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Effect of Gender on Clinical Presentation of SLE in Assiut University Hospitals

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune illness with an unknown cause. Autoantibody generation and probable involvement of practically every organ are hallmarks of SLE. There have been reports of significant regional variations in SLE prevalence. This difference is probably brought on by a number of sociodemographic factors, including ethnicity, geography, social support, medication compliance, environmental and occupational factors, as well as race and ethnicity. SLE generally affects women more frequently than it does men. But the severity of a disease is significantly impacted by gender difference.

Objective: The study's goals were to look at the impact of age at onset and gender on illness features.

Patients and methods: This was a prospective cross-sectional study carried out in Assiut University Hospital, Internal Medicine Department, registered in **Clinical trial.gov**: NCT04234633. SLE diagnosed based on criteria were recruited.

Results: Our study included 185 patients, 75 were males and 110 were females. It revealed that there was statistically significant increase in alopecia and arthritis in the female group while increased incidence of nephritis and thrombocytopenia in the male group. Also, male patients have higher Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC DI) compared to females. On the other hand, there was no difference between the two groups regarding other manifestations of SLE, serological markers or severity indices. **Conclusion:** We concluded that gender could influence the clinical picture of SLE and the outcome.

Keywords: Systemic lupus erythematosus, Gender influence, Nephritis, Male lupus.

INTRODUCTION

Systemic lupus erythematosus (SLE) commonly occurs in females at reproductive age which implicates that sex hormones play an essential role in disease pathogenesis. The risk of SLE flare is 1.34 times more with hormone-replacement therapy, it illustrates how sex hormones affect disease activity. Moreover, low levels of dehydroepiandrosterone (DHEA) and estrogen formation, have been linked to a propensity for SLE [1]. In comparison to those during childbearing years, the female to male SLE ratios in prepubertal and postmenopausal women range from 2 to 6:1 and 3 to 8:1, respectively. At the clinical level, when women and men exhibit different characteristics, the sex disparities in illness vulnerability are evident. Numerous research on progressive systemic sclerosis (PSS), multiple sclerosis, systemic sclerosis, and rheumatoid arthritis have emphasised sex variations in disease presentation with relation to disease severity, symptoms, or comorbidities [2]. When compared to controls of the same age, SLE patients were shown to have a lower relative mortality risk when they had low female sex hormone levels at the time of the disease's beginning [3]. In terms of clinical symptoms and prognosis, male sex has been linked to a more severe type of SLE [4].

The goal of this study was to elucidate the impact and the prognostic effect of age at onset and gender on SLE severity and manifestations.

PATIENTS AND METHODS

The current study was conducted at Internal Medicine Department of Assiut University Hospital, Assiut, Egypt. It enrolled patients with SLE. Disease activity for each patient was determined using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [5]. Organ involvement was also defined according to the SLICC/American College of Rheumatology-Damage Index (SLICC/ACR-DI) [6].

Inclusion Criteria: We included male and female patients with SLE ≥ 18 years old diagnosed with SLE

Exclusion Criteria:

We excluded SLE patients with drug-induced lupus, discoid lupus without systemic manifestations and pregnant women. In addition to patients with major comorbidities or concomitant malignancies.

Ethical approval: The Academic and Ethical Committee of Assiut University approved the study. All participants gave signed informed permission after being told of the study's goal. The worldwide medical association's code of ethics, the Declaration of Helsinki for Humans, was adhered to throughout the course of this study. The study was registered on ClinicalTrials.gov Identifier: NCT04234633

Statistical analysis: Version 24 of the Statistical Package for the Social Sciences (SPSS) was used to analyse the data. The mean ± standard deviation (SD), median and range were used to convey quantitative data. Frequency and percentage were used to convey qualitative data. When comparing two means, the independent-samples t-test of significance was used. Chi-square test was performed to compare qualitative data. P-values under 0.05 were regarded as significant.

RESULTS

Demographic data of studied participants according to gender (Table 1): We found statistically significant increased BMI in female group when compared to male group. The smoking status was significantly higher among the male group as compared to the female group.

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Table (1): Demographic data of studied participants according to gender (n=185)

Variable name	Male (n=75)		Female (n=110)		P value
Age (years)					0.695
• Mean ± SD	31.84 ± 5.87		31.61 ± 5.39		
• Median (range)	34 (21 – 40)		31 (21 – 40)		
Age of onset (years)					0.941
• Mean ± SD	25.69 ± 5.39		25.75 ± 5.35		
• Median (range)	26 (17 – 37)		26 (17 – 38)		
BMI (kg/m^2)					**0.000***
• Mean ± SD	26.64 ± 3.09		28.25 ± 2.98		
• Median (range)	26.6 (21.7 – 33.6)		27.8 (22.0 – 33.6)		
Disease duration (years)					0.289
• Mean ± SD	6.44 ± 2.91		6.14 ± 3.13		
• Median (range)	6 (1 – 13)		5 (1 – 15)		
Smoking status					**0.000***
• Non-smoker	44	(58.7)	110	(100.0)	
• Smoker	31	(41.3)	0	(0.0)	
Residence					0.987
• Urban	34	(45.3)	50	(45.5)	
• Rural	41	(54.7)	60	(54.5)	

*: Significant, BMI: Body mass index

Clinical presentations of studied participants according to gender (Table 2):

Alopecia was significantly more frequent in females than in males. Other mucocutaneous manifestations were not significantly different. Arthritis was more frequent in females than in males. Nephritis and thromboembolism were more frequent in males than in females.

Table (2): Clinical presentations of studied participants according to gender (n=185)

Clinical presentations	Male (n=75)		Female (n=110)		P value
Constitutional symptoms					
- **Fever**	36	(48.0)	46	(41.8)	0.406
- **Loss of weight**	14	(18.7)	14	(12.7)	0.268
Mucocutaneous manifestations					
- **Malar rash**	36	(48.0)	54	(49.1)	0.884
- **Oral ulcers**	26	(34.7)	38	(34.5)	0.986
- **Alopecia**	13	(17.3)	41	(37.3)	**0.003***
- **Photosensitivity**	32	(42.7)	49	(44.5)	0.800
Neuropsychiatric					
- **Seizures**	4	(5.3)	9	(8.2)	0.457
- **Psychosis**	5	(6.7)	12	(10.9)	0.327
Vasculitis	13	(17.3)	21	(19.1)	0.762
Serositis	20	(26.7)	27	(24.5)	0.745
Arthritis	49	(65.3)	88	(80.0)	**0.025***
Nephritis	51	(68.0)	51	(46.4)	**0.004***
Gastrointestinal tract symptoms	23	(30.7)	31	(28.2)	0.715
Thromboembolism	10	(13.3)	5	(4.5)	**0.032***

*: Significant

Laboratory data of studied participants according to gender (Table 3)

Thrombocytopenia was more frequent in males than in females. Other hematological manifestations were not significantly different. Regarding inflammatory markers; CRP was significantly higher in female group as compared to male group. ESR was comparable between both groups. No statistically significant difference was found between studied groups (males and females) as regard to disease activity (as measured by SLEDI), while SLICC DI was significantly higher among male patients.

Table (3): Laboratory data of studied participants according to gender (n=185)

Clinical presentations	Male (n=75)		Female (n=110)		P value
Hematological manifestations					
• Leukopenia	31	(41.3)	60	(54.5)	0.078
• Thrombocytopenia	24	(32.0)	21	(19.1)	**0.045***
• Hemolytic anemia	8	(10.7)	11	(10.0)	0.883
Serological markers					
ANA					1
• Negative	2	(2.7)	3	(2.7)	
• Positive	73	(97.3)	107	(97.3)	
Anti-dsDNA					0.306
• Negative	25	(33.3)	29	(26.4)	
• Positive	50	(66.7)	81	(73.6)	
Hypocomplementemia					0.656
• No	40	(53.3)	55	(50.0)	
• Yes	35	(46.7)	55	(50.0)	
Inflammatory markers					
ESR (mm/h)					0.152
• Mean ± SD	52.05 ± 13.00		54.86 ± 13.37		
CRP (mg/L)					**0.047***
• Mean ± SD	44.63 ± 10.95		47.76 ± 11.12		
SLEDAI					0.149
• Mean ± SD	11.27 ± 2.65		9.85 ± 2.45		
SLICC/ACR DI					**0.017***
• Mean ± SD	0.92 ± 0.21		0.54 ± 0.12		

*: Significant

DISCUSSION

There were 185 patients in the current research, with 75 (40.5%) men and 110 (59.5%) women, for a female:male ratio of 1.5:1. The recent study by **Margery-Muir *et al.*** [7] reported that the female to male (F:M) incidence of SLE varied with age, being approximately 1 during the first decade of life, followed by a sharp increase to 9 during the fourth decade, thence declining in subsequent decades before an increase during the seventh or eighth decade. This reported ratio is lower than the ratio documented by that study, and the study of **Mohamed *et al.*** [8], another Egyptian study, who reported a ratio of 10:1 ratio in adult patients with SLE. Meanwhile, difference in female: male ratio in our study was obeying our inclusion and exclusion criteria.

Both studied groups were matched regarding the baseline demographic data namely (age, age of disease onset, disease duration, and residence) to exclude the effect of these factors on our studied hypothesis.

In the current study, we found that the examined female group's BMI (kg/m^2) was substantially greater than the studied male group. Obesity is becoming more common and is associated with a higher risk of developing various autoimmune disorders, including SLE, most likely due to the production of inflammatory adipokines [9].

Also, we observed significantly higher smoking status among male patients. This is consistent with the data released by Global Adult Tobacco Survey (GATS) and the recent Egyptian demographic and health survey that smoking is a bad social habit among Egyptian males. This poll shows that 43% of men and 1% of women now use cigarettes [10].

Regarding a wide range of illness presentations and outcomes, we found variations between males and females. Among the variations identified in our investigation, some mucocutaneous features such as alopecia were significantly different in both studied groups, where alopecia was more common in males. Other mucocutaneous manifestations were not significantly different. Also, we observed that arthritis was more frequent (80.0%) in females than in males (65.3, and 13.3%).

The gender difference in clinical symptoms in SLE patients is still debated, and prior research in this field produced contradictory findings. A decrease in alopecia was reported in many previous studies. Also, in agreement with our study several others [11-18] that found less arthritis in male SLE. Also **Schwartzman-Morris and Putterman** [19] indicated that women were more likely to suffer from arthritis and/or arthralgia.

Tan *et al.* [20] showed no difference in arthritis according to patient gender, contrary to several research that indicated a greater incidence of arthritis in the male SLE group [17, 18, 21]. In a previous cross-sectional investigation, **Molina *et al.*** [22] compared a cohort of

1,209 Latin American female patients with SLE to 107 Latin American male patients. In this population, arthritis, skin, involvement, and renal disease were the three most prevalent findings in males.

The frequency of thrombotic events is another illustration. We found that thromboembolism was more frequent (13.3%) in males than in females (4.5%). In accordance, some studies found a similar higher incidence in male SLE [23, 24], on the other hand, a recent Egyptian research by **Niazy *et al.*** [25] reported no statistically significant difference in the incidence of thrombosis between male and female SLE patients. The variations in patient selection, illness durations, presentations, and ethnicity are mostly to blame for the variations in findings. We made every effort to combine these parameters as much as possible in the current investigation. Males and females in the current sample were of the same ethnicity and had similar illness durations, ages, and presentation ages.

In the current study we found that nephritis and thromboembolism were more frequent (68.0% and 13.3%) in males than in females (46.4, and 4.5%) respectively. Other clinical manifestations were not significantly different between both studied groups.

Males had a greater frequency of proliferative nephritis, according to several data with biopsy findings [19, 26]. Men with renal involvement have a dismal prognosis. Contrary to the male hormones, testosterone and dehydroepiandrosterone, the major female hormone, 17-estradiol, has been shown to be able to control inflammatory and proapoptotic processes as well as preserve the renal tissue [2, 19].

The reason for the gender difference in SLE, despite its obvious existence, is still unknown. Different explanations have been proposed by researchers from throughout the world. However, none of these hypotheses can fully account for the gender disparity in clinical findings and prognosis, which is primarily the result of the interplay of sex hormones, genetics, and environmental variables [25].

Regarding serological findings namely (ANA, anti-ds DNA antibody, and hypocomplementemia) no significant difference was observed between both studied groups. Conversely; **Molina *et al.*** [22] in Latin American patients, and **Niazy *et al.*** [25] observed an increase in anti-ds DNA antibody positivity in male SLE patients in Egyptian patients.

For inflammatory markers, no significant difference was observed between both studied groups regarding to ESR level, significant difference was found between both studied groups regarding to CRP, which was higher in female patients. Despite this, the significance of CRP in active SLE is still unclear and debatable. According to some research, CRP levels in active SLE are either normal or very mildly raised, and there is no correlation between CRP levels and clinical disease activity [27].

Male lupus patients had higher SLEDAI scores than female lupus patients had during their most recent visit, according to **Niazy *et al.*** [25], who observed that there was no difference in baseline SLEDAI between the two lupus groups.

CONCLUSION

We concluded that the age of onset is similar in male and female patients with lupus. Arthritis, nephritis, malar rash and photosensitivity represented the most common clinical manifestations in both sexes. Although, men with lupus display decreased arthritis and alopecia than women, renal disease and thromboembolic events are more prevalent as well as thrombocytopenia.

To confirm this conceivable casual relationship and determine if male patients are more likely to experience poorer outcomes and more severe types of lupus nephritis, further large-scale research are necessary. A national data register for lupus patients is also advised to be established.

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