in males. This problem has been circumvented by the use of case-control studies and a multicentre approach with more recent reports describing larger inception cohorts. Both ethnicity and age have a strong influence on SLE expression; in particular, patients of African American extraction frequently exhibit more significant renal disease, hypertension and discoid lupus and less photosensitivity [27, 28]. In comparison with Caucasians, Hispanics also have a greater incidence of arthritis [29]. Differences are also noted within ethnic subpopulations. For example, Hispanics from Texas (of Mexican/Central American ancestry) more frequently suffer from serositis, renal involvement, psychosis and thrombocytopenia and less frequently from photosensitivity and malar or discoid rash than Puerto Rican Hispanics [30]. While this may reflect the complex interplay of genetics and environment, it highlights the great difficulties in dissecting the role of gender in altered disease phenotypes from what are typically heterogeneous populations.

It seems prudent to distinguish studies from different geographical regions and ethnic populations to make cohort comparisons more meaningful. This approach may enable a better assessment of the role that gender plays in disease expression within particular population subgroups.

Asia

Previous studies have reported that Asian patients have higher rates of renal involvement, more active renal disease and higher rates of nephritis-associated autoantibodies in comparison with predominant white populations [31]. To characterize the gender-specific symptomatology in Asian patients, Mok et al. [23] performed a case-control study of 51 male and 201 female patients followed in rheumatology or nephrology outpatients. After a median disease duration of 103.6 months in males (101.6 months in females), no significant differences in major organ involvement were identifiable, despite a trend towards less RP, alopecia and arthritis in men. Importantly, there was no evidence of increased damage using the SLICC/ACR index and treatment modalities were not influenced by gender. Interestingly, male subjects appeared to have a lower number of disease flares per patient-year (P = 0.04). Serologically only anti-Ro antibody status differed by gender, present in 62% of females and 47% of men (P = 0.05). Some similarities are found between these results and an earlier case-control study by Koh et al. In this group, the incidence of renal disease and serositis was similar between Oriental male and female patients with SLE, but fewer males were seropositive for anti-Ro antibodies (P < 0.001) [32]. This group demonstrated an increased frequency of arthritis and leucopenia in females (P < 0.04). A more recent study of a Chinese cohort failed to detect a significant difference in the clinical phenotype of male patients with SLE, although a trend towards higher rates of renal involvement was reported and SLEDAI scores were significantly high in the male subgroup [33].

Thai males have also been shown to have less arthralgia than females in addition to less RP and alopecia and more prevalent thrombocytopenia (P < 0.05 for all) [18]. While the incidence of overt nephropathy did not differ, there were significantly more male subjects with increased creatinine levels over an average follow-up of 2 years (P = 0.006). A smaller study aimed primarily at dissecting the impact of gender on cutaneous manifestations of SLE found no difference between male and female patients in non-cutaneous manifestations by retrospective chart review [34].
Many large European studies have addressed the modifying effect of gender on disease expression. Even within the same population, conflicting results are reported. Both Stefanidou et al. [24] and Voulgarl et al. [26] examined the clinical phenotype of SLE in Greek patients. The latter found that men had significantly more serositis ($P < 0.01$), less photosensitivity ($P < 0.05$), oral ulcers ($P < 0.01$), RP ($P < 0.05$), thrombocytopenia ($P < 0.05$) or increased ESR ($P < 0.01$) in comparison with women [26]. There was no overall increase in renal involvement in men. In contrast, Stefanidou et al. [24] found that male SLE patients had higher rates of nephropathy ($P = 0.009$), myositis ($P = 0.023$) and tendonitis ($P = 0.007$) at follow-up, with no discernible difference in the prevalence of cutaneous or mucosal features as reported by Voulgarl et al. [26]. These differences may be somewhat biased by the recruitment process, with Stefanidou et al. basing their study on patients attending rheumatology or nephrology clinics, and by both disease duration and study type. It is interesting, however, that despite using a patient group specifically recruited from nephrology outpatients, which might be expected to result in an overall higher prevalence of nephropathy, both Voulgarl et al. (24.6% males) and Stefanidou et al. (27.1% males) report rates of renal involvement much lower than many reported studies. In terms of overall disease activity, assessed by the ECLAM index, and damage, assessed by the SLICC/ACR index, Voulgarl et al. showed no significant gender difference.

Focusing on Western European populations, four additional studies have been published addressing gender and SLE [16, 22, 25, 35]. Lopez et al. [35] examined the demographic and immunological features of a homogeneous cohort of SLE patients. Females were more commonly anti-Ro antibody positive ($P = 0.047$) and younger ($P < 0.01$) at diagnosis. In patients of similar ethnicity, Font et al. [25] failed to show a significant difference in onset age or serology, but demonstrated a lower incidence of arthritis and malar rash at follow-up ($P < 0.01$), with increased frequencies of discoid and subacute cutaneous lupus ($P < 0.03$). No difference in the incidence of nephropathy was detected. In contrast, a report from a Danish cohort described an increased incidence of nephropathy, including end-stage renal failure. The prevalence of serositis was also higher and photosensitivity less. Again this study used a recruitment approach that included nephrology outpatients, which must be borne in mind when interpreting these results [16].

UK populations, which are more ethnically diverse, are represented in a study by Renau et al. [22] using a retrospective approach. In contrast to the above, a trend towards an increase in renal failure and death was noted in females with SLE, with a significant increase in oral ulceration ($P < 0.05$) and IgM aCLs in women ($P < 0.05$).

While these studies vary considerably by design and duration of follow-up and are open to many biases, including selection bias, no clear patterns of gender-specific disease expression have emerged in European populations.

Europe

Many large European studies have addressed the modifying effect of gender on disease expression. Even within the same population, conflicting results are reported. Both Stefanidou et al. [24] and Voulgarl et al. [26] examined the clinical phenotype of SLE in Greek patients. The latter found that men had significantly more serositis ($P < 0.01$), less photosensitivity ($P < 0.05$), oral ulcers ($P < 0.01$), RP ($P < 0.05$), thrombocytopenia ($P < 0.05$) or increased ESR ($P < 0.01$) in comparison with women [26]. There was no overall increase in renal involvement in men. In contrast, Stefanidou et al. [24] found that male SLE patients had higher rates of nephropathy ($P = 0.009$), myositis ($P = 0.023$) and tendonitis ($P = 0.007$) at follow-up, with no discernible difference in the prevalence of cutaneous or mucosal features as reported by Voulgarl et al. [26]. These differences may be somewhat biased by the recruitment process, with Stefanidou et al. basing their study on patients attending rheumatology or nephrology clinics, and by both disease duration and study type. It is interesting, however, that despite using a patient group specifically recruited from nephrology outpatients, which might be expected to result in an overall higher prevalence of nephropathy, both Voulgarl et al. (24.6% males) and Stefanidou et al. (27.1% males) report rates of renal involvement much lower than many reported studies. In terms of overall disease activity, assessed by the ECLAM index, and damage, assessed by the SLICC/ACR index, Voulgarl et al. showed no significant gender difference.

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USA

The significant ethnic diversity of the US population makes discerning the impact of gender, independent of ethnicity, more difficult. This problem is further complicated by differences in age of onset between ethnic populations [36, 37], given the known modifying effect this has on disease expression [38–40]. However, several large studies have been reported that have attempted to circumvent these issues and correct for the effect of ethnicity on disease expression.

Two recent cohorts have suggested that male patients have an increase in renal disease independent of ethnicity and age [14, 41]. Both used systematic follow-up and included a large number of patients (618 and 1979 patients). Andrade et al. [41] correlated male gender with reduced musculoskeletal symptoms and higher frequencies of LA antibodies. Tan et al. showed that men had significantly increased disability, lymphopenia, thrombocytopenia and a spectrum of manifestations of renal disease (nephritic syndrome, proteinuria, haematuria, renal insufficiency and failure) ($P < 0.05$) [14]. In addition to corroborating the lower risk of musculoskeletal involvement, in the latter study men were protected from malar rash, photosensitivity, oral ulcers, alopecia and RP ($P < 0.05$). Serologically, in the Tan et al. study, men had a greater prevalence of Coombs positivity, lupus anticoagulant, low C3 anti-Sm, anti-dsDNA, anti-RNP and anti-La antibodies than females ($P < 0.05$). These results are notably out of line with any other study of male lupus. Both Tan et al. and Andrade et al. also highlighted a potential association between gender and damage. Andrade et al. reported a higher mean SDI in men at baseline and showed a positive correlation between male sex and further damage accrual [41]. Tan’s group showed evidence of increased neuropsychiatric, renal and cardiovascular damage in African American and white males in comparison with females. Interestingly, African American men were more likely than Caucasians to have discoid lupus, alopecia, renal involvement, anti-Sm antibodies and greater damage in renal and cardiovascular domains. Looking specifically at recently diagnosed disease (median duration from diagnosis to enrolment 13 months), the Carolina Lupus study showed an increase in proteinuria and haematological dyscrasias in men [42].

These data contrast notably with earlier studies that failed to identify an association between gender and renal disease. One of these studies included 2188 patients identified through the US Veterans Administration database [20]. As would be expected, this cohort was significantly older than those in other studies. While no difference in renal disease was observed, male patients had higher rates of myocardial infarction and neoplasm. Ward et al. [43] found that only an increased risk of seizures could be attributed to male gender, while Miller et al. [6] associated serositis with male SLE and females had a greater incidence of neurological involvement, thrombocytopenia and alopecia.

Clearly these studies have reported significantly differing results. It is of interest that it is the more recently
performed studies that have suggested that renal disease is more prevalent in men, even after adjusting for ethnicity. Whether this truly reflects better detection or whether it is the result of selection, referral bias or differences in other demographic details is unclear.

Latin America

There have been two large studies examining the question of disparate clinical phenotypes in men with lupus in Latin America [17, 21]. The first, a multicentre study (GLADEL cohort), found that men were significantly more likely to experience constitutional symptoms, e.g. fever and weight loss, in addition to having more cardiovascular disease (hypertension), proteinuria, cellular casts and haemolytic anaemia ($P < 0.05$) [17]. There was a nonsignificant trend towards a higher frequency of glomerulonephritis and no difference in the incidence of nephrotic syndrome or serositis. Women, on the other hand, suffered from more alopecia, photosensitivity, arthralgia and RP. Serologically only IgG aCLs and low C3 demonstrated any gender predilection (more common in men). Despite 68% of male patients having aCLs, there was no significant increase in vascular thromboses. Important, no significant difference in the objective assessments of disease activity (SLEDAI index), damage (SLICC index) or mortality was detected following adjustment for confounders.

Interestingly, an earlier cross-sectional study also found an elevated incidence of renal disease in male SLE patients (58% vs 44%) and suggested an increase in vascular thrombosis and protection from RP ($P < 0.03$) [21]. While no difference in the prevalence of IgG aCLs was detectable in this cohort, they found that anti-dsDNA antibodies appeared to be more prevalent in the male subgroup ($P = 0.002$) [21].

Renal involvement

The presence of LN impacts significantly on prognosis in SLE. Underrecognition or delayed treatment may increase the risk of chronic kidney disease and careful screening for early nephritis/nephropathy is essential. A number of studies have reported an increased incidence of renal disease in men with SLE [14, 21]. However, a greater number of studies have failed to support this.

The prevalence of renal disease varies widely among studies and may depend on the definition of renal involvement used. While a number of groups from different geographic regions have shown that male subjects had an increased incidence of proteinuria [14, 17], cellular casts or renal insufficiency (elevated serum creatinine) [14, 17], this was not associated with an increase in end-stage renal failure or patients requiring transplantation. Indeed, only two studies were able to demonstrate an increase in renal failure in male subjects [14, 16]. Interestingly, there is no evidence to suggest a predilection for any particular histological class of LN in males [23]. Moreover, the use of cytotoxics, commonly required to treat LN, has not been shown to associate with male gender.

De Carvalho et al. [44] specifically addressed the question of gender outcomes in LN and found no increase in mortality in men with LN. While they found no gender-specific pattern of histological class, male patients had higher activity scores and higher serum creatinine. No difference was detectable in histological chronicity scores or in the requirement for dialysis/transplantation. More recently, Wang et al. [45] reported that Chinese males had significantly lower ratios of complete and partial remission and had higher serum creatinine. However, using multivariate analysis, male gender was not found to be associated with an adverse renal outcome.

The association between male gender and nephropathy in SLE remains tenuous at best. There is limited evidence from many geographic regions, perhaps most consistently in Latin America and more recently in the USA, to suggest a weak association. It is known that multiple other confounding factors such as hypertension (known to be increased in males), ethnicity and onset age also influence renal disease and not all studies make the appropriate statistical adjustment to account for such variables.

Morbidity/mortality

Life expectancy of patients with SLE is reduced in comparison with that of an age-matched general population [46]. The suggestion by some that a number of aspects of disease thought to carry a worse prognosis, notably renal disease, are amplified in men might suggest that mortality rates would be increased in men with SLE.

Interestingly among those studies that have addressed this outcome measure, the most consistent finding is that the overall mortality rates in men are comparable to those in women. Of the studies that have addressed mortality rates, four found no difference overall between male and female patients [17, 21, 22, 44] and three suggested an increase in mortality in male patients [14, 20, 45]. Tan et al. [14] showed that the mortality rate was significantly elevated in male lupus patients, with a mortality rate of 11.5% in comparison with 6.2% in the female cohort. Prete et al. [20] also found an elevated mortality rate in males, but only within the first year after diagnosis. It should be highlighted that the latter study of the US veteran population included an older population, and the male cohort was significantly older than the female cohort. Specifically men had increased rates of myocardial infarction and neoplasia [20]. Finally, Wang et al. [45] reported higher rates of mortality in men with LN; however, this study had a small number of male subjects, which limits its power to detect a statistically relevant effect. The causes of death outlined in both these and other studies, which did not detect a difference by gender, included both SLE-specific and other causes. The low overall numbers do not permit a conclusive analysis of whether SLE-specific mortality is more associated with male gender and this needs to be addressed in prospective cohorts of greater duration.

Given the magnified cardiovascular risk recognized in SLE patients [47], it is an interesting variable to study as it may confer an increased risk over a longer time frame than may be captured within current studies. Many use the term cardiovascular disease as an all-embracing term...
to encompass a spectrum of disease from arterial hypertension to angina/myocardial infarction. A number of studies have shown that cardiovascular disease is amplified in men with SLE [16]. In particular, in a few studies male gender has been associated with greater hypertension [14, 16, 21], angina, MI and even CVA [24] in early disease. Whether this reflects the general enhanced cardiovascular risk in the male population or is further magnified by the inflammatory state of SLE in men is unknown.

Previous evidence also emphasizes the importance of capturing information on SLE-related damage as a prognostic indicator, with elevated damage scores associated with greater mortality [48]. Of the many studies that have included information on damage, only one showed an association between male gender and damage at baseline, with a shorter time to accrual of further damage [41]. Certainly the evidence from research to date is that despite the suggestion of greater frequencies of particular organ involvement in male subjects of certain ethnicities, this is not reflected in the limited information on mortality and morbidity captured by the SLICC index.

Discussion

The debate as to whether there truly is a different disease course in men with SLE has continued. Complicated by low patient numbers, studies that fail to correct for differences in disease duration, ethnicity, co-morbidities or that have potential selection bias may lead to a skewed representation of the clinical phenotype in men. Nonetheless there are suggestions that a number of clinical characteristics may be differentially expressed (Table 1 presents a summary of clinical and demographic findings from main studies summarized in Table 2). There is consistent evidence for a reduced incidence of RP, alopecia, malar rash and arthralgia/arthritis in men at presentation and in the subsequent disease course. In contrast, it cannot be reliably said that there is a definite increased incidence of nephropathy, thrombotic episodes, damage or, most importantly, a greater mortality risk. Prognostically it appears evident from the available literature that disease severity in male lupus is little different overall than in female patients.

There is no doubt that males are protected, in incidence, from SLE, and this has been ascribed to many things. In particular, the role of oestrogen and other gonadal hormones in the alteration of immune cell function has been explored [49-52]. Other alternate theories abound, including an X-chromosome hypothesis (as supported by the increased incidence of SLE in patients with Klinefelter’s syndrome) [53], various somatic genetic polymorphisms [54] and disparities within the Toll-like receptor and interferon pathway [55, 56]. Interestingly, despite the strong evidence implicating sex hormones in SLE pathogenesis, there is limited evidence to suggest an altered hormonal milieu in men with lupus [57, 58]. While some have documented biochemical hypoandrogenism in this cohort [59], this is complicated by concomitant corticosteroid therapy, which can have a similar effect [60]. While it may be a contributing factor, more work is required to clarify the true reasons for the protection of the male gender from SLE.

<table>
<thead>
<tr>
<th>Increased in men</th>
<th>Decreased in men</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>[19]</td>
<td>[14, 17, 18, 24, 25, 32, 40]</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>[14, 17, 19, 24, 26]</td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>[14, 26]</td>
<td>[14, 17, 19, 18, 21, 23, 24, 26]</td>
</tr>
<tr>
<td>RP</td>
<td>[14, 17, 19, 21, 23, 24]</td>
<td></td>
</tr>
<tr>
<td>Discoid lesions</td>
<td>[23, 25, 33]</td>
<td>[14, 22, 26]</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>[14, 22, 26]</td>
<td>[6, 14, 17, 18, 19, 23, 24]</td>
</tr>
<tr>
<td>Alopecia</td>
<td>[6, 14, 17, 18, 24, 26]</td>
<td></td>
</tr>
<tr>
<td>Any renal disease</td>
<td>[14, 16, 17, 18, 21, 41]</td>
<td></td>
</tr>
<tr>
<td>CNS disease</td>
<td>[42]</td>
<td>[6]</td>
</tr>
<tr>
<td>Serositis</td>
<td>[6, 16, 19, 26]</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>[14, 18, 41]</td>
<td>[6, 26]</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td>Recorded in five other studies. No change in [17, 23, 26, 40, 43]</td>
</tr>
<tr>
<td>Damage</td>
<td>[14, 40] (baseline)</td>
<td>Recorded in three other studies with no significant effect of gender [17, 23, 26]</td>
</tr>
<tr>
<td>Mortality</td>
<td>[14, 20, 44]</td>
<td>No change in [17, 21, 22, 43]</td>
</tr>
<tr>
<td>Thromboses</td>
<td>[14, 21, 24]</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>[24]</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>[14, 16, 17, 24] (CVA)</td>
<td>Flares/severe flares [23]</td>
</tr>
<tr>
<td>Other</td>
<td>[17]</td>
<td>(constitutional symptoms)</td>
</tr>
</tbody>
</table>

The results depict studies where significant ($P < 0.05$) differences were detected. *Seizures.*
TABLE 2 Summary of main clinical and demographic findings of comparative studies of male and female lupus

<table>
<thead>
<tr>
<th>Country (ethnicity)</th>
<th>Study type</th>
<th>Size (% male)</th>
<th>Age at onset</th>
<th>Features increased in men</th>
<th>Features increased in women</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (multi-ethnic) [40]</td>
<td>Prospective cohort</td>
<td>618 (10.2)</td>
<td>37.1 (M), 36.5 (F)</td>
<td>Renal</td>
<td>Musculoskeletal</td>
<td>LAC (M)</td>
</tr>
<tr>
<td>US (multi-ethnic) [41]</td>
<td>Case control</td>
<td>265 (9)</td>
<td>NA</td>
<td>Proteinuria, lymphopenia, ↓ platelets</td>
<td>6 antibodies assayed, P &gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Greek [26]</td>
<td>Retrospective</td>
<td>580 (1.4)</td>
<td>34.6 (M), 31.4 (F)</td>
<td>Photosensitivity, RP, oral ulcers, anaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian [32]</td>
<td>Retrospective</td>
<td>147 (41.5)</td>
<td>28.2 (M), NA (F)</td>
<td>Arthritis, leucopenia</td>
<td>Anti-Ro (F)</td>
<td></td>
</tr>
<tr>
<td>UK (multi-ethnic) [22]</td>
<td>Retrospective</td>
<td>484 (9.3)</td>
<td>30.9 (M), 29.1 (F)</td>
<td>Oral ulcers</td>
<td>IgM aCL (F)</td>
<td></td>
</tr>
<tr>
<td>Latin America [17]</td>
<td>Inception cohort</td>
<td>1213 (10.1)</td>
<td>27 (M), 29.2 (F)</td>
<td>Constitutional symptoms, proteinuria, any renal, haemolytic anaemia</td>
<td>Arthralgia, alopecia, photosensitivity, RP, any cutaneous Low C3, IgG aCL (M)</td>
<td></td>
</tr>
<tr>
<td>Latin America [21]</td>
<td>Cross-sectional</td>
<td>1316 (8.1)</td>
<td>26 (M), 28 (F)</td>
<td>Renal</td>
<td>RP</td>
<td>dsDNA (M)</td>
</tr>
<tr>
<td>Thai (Asian) [18]</td>
<td>Retrospective case-control</td>
<td>111 (33.3)</td>
<td>34.6 (M), 34.4 (F)</td>
<td>↓ Platelets, ↑ serum creatinine</td>
<td>Alopecia, arthralgia, RP, psychosis</td>
<td>7 antibodies assayed, P &gt; 0.05</td>
</tr>
<tr>
<td>Oriental [23]</td>
<td>Retrospective control</td>
<td>252 (20.2)</td>
<td>31 (M), 31.9 (F)</td>
<td>Serositis, nephropathy, hypertension</td>
<td>RP, alopecia</td>
<td>Anti-Ro (F)</td>
</tr>
<tr>
<td>Danish [45]</td>
<td>Retrospective</td>
<td>513 (11.5)</td>
<td>46.2 (M), 36.2 (F)</td>
<td>Nephropathy, tendonitis, myositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greek [24]</td>
<td>Retrospective</td>
<td>743 (7.9)</td>
<td>34 (M), 31 (F)</td>
<td>Serositis, subacute cutaneous LE</td>
<td>Photosensitivity</td>
<td>3 antibodies assayed, P &gt; 0.05</td>
</tr>
<tr>
<td>Spanish [25]</td>
<td>Prospective</td>
<td>261 (11.5)</td>
<td>34 (M), 31 (F)</td>
<td>Discoid LE, Malar rash</td>
<td>6 antibodies assayed, P &gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>US (multi-ethnic) [14]</td>
<td>Retrospective</td>
<td>1979 (7.9)</td>
<td>49.8 (M), 37.6 (F)</td>
<td>Hypertension, renal disease, thrombotic episode, hypertension, disability, lymphopenia</td>
<td>Malar rash, photosensitivity, oral ulcers, alopecia, RP, arthralgia</td>
<td>Anti-Sm, DAT, LAC, anti-dsDNA, low C3 (M)</td>
</tr>
<tr>
<td>US [6]</td>
<td>Prospective control</td>
<td>100 (50)</td>
<td>45 (M), 44 (F)</td>
<td>Serositis</td>
<td>Neurological, alopecia, ↓ platelets</td>
<td></td>
</tr>
<tr>
<td>US [27]</td>
<td>Inception</td>
<td>361 (17.2)</td>
<td>44.7 (M), 35.2 (F)</td>
<td>Seizures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Findings with a significant difference between genders are reported (P < 0.05). Not all studies report figures adjusted for multiple comparisons. DAT: direct antiglobulin test; F: female; LAC: lupus anticoagulant; M: male; NA: not applicable.
Conclusion

Despite the suggestion by many that men with lupus demonstrate a distinct disease profile and a more aggressive disease course, notably of LN, this has not been consistently found in the literature and has not translated into significant differences in objective indices of disease activity, damage or mortality. While some of the more typical mucocutaneous features of SLE appear to affect females preferentially, the frequency of such manifestations varies widely between studies and still remains the most prevalent of lupus manifestations in men. Moreover, certain lupus features, such as thrombocytopenia and neurological involvement, have been shown by some to be more prevalent and others to be reduced in male lupus sufferers. Too few studies have consistently provided evidence for correction of the effect of notable confounders, such as ethnicity, duration of follow-up, age of onset and comorbidities, or indeed for multiple comparisons that would likely alter the significance of studies with weaker results. It is evident that a clear gender effect on SLE phenotype remains elusive.

Rheumatology key messages

- The age of onset is similar in male and female patients with lupus.
- Men with lupus display decreased musculoskeletal symptoms, photosensitivity, oral ulcers and RP than women.
- There is no clear association between gender and mortality or disease activity in SLE.

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References


31 Mok MY, Li WL. Do Asian patients have worse lupus. Lupus 2010;19:1384–90.


