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PAPER

Male systemic lupus erythematosus in a Latin-American inception cohort of 1214 patients

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The objective of the study was to evaluate the influence of the male gender in the clinical presentation and outcome of systemic lupus erythematosus in a prospective inception cohort of Latin-American patients. Of the 1214 SLE patients included in the GLADEL cohort, 123 were male. Demographic characteristics as well as clinical manifestations, laboratory profile, activity and damage scores were evaluated at onset and during the course of the disease and compared with female patients. The median age at onset of the male patients was 27 and that at diagnosis 29.2 years. Delay to diagnosis was shorter in males (134 versus 185 days, $P = 0.01$). At onset, men more frequently showed fever (42.3 versus 27.0%, $P = 0.001$) and weight loss (23.6 versus 11.8%, $P = 0.001$). During disease course the incident of symptoms was: fever, 67.8 versus 55.6%, $P = 0.012$; weight loss, 47.2 versus 24.3%, $P = 0.001$; arterial hypertension, 37.4 versus 25.8%, $P = 0.007$; renal disease (persistent proteinuria and/or cellular casts), 58.5 versus 44.6%, $P = 0.004$); and hemolytic anemia, 19.5 versus 10.9%, $P = 0.008$. The laboratory results showed that: men more frequently had IgG anticardiolipin antibodies (68.2 versus 49%, $P = 0.02$) and low C3 (61.3 versus 48.1%, $P = 0.03$); 5/123 men died (4%) compared with 29/1091 women (2.7%). In conclusion, 10% of GLADEL's cohort patients were male. They showed a distinctive profile with shorter delay to diagnosis, higher incidence of fever, weight loss, arterial hypertension, renal disease, hemolytic anemia, IgG anticardiolipin antibodies and low C3. Although not statistically significant, mortality was higher in men. *Lupus* (2005) **14**, 938–946.

Key words: gender; Latin-American; male SLE; systemic lupus erythematosus

Introduction

An old observation in systemic lupus erythematosus (SLE) is the female preponderance, especially in young adults. This female-to-male ratio is much lower in prepuberal children and after menopause.[1,2]

A higher frequency of renal disease was described in male patients without significant differences in survival rates and main causes of death.[3] It has been reported that males with lupus showed more hemolytic anemia, seizures, lupus anticoagulant, low complement and morbidity than females.[4] In fact, supporting evidence is provided by the literature showing that males have either a worse or the same prognosis, but not better, than females.[5]

The grupo latinoamericano de estudio del lupus (GLADEL), started in 1997 as a multinational inception prospective cohort in Latin American centres having expertise in the diagnosis and management of SLE. The data from the first 1214 patients was incorporated in a computer database available to all groups and interconnected among them.

The main purpose of the present study was to analyse the influence of gender in the disease pattern and prognosis in a prospective cohort of SLE patients from 34 centres from nine Latin-American countries: Argentina, Brazil, Colombia, Cuba, Chile, Guatemala, México, Peru and Venezuela.

In memory of Dr Donato Alarcón-Segovia.

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Patients and methods

Selection of centers was undertaken according to the following criteria: experience in SLE (tertiary referral centres with a lupus clinic, an academic profile and a rheumatology training programme); a genuine interest in the research project; the presence of an identified leader; and adequate human, technical and communication facilities.

In the initial cohort each center was asked to incorporate a minimum of 20 and a maximum of 30 randomly selected patients. Randomization was performed locally in each centre.[6]

The first patients were entered in October 1997, and to insure their recent onset they could only be included if the diagnosis of SLE had been made after 1 January 1996. Fulfillment of four ACR 1982 SLE criteria[7] at the time of diagnosis was not mandatory and diagnosis of SLE was performed based on clinical and laboratory data at that time and according to the expertise of the investigator. After incorporating the initial 30 patients, each group continued to include one new randomly selected patient per month diagnosed within the previous two years.

Every group used ARTHROS as a common database to collect information and analyse data. ARTHROS 6.0 is a user-friendly database developed by Argentine rheumatologists using a Windows platform, Visual Basic language and Microsoft Access. It is compatible with Microsoft Excel. The database includes patient-level information about socio-demographic characteristics, clinical manifestations, classification criteria, activity and damage ratios, treatments, and a complete list of the most available laboratory tests.[6]

The clinical and laboratory manifestations were evaluated at onset of disease and during the course (cumulative incidence). Studies were performed in the standard routine laboratory at each centre. Autoantibodies and complement tests were performed at each centre and the cutoff values were considered valid. Standardization of immunologic tests between centres is being incorporated but was not yet available at the time of the current study.

The activity index (SLEDAI) was measured at the time of entry and then twice a year, and the damage index (SLICC/ACR- ID) at entry and then yearly.[8–10]

Statistical analysis

Comparisons by gender were performed for categorical variables using Fisher's exact test. The comparisons for continuous variables were carried out using the Wilcoxon sum rank test. To analyse the impact of the gender on the disease activity, a logistic regression model for the outcome variable 'maximum SLEDAI score' considered as a binary variable (>12 versus ≤ 12) was developed. Covariates included in the model besides gender were those socio-demographic variables associated with the outcome that can play a role as potential confounders. The results of the models are presented as adjusted odds ratios which compare the odds of presenting the outcome for males versus the odds of presenting the outcome for females, adjusting for confounders.

Likewise, logistic regression models were developed for the outcomes: maximum SLICC score (≥ 1 versus 0), cardiovascular manifestations (yes/no) and infections (yes/no). *P*-values less than 0.05 were considered statistically significant.

Mortality rates were estimated using the Kaplan–Meyer method with differences between being evaluated using the log-rank test.[11]

Results

Demographic variables

Of the 1214 patients included in the GLADEL cohort, 123 (10.1%) were men. In 77 out of 123 male patients (62.6%) the onset of the disease was registered in the range of 11–40 years of age, with the maximum peak between 31 and 40 years of age. On the other hand, the female patients had their maximum peak between 21 and 30 years of age (Figure 1).

No statistical imbalances were observed between men and women with respect to ethnic group, medical insurance, education and socioeconomic status. Even though significant differences were not observed in both age at onset and age at diagnosis between genders, the delay to diagnosis was significantly higher in women than in men ($P = 0.011$; Table 1).

Clinical data

Clinical manifestations observed during the first month of onset, and evolving, are summarized in Table 2.

Onset of the disease. When compared with women, male gender was significantly associated with a compromised general condition (56.1 versus 42.2%, $P = 0.004$), fever (42.3 versus 27%, $P = 0.001$) and loss of weight (23.6 versus 11.8%, $P = 0.001$). The rest of the clinical manifestations did not differ between men and women, except for a higher prevalence of neurological manifestations in women (4.5 versus 0.8%, $P \leq 0.053$).

Cumulative manifestations (Table 2). Compared with women, male patients had more frequent fever (67.8

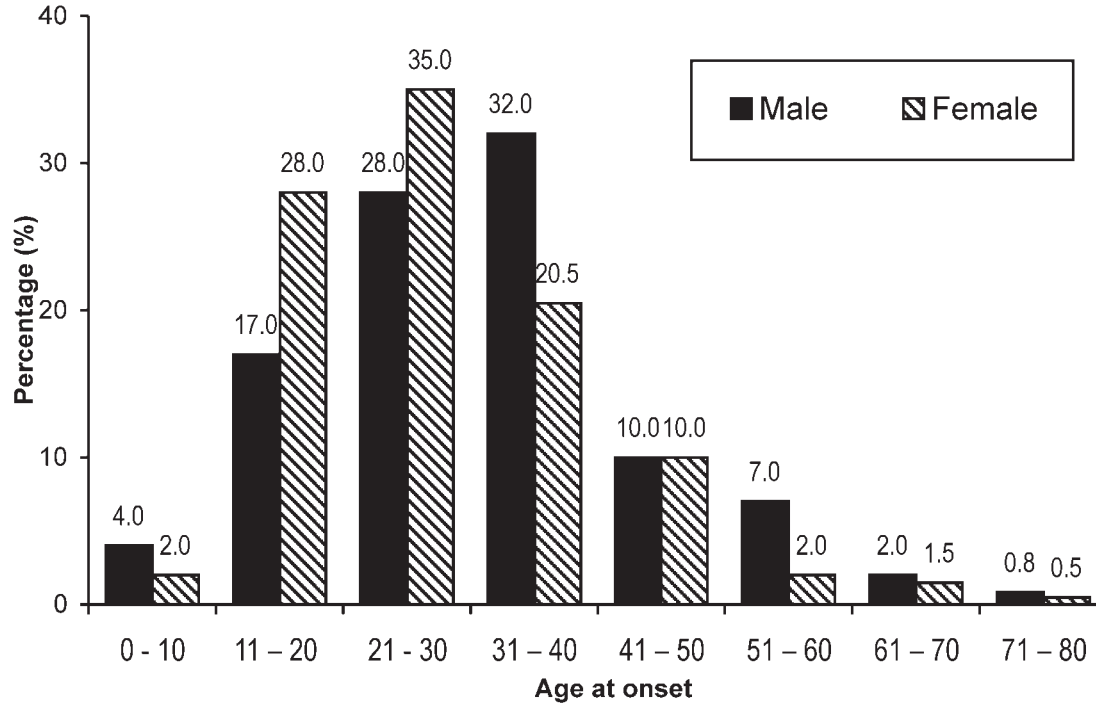

Figure 1 Age distribution of patients at onset by gender.

Table 1 Socio-demographic characteristics of the GLADEL cohort. Comparison between male and female patients

		Male (N = *123*)		*Female* (N = *1091*)		
Characteristic	N	N	*%*	n	*%*	P-*value*
Ethnic group[a]						
White	507	47	9.3	460	90.7	0.6508
Mestizo	537	59	11.0	478	89.0	
African Latin American	152	16	10.5	136	89.5	
Medical insurance						
No coverage	214	15	7.0	199	93.0	0.2244
Partial coverage	248	25	10.1	223	89.9	
Full coverage	751	83	11.0	668	89.0	
Education (years)						
1–7	374	41	11.0	333	89.0	0.7032
8–12	561	57	10.2	504	89.8	
13 or more	279	25	9.0	254	91.0	
Socioeconomic status						
Upper/upper-middle	133	15	11.3	118	88.7	0.8884
Middle	337	33	9.8	304	90.2	
Middle lower/lower	774	75	10.1	669	89.9	
	Median	Q_1–Q_3	*Median*	Q_1–Q_3		
Age at onset (years)	27.0	18.7–35.0	26.3	19.6–35.1		0.9461
Age at diagnosis (years)	29.2	18.9–36.0	28.3	21.0–37.1		0.5938
Delay to diagnosis (days)	134	54–334	185	77.0–518		0.0111

[a]Eighteen patients belonging to other ethnic groups were excluded in this section.
Q_1, 25% percentile; Q_3, 75% percentile.

versus 55.6%, $P = 0.012$) and loss of weight (47.2 versus 24.3%, $P \leq 0.0001$).

Renal disease was more frequent in men (61 versus 50.7%, $P = 0.036$). The male : female ratio in the last group was 1 : 7. The most frequent contributing factors towards the diagnosis of renal disease were proteinuria and cellular casts (58.5 versus 44.6%, $P \leq 0.004$).

Any form of cardiovascular manifestation was more prevalent in men (56.1 versus 41.4%, $P = 0.002$), particularly arterial hypertension (37.4 versus 25.8%, $P = 0.007$).

On the other hand, arthralgia and/or arthritis (93.9 versus 87.8%, $P = 0.021$) and skin disease (90.9 versus 83.7%, $P = 0.016$) were more frequent among women.

With reference to hematological manifestations 38.2% of men suffered from leukopenia compared with 42.8% of women ($P = 0.337$); lymphopenia 60.2 versus 59.2% ($P = 0.922$); thrombocytopenia 20.2 versus 19.1% ($P = 0.718$) and hemolytic anemia 19.5 versus 10.9% ($P = 0.007$).

Cumulative immunologic laboratory results (Table 3)

Ninety-eight per cent of male patients and 97.9% of females showed antinuclear antibodies ($P = 1.000$). Antibodies to native or double-stranded DNA were found in 79.1% of men and in 69.6% of women ($P = 0.069$). Anti-nRNP was found in 46.7 versus 51.7% ($P = 0.735$), anti-Sm in 48.9 versus 48.3% ($P = 1.000$), anti-Ro/SSA in 51.1 versus 48.6%

Table 2 Clinical manifestations of SLE patients in the GLADEL cohort at onset and during course of disease (cumulative). Comparison between male and female patients

	At onset					*Cumulative*				
	Male (n = *123)*		*Female* (n = *1091)*			*Male* (n = *1091)*		*Female* (n = *123)*		
Manifestations	N	*%*	n	*%*	P-*value*	N	*%*	n	*%*	P-*value*
Fever	52	42.3	295	27.0	0.001	83	67.8	606	55.6	0.012
Weight loss	29	23.6	129	11.8	0.001	58	47.2	265	24.3	0.001
Poly adenopathy	6	4.9	49	4.5	0.819	18	14.6	160	14.7	1.000
General manifestations	69	56.1	460	42.2	0.004	100	81.3	822	75.3	0.150
Arthralgias/arthritis	82	66.7	735	67.4	0.919	108	87.8	1024	93.9	0.021
Mialgias/miositis	11	8.9	81	7.4	0.588	29	23.6	184	16.9	0.079
Alopecia	23	18.7	223	20.4	0.723	60	48.8	639	58.6	0.043
Photosensitivity	30	24.4	267	24.5	1.000	58	47.2	623	57.1	0.044
Malar rash	35	28.5	252	23.1	0.181	66	53.7	678	62.1	0.079
Discoid lesions	7	5.7	57	5.2	0.831	14	11.4	129	11.8	1.000
Oral/nasal ulcers	16	13.0	112	10.3	0.353	44	35.8	462	42.4	0.177
Livedo reticularis	2	1.6	20	1.8	1.000	7	5.7	113	10.4	0.112
Raynaud phenomenom	8	6.5	116	10.6	0.207	24	19.5	318	29.2	0.026
Any cutaneous	56	45.5	507	46.5	0.850	103	83.7	992	90.9	0.016
Serositis	9	7.3	47	4.3	0.168	43	35.0	299	27.4	0.090
Pleuritis	7	5.7	37	3.4	0.200	33	26.8	235	21.5	0.207
Any respiratory	0	0.0	6	0.6	–	8	6.5	67	6.1	0.843
Pericarditis	5	4.1	28	2.6	0.372	28	22.8	181	16.6	0.101
Arterial hypertension	0	0.0	25	2.3	–	46	37.4	281	25.8	0.007
Vascular thrombosis	2	1.6	15	1.4	0.688	9	7.3	59	5.4	0.405
Any cardiovascular	8	6.5	69	6.3	0.847	69	56.1	452	41.4	0.002
Glomerulonephritis	3	2.4	12	1.1	0.188	16	13.0	86	7.9	0.059
Nephrotic syndrome	3	2.4	10	0.9	0.137	13	10.6	69	6.3	0.087
Proteinuria	7	5.7	37	3.4	0.200	68	55.3	425	39.0	0.001
Cellular casts	3	2.4	26	2.4	1.000	51	41.5	328	30.1	0.013
Persistent proteinura and/or cellular casts	8	6.5	47	4.3	0.254	72	58.5	487	44.6	0.004
Any renal	9	7.3	55	5.0	0.286	75	61.0	553	50.7	0.036
Psychosis/seizures	0	0.0	25	2.3	0.167	12	9.8	126	11.6	0.654
Any neurologic	1	0.8	49	4.5	0.053	33	26.8	287	26.3	0.914
Hemolytic anemia	5	4.1	24	2.2	0.206	24	19.5	119	10.9	0.008
Leukopenia	7	5.7	55	5.0	0.669	47	38.2	467	42.8	0.338
Lymphopenia	9	7.3	63	5.8	0.543	74	60.2	646	59.2	0.923
Thrombocytopenia	8	6.5	55	5.0	0.517	25	20.3	208	19.1	0.718
Any hematologic symptoms	17	13.8	136	12.5	0.667	87	70.7	796	73.0	0.596
Infections	5	4.1	20	1.8	0.100	34	27.6	283	25.9	0.666

Table 3 Cumulative immunologic laboratory

	Male (n = *123)*		*Female* (n = *1091)*		
	Positives	*%*	*Positives*	*%*	P-*value*
ANA	112/114	98.3	1025/1047	97.9	1.0000
Anti-dsDNA	72/91	79.1	592/851	69.6	0.0691
Anti-U1-nRNP	18/37	46.7	218/422	51.7	0.7352
Anti-Sm	23/47	48.9	244/505	48.3	1.0000
Anti-Ro (SSA)	24/47	51.1	223/459	48.6	0.7617
Anti-La (SSB)	14/42	33.3	127/441	28.8	0.5947
LAC	3/19	15.8	56/175	32.0	0.1922
Anti-IgG anti-cardiolipin	30/44	68.2	232/474	49.0	0.0176
Anti-IgM anti-cardiolipin	11/35	31.4	166/417	39.8	0.3715
Low C3	49/80	61.3	382/795	48.1	0.0260
Low C4	44/77	57.1	418/782	53.5	0.5517
Low CH50	21/34	61.8	218/384	56.8	0.5939

($P = 0.761$) and anti La/SSB in 33.3 versus 28.8% ($P = 0.594$).

Lupus anticoagulant was positive in 15.8% of men versus 32% of women ($P = 0.192$). IgG anti-cardiolipin in 68.2 versus 49% ($P = 0.017$) and IgM anti-cardiolipin in 31.4 versus 39.8% ($P = 0.371$).

Low C3 was found in 61.2% of men versus 48.1% of women ($P = 0.026$), low C4 in 57.1 versus 53.5% ($P = 0.551$) and low CH50 in 61.8 versus 56.8% ($P = 0.593$).

Therapy

Eighty-five per cent of male patients and 77.5% of female patients received prednisone ($P = 0.049$), antimalarial drugs 66.7 versus 75.6% ($P = 0.037$).

There was no significant difference regarding methotrexate, azathioprine or danazol treatment.

Multivariate analysis

SLEDAI score was recorded in at least one visit for 116 men and 1036 women. Patients were classified according to their maximum SLEDAI score during follow-up in two groups: those with a score greater than 12 and those with scores equal to or less than 12.

Fifty-three out of 116 men (45.7%) had scores equal to or greater than 12 while 453 out of 1036 women (43.7%) were found with a score higher than 12 ($P = 0.694$).

The logistic regression model for the outcome previously described showed that gender is not associated with a higher SLEDAI score after adjusting for confounding variables [adjusted odds ratio (OR) =0.993, 95% CI = 0.659–1.497]. Confounding variables associated with higher SLEDAI scores and therefore adjusted in this analysis were ethnic group, age at onset, medical insurance, education and delay to diagnosis.

Similarly, patients were divided into two groups according to their maximum SLICC damage score. Patients with scores greater than 0 were considered as patients with cumulative damage. Out of 106 men with at least one SLICC score recorded, 42 (39.6%) presented a maximum SLICC greater than 0. For women, 311 out of 938 (33.2%) presented maximum SLICC greater than 0 ($P = 0.194$). The logistic regression model for the maximum SLICC score revealed that males have a 38% greater chance of having a SLICC score greater than 0 than females after adjusting for confounding variables (ethnic group, medical insurance and socioeconomic status). However that increase is not statistically significant (adjusted OR = 1.39, 95% CI = 0.91–2.11).

The logistic regression model for cardiovascular complications showed a statistically significant 82% increase in the risk of cardiovascular complications for males as compared with the risk in females after adjusting for ethnic group (adjusted OR = 1.83, 95% CI =1.25–2.67).

A very small, non-significant increase in the risk of infections was observed in males as compared with females (adjusted OR = 1.08, CI = 0.71–1.64).

Mortality

During the period of follow-up 34 patients died (2.8%). There were no differences between the mortality in males (5/123, 4.1%) and females (29/1091, 2.7%), $P = 0.380$. The male : female ratio in the group of dead patients was 1 : 6.

The five male patients who died were suffering from an active disease, four of them with severe renal involvement. In one case, septic manifestations were established. The prime cause of death in two of the patients was lung hemorrhage. In one other case, multi-organic failure was the cause. Another patient died from acute heart failure. The cause is not known in the fifth case.

There was no difference in survival between men and women from first symptom onset to death. However when the analysis was performed at different stages of follow-up, we found that mortality at 6 months was 0.84% for men versus 0.19% for women; at 1 year, 1.68 versus 0.58%; at 2 years, 4.68 versus 1.31%; at 3 years, 4.68 versus 2.87% and at 5 years, 4.68 versus 4.72%.

Discussion

Male sex has been historically identified as a factor of bad prognosis for lupus and rheumatoid arthritis. This is consistent with a recent retrospective study of 338 patients suffering from SLE where male sex was a risk factor for mortality.[12]

Low male prevalence and ethnic variations is a particularity shared by different populations studied all over the world. In a recent study, a Caucasian Spanish population had an annual incidence rate of 0.54 every 100 000 inhabitants for men, while in another study among an Afro-American population, the male incidence was 0.7 for every 100 000.[13,14]

In the GLADEL cohort 42% of the patients were Caucasian, 44% Mestizos and 12.5% African Latin-American. When ethnic origin, medical coverage, education and socioeconomic level were analysed, no difference was established between sexes.[6]

Ten per cent of the total population were men, with a ratio of one man for every nine women (1 : 9), but this ratio decreased (1 : 7) when there was renal disease and decreased further (1 : 6) when patients who died were analysed.

The median age at the beginning of symptoms in GLADEL's males was 27 years and at the time of the diagnosis 29 years. This data did not vary in comparison with female patients; nevertheless, it was lower in relation to other populations, including some Latin-Americans.[15,16]

In our cohort the delay to diagnosis was significantly lower in men, as has been recently described in Afro-American patients. This difference might be explained by the severity of the manifestation and the fast progression of symptoms until they fulfilled the ACR classification criteria.[17]

The GLADEL cohort shows that, at onset as well as during the course of disease, general manifestations

such as fever and weight loss were predominant in men. This implies that pathologies with infectious origin must be considered in the first place, in particular viral diseases such as HIV. In order to make a precise diagnosis, it is important to remember that some manifestations due to viral infections may mimic those of SLE, such as cytopenias, vasculitis, neuropathy and glomerulopathy.[18,19] On the other hand, when patients with fever of unknown origin are analysed, once an infectious cause is dismissed, the possibility of SLE should be evaluated.[20]

The remaining initial manifestations of GLADEL were similar in both sexes, except for the fact that women had a higher frequency of neurological manifestations, these being so heterogeneous and non-characteristic that this may be one of the causes of the delay in diagnosis. Hemolytic anemia, a severe complication, was the only hematologic manifestation that prevailed in men, as has been described.[4]

In the GLADEL cohort more than 50% of the patients had some form of renal involvement at some point in time, with a frequency of 61% in men. This data emphasizes the concept of severity associated with male sex, with a proven higher risk of developing chronic renal failure and lower survival of the patients.[21,22] It is important to point out that four out of the five dead male patients of the GLADEL cohort suffered from acute nephropathy and two of them required hemodialysis. In accordance with this data, a 1996 Chilean publication stressed the aggressive course of nephropathy in Chile compared with developed countries.[23]

In another study of Latin-American patients, Molina JF *et al*. reported that men showed a higher incidence of nephropathy, thrombotic phenomenon and anti-dsDNA antibodies as well as higher SLE related mortality rate.[24]

In the LUMINA study the Latin-American and Afro-American patients had more renal disease than did Caucasians (62, 59 and 32% respectively).[25]

A more recent publication on a US Afro-American population showed that men had a higher risk of developing nephropathy than Afro-American women and the European-American population.[26]

On the other hand, the patients from the Euro-Lupus Project Group, showed active nephropathy in 27.9% of the cases.[27] Probably this difference in the prevalence of renal disease when compared with the Caucasian population may reflect the strong influence of genetic factors, in fact SLE nephropathy has been related to HLA-class II antigens and genetic variants such as polymorphisms in the genes of inflammatory response.[28,29]

In the present study some form of cardiovascular disease was a distinctive characteristic for males, with the multivariate analysis showing a significant 82% risk of having these complications. Arterial hypertension was the most frequent manifestation, which points towards the aggressiveness of the disease since this complication is more frequent in populations with a long disease course.

The prevalence of vascular thrombosis did not show significant differences between sexes, either at the initial stage or during course of the disease, in spite of the fact that males had a higher prevalence of anti-cardiolipin IgG antibodies.

Atherosclerotic cardiovascular involvement is cause for health concern for the general population and in particular in the SLE population, as it has been observed that the disease itself is a risk factor.[30] Different studies have confirmed the increased prevalence of coronary atherosclerosis at a lower age when compared with the general population, and male sex is also pointed out as an independent risk factor.[31]

From the immunologic laboratory standpoint, it is important to highlight the high frequency of anti-Sm in the total group of patients of the GLADEL cohort. This seems to be a common denominator of the non-Caucasian populations, clearly showing the genetic influence on the serology.[24]

Forty-six per cent of male patients had a high SLEDAI score at least in one determination, but there was no difference from female patients. This agrees with the fact that GLADEL is a population characterized by a short disease course as yet. In spite of this, there were a high number of patients with a SLICC damage score greater than 0 and men had 38% more chance of damage than women.

There were no statistical differences in sex regarding mortality but, interestingly, the principal cause of death in five women and two men was lung hemorrhage. This is a rare, life-threatening complication with an estimated frequency of 2–5.4% in a cohort of patients suffering from lupus.[32]

It has been proved in experimental models that either the humoral or cellular-mediated response is higher in women, providing them with more protection against infections.[33] Nevertheless, in the present study a small non-significant increase in the risk of infections was associated with male gender.

The hormonal influence in the developing process of lupus seems to be undisputed and it is probably responsible for some of the differences found between the sexes.

Hypogonadism has been associated with male SLE and reactivation of the disease, greater compromise of the central nervous system and serositis. The ratio of prolactin to testosterone showed a significant correlation with SLEDAI scores.[34,35]

However, recent studies have not found any difference between men suffering from lupus and healthy ones with regard to hormonal blood level of follicle-stimulating hormone, luteinizing hormone, testosterone, oestradiol and β-human chorionic gonadotropin. There was no difference, either, as regards the production of IL-1 and IL-1ra from monocytes and neutrophils among male and female lupus patients and healthy individuals. Higher levels of prolactin have been found in men with lupus, as well as a minor distribution of the receptor for immunoglobulin FcgammaRII on monocytes and neutrophils, findings that are supposed to have a role in the pathogenesis and prognosis of lupus in men.[36]

The difference between men and women with SLE can be explained not only by biological reasons. It has been repeated that women, regardless of the socio-economic or cultural situation, are more likely to ask for medical care, either for acute or chronic conditions.[37] It is possible that male patients only suffering from cutaneous or articular disease rarely consult, biasing statistics towards the more severely ill.

In conclusion, male SLE in the GLADEL cohort, as Wallace said, 'have a worse or same prognosis but not better than females'.[5]

Fever and weight loss should arouse suspicion of SLE in males with an otherwise compatible clinical picture. Renal and cardiovascular involvements occur early in the course of disease, signalling severity and poor prognosis. This is also supported by an increased mortality at two years when compared with women.

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GLADEL co-authors

Besides the authors, the following persons are also members of GLADEL and have incorporated at least 20 patients into the database.

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