Epidemiologic Profile of Erectile Dysfunction in Patients with Systemic Lupus Erythematosus: The Latin American Landscape

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ABSTRACT. ***Objective.*** The aim of this study was to describe the prevalence of erectile dysfunction (ED), as well as associated demographic and clinical features, in men with systemic lupus erythematosus (SLE), by means of a systematic, standardized evaluation.

Methods. We performed a transversal study in 8 tertiary care centers in Latin America. We included male patients ≥ 16 years who fulfilled ≥ 4 American College of Rheumatology criteria for SLE and had regular sexual activity, and evaluated them with the International Index of Erectile Function-5 questionnaire. Relevant demographic, clinical, and serological characteristics were recorded. We included 2 control groups: the first was made up of healthy men and the second of men with autoimmune diseases other than SLE (non-SLE group).

Results. We included 590 subjects (174 SLE, 55 non-SLE, and 361 healthy controls). The prevalence of ED in the SLE group was 69%. Mean age in that group was 36.3 ± 1.03 years. Among SLE patients with and without ED, these factors were significantly different: the presence of persistent lymphopenia (p = 0.006), prednisone dose (9.3 ± 1.2 vs 5.3 ± 1.3 mg, p = 0.026), and the Systemic Lupus International Collaborating Clinics damage score (1.25 ± 0.14 vs 0.8 ± 0.16 points, p = 0.042). Independent risk factors for ED in patients with SLE were persistent lymphopenia (OR 2.79, 95% CI 1.37–5.70, p = 0.001) and corticosteroid use in the previous year (OR 2.15, 95% CI 1.37–3.37, p = 0.001).

Conclusion. Regardless of comorbidities, treatment (excluding steroids), and type of disease activity, patients with SLE have a high prevalence of ED, especially considering that most patients are young. Recent corticosteroid use and persistent lymphopenia, which could be related to endothelial dysfunction, are risk factors for this complication in men with SLE. (J Rheumatol First Release January 15 2019; doi:10.3899/jrheum.180292)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) predominantly affects women[1], but usually has worse prognosis, higher activity scores, and an increased mortality in men[2,3,4], both globally as well as in Latin American patients[5]. Sexual function, which directly affects quality of life, has different domains that can be affected by disease. In male patients, erectile function is especially relevant, because this disorder is associated with both neuropsychiatric problems (mainly anxiety and depression) and cardiovascular (CV) disease[6]. Whereas there are different studies regarding sexual function in men with autoimmune diseases [mainly rheumatoid arthritis (RA), spondyloarthritis (SpA), and systemic sclerosis (SSc)][7,8,9,10,11,12,13], as well as studies about reproductive function[14,15,16,17,18] and alterations regarding penile anthropometry in SLE[19], information about erectile dysfunction (ED) in patients with SLE is quite scant[20,21,22].

Males with SLE are mostly young. However, many of them are taking intense immunosuppressive therapies or high-dose steroids, and are at risk for accelerated atherosclerosis[2,3,4]. Taking these factors into account, as well as the absence of studies performed with a validated instrument that allows a systematic analysis about ED in this group of patients, the main aim of our study was to describe the prevalence, risk factors, and features associated with ED in patients with SLE.

MATERIALS AND METHODS

We performed a transversal study in 8 tertiary care centers throughout Latin America (5 in Mexico, 1 Nicaragua, 1 in El Salvador, and 1 in Colombia) between October 2015 and November 2016. All subjects were included during outpatient visits. Three study groups were formed: men with SLE, men with autoimmune diseases other than SLE (non-SLE group), and healthy controls. In the first group, patients were ≥ 16 years old, fulfilled ≥ 4 American College of Rheumatology classification criteria, and had regular sexual activity in the prior 6 months (with intercourse at least once per week). Patients with other autoimmune diseases were excluded [except for antiphospholipid syndrome (APS), chronic viral infections (human immunodeficiency virus, hepatitis B or C), cancer, and late-onset SLE (diagnosis after the age of 50 yrs)][23]. We included 2 control groups — 1 with autoimmune diseases other than SLE (non-SLE group, which included RA, SpA, SSc, Sjögren syndrome, systemic vasculitides, adult-onset Still disease, inflammatory myopathies, and primary APS), and the other with healthy controls from each center, who were matched by age with the SLE subjects. Those with diagnosis of a chronic disease or who were using any prescription drug were excluded from this last group. In all groups, patients with incomplete clinical information in their clinical records were excluded.

All included subjects filled out the 5-item version of the International Index of Erectile Function (IIEF-5; Supplementary Table 1, available from the authors on request) in the Spanish-validated version[24,25]. The questionnaire was completed anonymously by each subject, in an isolated room, without any other person present, and was finally placed into a covered box. In the IIEF-5, the lowest score per question is 1 and the highest is 5. A normal erectile function is considered when scores are between 22 and 25, and ED is graded as mild (17–21 points), mild to moderate (12–16 points), moderate (8–11 points), and severe (5–7 points)[24]. Two last questions were added for patients, asking whether their rheumatologist had queried them about sexual issues during the previous 3 visits, and whether they would like their rheumatologist to inquire about those issues.

For patients in the SLE group, we recorded demographic information, history of disease activity, comorbidities, autoantibody profile, the SLE Disease Activity Index (SLEDAI)[26] activity score, the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index[27], and immunosuppressive and nonimmunosuppressive medications. Active disease was defined as SLEDAI ≥ 6 points. Lymphopenia was defined as a total lymphocyte count ≤ 1000 cells/m^3 and persistent lymphopenia as at least 3 consecutive measurements ≤ 1000 cells/m^3. For patients in the non-SLE group, disease activity was established according to the physician's global assessment. Briefly, we defined disease activity in this group of patients when it was considered after the clinical evaluation by their attending rheumatologist, and immunosuppressive treatment was adjusted accordingly. Regarding healthy controls, age and anthropometric measurements were recorded.

The study was approved by the local Research and Ethics Institutional Committee (Ref 1661). Variables were described in terms of mean and SD or proportions, as convenient. For comparison between groups, the SLE group was compared with each control group; chi-square test was used for categorical variables or Student t test for quantitative variables. Association between variables was assessed by OR with 95% CI. Variables that showed statistical significance in the univariate analysis or those with clinical relevance were included in the multivariate analysis, which was performed through binary logistic regression. A p value < 0.05 was considered statistically significant. Statistical analyses were performed with support of the software SPSS, version 21.

RESULTS

We included 590 subjects (SLE n = 174, non-SLE n = 55, healthy controls n = 361). According to the setting, the patients with SLE were included as follows: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Mexico City, Mexico), 43 patients; Hospital Central Ignacio Morones Prieto (San Luis Potosí, Mexico), 24 patients; Hospital Universitario Dr. José E. González (Monterrey, Mexico), 22 patients; Hospital Metropolitano Vivian Pellas (Managua, Nicaragua), 19 patients; Instituto Salvadoreño del Seguro Social (San Salvador, El Salvador), 18 patients; Instituto Mexicano del Seguro Social (Guadalajara, Mexico), 18 patients; Hospital General de México Dr. Eduardo Liceaga (Mexico City, Mexico), 15 patients; Hospital Universitario de la Samaritana (Bogotá, Colombia), 15 patients. Patients in the non-SLE group had the following diagnoses: RA (34.54%), SpA (20%), primary APS (14.54%), inflammatory myopathies (7.27%), SSc (5.45%), systemic vasculitides (9.09%), juvenile idiopathic arthritis (3.63%), Sjögren syndrome (1.81%), relapsing polychondritis (1.81%), and Still disease (1.81%). Table 1 displays the main clinical and demographic features in the SLE and non-SLE groups. Information regarding healthy controls is shown in Supplementary Table 2 (available from the authors on request).

The prevalence of ED in the SLE group was 68.96% versus 23.26% in healthy controls (p = 0.001). There was no statistically significant difference in the ED prevalence when compared with the non-SLE group, but patients with SLE presented with ED at a significantly younger age (36.3 ± 1.03 in SLE vs 46.3 ± 2.2 yrs in non-SLE, p < 0.0001; Table 1).

Table 1. Demographic, clinical and serological features of SLE and non-SLE patients with and without erectile dysfunction.

Variables	With Erectile Dysfunction, n = 153			Without Erectile Dysfunction, n = 76		
	SLE, n = 120, mean ± SEM	Non-SLE, n = 33, mean ± SEM	p	SLE, n = 54, mean ± SEM	Non-SLE, n = 22, mean ± SEM	p
Demographic						
Age, yrs	36.3 ± 1.03	46.3 ± 2.2	**< 0.0001**	32.5 ± 1.27	40.5 ± 2.25	**0.002**
Weight, kg	77.7 ± 1.41	77.5 ± 2.8	0.92	77 ± 1.83	77.6 ± 3.77	0.87
Height, cm	171 ± 1.4	166 ± 5.4	0.18	171 ± 0.99	168 ± 1.67	0.09
BMI, kg/m^2	26.9 ± 0.46	26.2 ± 0.68	0.44	26 ± 0.60	27.1 ± 1.03	0.37
Time since diagnosis, yrs	8.1 ± 0.68	10.5 ± 1.32	0.10	7.9 ± 1.03	10.6 ± 1.69	0.16
Activity of connective tissue disease[a]	69 (57)	7/33 (21)	**< 0.0001**	28/54 (51)	4/22 (18)	**0.01**
Laboratory features						
Hemoglobin, g/dl	14.1 ± 0.24	15.2 ± 0.33	**0.02**	16.2 ± 1.18	15.4 ± 0.54	0.66
Leukocytes, cells/µl × 10^3	6.3 ± 0.22	7.7 ± 0.43	**0.006**	10.4 ± 3.23	10.4 ± 3.02	0.99
Lymphocytes, cells/µl	1333 ± 54	1707 ± 104	**0.002**	1644 ± 106	1774 ± 190	0.53
Platelets, cells/µl × 10^3	232 ± 7.8	271 ± 20	**0.03**	229 ± 11.3	278 ± 22.1	**0.03**
Creatinine, mg/dl	1.72 ± 0.31	0.87 ± 0.04	**0.008**	1.38 ± 0.23	1.01 ± 0.18	0.35
APS serology, n (%)	29 (24)	5 (15)	0.47	13 (24)	4 (18)	0.76
Use of immunosuppressive treatment, n (%)	108 (90)	26 (78)	0.13	46 (85)	17 (77)	0.31
Prednisone, n (%)	82 (68)	14 (42)	**0.008**	28 (51)	8 (36)	0.31
Current dose, mg/day	9.3 ± 1.20	3.5 ± 1.12	**0.017**	5.32 ± 1.29	4.88 ± 1.96	0.85
Cumulative dose, previous year, mg	2525 ± 337	1555 ± 590	0.15	2398 ± 591	1236 ± 491	0.18
Cumulative dose, 5 yrs, mg	11584 ± 1167	5016 ± 1395	**0.003**	11278 ± 1836	5835 ± 2328	0.09
Non-exposure to any steroid in previous year, n (%)	29 (24)	15 (45)	**0.029**	23 (42)	12 (54)	0.45
Azathioprine, n (%)	39 (32)	6 (18)	0.13	18 (33)	2 (9)	**0.04**
Current dose, mg/day	32.9 ± 4.7	17.4 ± 6.5	0.11	31.9 ± 7.22	10.2 ± 5.85	**0.02**
Antimalarial, n (%)	73 (60)	8 (24)	**< 0.0001**	34 (62)	4 (18)	**0.01**
Current dose, mg/day	137.2 ± 11.8	37.8 ± 14.1	**< 0.0001**	123.1 ± 15.1	31.8 ± 14.9	**< 0.0001**
Methotrexate, n (%)	16 (13)	15 (45)	**< 0.0001**	7 (12)	10 (45)	**0.005**
Current dose, mg/week	2.21 ± 0.53	7.73 ± 1.58	**< 0.0001**	1.60 ± 0.71	7.73 ± 2.10	**0.01**
Mycophenolate mofetil, n (%)	48 (40)	1 (3)	**< 0.0001**	18 (33)	1 (4)	**0.008**
Current dose, mg/day	665 ± 88	37 ± 37.8	**< 0.0001**	517 ± 123	90.9 ± 90.9	0.07
Cumulative dose, 5 yrs, g	804 ± 154.4	195 ± 195	**0.034**	743 ± 179	235 ± 235	0.09
Cyclophosphamide exposure previous 6 mos, n (%)	12 (10)	1 (3)	0.30	4 (7)	0 (0)	0.31
Cumulative dose, 6 mos, g	0.36 ± 0.13	0.18 ± 0.18	0.52	0.31 ± 0.18	0 ± 0	0.09
Cyclophosphamide exposure, lifelong, n (%)	62 (51)	3 (9)	**< 0.0001**	23 (42)	1 (4)	**0.001**
Cumulative dose, lifelong, g	10.9 ± 3.6	0.22 ± 0.19	**0.004**	11.5 ± 6.2	0.70 ± 0.52	0.09
Nonimmunosuppressive treatment, n (%)	97 (80)	25 (75)	0.65	41 (75)	15 (68)	0.56
Any comorbidities, n (%)	63 (52)	14 (42)	0.33	24 (44)	10 (45)	1
Type 2 diabetes mellitus, n (%)	6 (5)	6 (18)	**0.02**	0 (0)	4 (18)	**0.006**
Hypertension, n (%)	44 (36)	14 (42)	0.54	14 (25)	4 (18)	0.56
Major depressive disorder, n (%)	5 (4)	0 (0)	0.32	3 (5)	0 (0)	0.54
Dyslipidemia[b], n (%)	33 (27)	9 (27)	1	12 (22)	6 (27)	0.76
Coronary heart disease[c], n (%)	5 (4)	0 (0)	0.58	0 (0)	2 (9)	0.08
Arterial and/or venous thrombosis, n (%)	32 (26)	5 (15)	0.25	12 (22)	2 (9)	0.21
Peripheral arterial disease[d], n (%)	0 (0)	1 (3)	0.21	0 (0)	0 (0)	ND
Smoking[e], n (%)	32 (26)	7 (21)	0.90	11 (20)	4 (18)	1
Genitourinary surgery[f], n (%)	6 (5)	2 (6)	0.68	3 (5)	0 (0)	0.55

Values shown in bold represent statistically significant p values. [a] Disease activity was defined for non-SLE as an increase or addition of any immunosuppressive treatment according to physician's assessment; activity for SLE group was defined by SLEDAI ≥ 6 points. [b] Hypercholesterolemia ≥ 200 mg/dl (5.18 mmol/l) and/or hypertriglyceridemia ≥ 150 mg/dl (1.69 mmol/l). [c] Proven by angiography in the last 10 years. [d] Proven by angiography and/or Doppler ultrasound in the last 10 years. [e] Current or in the past 5 years. [f] Any urinary tract, prostate, penis, or testicle surgery, excluding circumcision. SLE: systemic lupus erythematosus; SEM: standard error of the mean; BMI: body mass index; APS: antiphospholipid syndrome; SLEDAI: SLE Disease Activity Index; ND: not determined.

ED in the SLE group was mostly mild to moderate (108/120 patients, 90%). Men with SLE had a mean IIEF-5 score of 17.2 ± 0.33 points. Table 2 shows individual scores per question in patients with SLE, as well as total score and the ED category. Table 1 shows the comparison between patients with and without ED in the SLE and non-SLE groups. Remarkably, prednisone use was more frequent in patients with ED than in those without it (p = 0.026). Regarding comorbidities, the only difference among groups was a higher prevalence of type 2 diabetes mellitus (DM) in non-SLE patients, but there was no difference in patients with or without ED.

Table 2. Itemized International Index of Erectile Function-5 in patients with SLE.

Variable	SLE with ED, n = 120	SLE without ED, n = 54	p
Question 1 (1–5 points)	3.03 ± 0.08	4.17 ± 0.09	**< 0.0001**
Question 2 (1–5 points)	3.41 ± 0.10	4.89 ± 0.04	**< 0.0001**
Question 3 (1–5 points)	3.32 ± 0.08	4.81 ± 0.05	**< 0.0001**
Question 4 (1–5 points)	3.84 ± 0.08	4.89 ± 0.04	**< 0.0001**
Question 5 (1–5 points)	3.63 ± 0.09	4.89 ± 0.04	**< 0.0001**
Total score (5–25 points)	17.2 ± 0.33	23.6 ± 0.14	**< 0.0001**
Erectile dysfunction category, n (%)			
Mild	84/120 (70)	NA	
Mild to moderate	24/120 (20)	NA	
Moderate	9/120 (7.5)	NA	
Severe	3/120 (2.5)	NA	

Question 1–5 and total scores are mean ± SEM. Values shown in bold represent statistically significant p values.
SLE: systemic lupus erythematosus; ED: erectile dysfunction; NA: not applicable.

Table 3 contains relevant information about all patients with SLE. As shown, SLE patients with ED were slightly older than those without ED (36.3 ± 1.03 vs 32.5 ± 1.27 yrs, p = 0.022), without differences in weight, height, body mass index, or time since SLE diagnosis. SLE patients with ED had a lower count of total lymphocytes at the time of the study (p = 0.005), as well as a higher prevalence of persistent lymphopenia (p = 0.006). Regarding immunosuppressive therapy, the use of any of these drugs was equal between groups (p = 0.6). However, patients with ED had a higher frequency of exposure to any dose of corticosteroids in the previous year (p = 0.019), and also a higher prednisone dose at the time of the study (9.31 ± 1.20 vs 5.32 ± 1.29 mg/day, p = 0.02). There were no other significant differences regarding the rest of the immunosuppressive treatment between groups, both at the time of the study and with cumulative doses. There were no relevant differences in comorbidities (p = 0.41) or in nonimmunosuppressive treatments (p = 0.54) between groups. Further, there was no difference regarding disease activity (SLEDAI score 4.89 ± 0.54 vs 3.65 ± 0.52, p = 0.16), but patients with ED had significantly more damage accrual according to the SLICC Damage Index (1.25 ± 0.14 vs 0.80 ± 0.16 points, p = 0.042).

After multivariate analysis, risk factors associated with ED in patients with SLE were persistent lymphopenia (OR 2.79, 95% CI 1.37–5.70, p = 0.001) and exposure to any corticosteroid dose in the previous year (OR 2.15, 95% CI 1.37–3.37, p = 0.001).

Finally, we found that most patients who attended the different rheumatology clinics were not questioned about erectile function (86%), at least during the previous 3 visits. Also, most patients (82%) would consider it appropriate to discuss erectile and sexual function in their usual visits (Figure 1).

DISCUSSION

To our knowledge, this is the first study to evaluate the prevalence of ED in patients with SLE by using an adequate, validated questionnaire[24]. We found a prevalence close to 70%, whereas in the healthy population the prevalence of ED is between 10 and 22%[28]. Our findings are similar to those described in patients with DM; however, it is important to note that patients with type 2 diabetes in whom that prevalence has been found were 22 years older than our population, on average[29]. There are various possible explanations for such a high prevalence of ED in young patients with SLE (mean age 36.3 yrs). Currently, well-known risk factors for ED are obesity (RR 1.9, 95% CI 1.6–2.2), smoking (RR 1.5, 95% CI 1.3–1.7)[30], DM (OR 3, 95% CI 1.5–5.8), hypertension (OR 2.05, 95% CI 1.6–2.6), hyperlipidemia (OR 2.2, 95% CI 1.4–3.7), lower urinary tract symptoms (OR 2.2, 95% CI 1.7–2.7), psychological stress (OR 1.6, 95% CI 1.4–1.9), low physical activity (OR 1.3, 95% CI 1.1–1.6), and age[31]. Whereas the physiopathology of ED involves multiple mechanisms, including the use of certain drugs, history of pelvic surgery or pelvic irradiation, as well as endocrine, neurologic, and psychogenic factors, the main cause associated with ED is local vascular damage[32]. Interestingly, most of these conventional risk factors were absent in our patients, but the recent use of glucocorticoids was found to be of particular relevance.

Because men with SLE have higher disease activity scores[2], they use glucocorticoids more frequently and in higher doses[33]. We found glucocorticoid use to be a risk factor for ED. Although the use of systemic corticosteroids has not been previously directly related to ED[34], up to 70% of patients with Cushing syndrome have sexual dysfunction. It has been suggested that cortisol plays an inhibitory role in male sexual response[35]. Indeed, hypercortisolism leads to a decreased concentration of luteinizing hormone and testosterone. It also inhibits the pituitary secretion of gonadotrophins and the androgen production in Leydig cells[36,37]. Also, this effect seems to be reversible, which would explain why recent exposure to glucocorticoids was found to be a risk factor for ED, but the cumulative corticosteroid dose was not. Further, glucocorticoids have been associated with

Table 3. Demographic, clinical, and serological features of SLE patients with and without erectile dysfunction.

Variable	SLE without ED, n = 54, mean ± SEM	SLE with ED, n = 120, mean ± SEM	p
Demographic			
Total IIEF-5 score, points	23.6 ± 0.14	17.3 ± 0.33	**< 0.0001**
Age, yrs	32.5 ± 1.27	36.3 ± 1.03	**0.022**
Weight, kg	77 ± 1.83	77.7 ± 1.41	0.76
Height, cm	171.9 ± 0.99	171.4 ± 1.42	0.83
BMI, kg/m^2	26 ± 0.60	26.9 ± 0.46	0.25
Time since diagnosis, yrs	7.93 ± 1.03	8.13 ± 0.68	0.87
SLEDAI score, points	3.62 ± 0.52	4.89 ± 0.54	0.16
SLICC score, points	0.80 ± 0.16	1.25 ± 0.14	**0.042**
Laboratory features			
Hemoglobin, g/dl	16.2 ± 1.18	14.1 ± 0.24	**0.015**
Leukocytes, cells/µl × 10^3	10.4 ± 3.23	6.36 ± 0.22	0.21
Lymphocytes, cells/µl	1644 ± 116	1333 ± 54.9	**0.005**
Platelets, cells/µl × 10^3	229 ± 11.3	232 ± 7.86	0.83
Creatinine, mg/dl	1.38 ± 0.23	1.72 ± 0.31	0.48
C3 levels, g/l	93 ± 4.59	92.8 ± 4.28	0.97
C4 levels, g/l	18 ± 1.94	19.8 ± 1.20	0.38
Anti-dsDNA, IU/ml	114 ± 37.3	135 ± 50.1	0.78
Use of immunosuppressive treatment, n (%)	46 (85)	108 (90)	0.60
Prednisone, n (%)	28 (51)	82 (68)	**0.043**
Current dose, mg/day	5.32 ± 1.29	9.31 ± 1.20	**0.02**
Cumulative dose, previous year, mg	2398 ± 591	2525 ± 337	0.85
Cumulative dose, 5 years, mg	11278 ± 1836	11584 ± 1167	0.88
Nonexposure to any steroid in previous year, n (%)	23 (42)	29 (24)	**0.019**
Azathioprine	18 (33)	39 (32)	1
Current dose, mg/day	31.9 ± 7.22	32.9 ± 4.78	0.91
Antimalarial	34 (62)	73 (60)	0.86
Current dose, mg/day	123 ± 15	137 ± 11	0.48
Methotrexate	7 (12)	16 (13)	1
Current dose, mg/week	1.60 ± 0.71	2.21 ± 0.53	0.52
Mycophenolate mofetil, n (%)	18 (33)	48 (21)	0.50
Current dose, mg/day	517 ± 123	665 ± 88	0.34
Cumulative dose, 5 yrs, g	743 ± 179	804 ± 154	0.81
CYC exposure previous 6 mos, n (%)	4 (7)	12 (10)	0.77
Cumulative dose, 6 mos, g	0.31 ± 0.18	0.36 ± 0.13	0.85
CYC exposure to any dose, lifelong, n (%)	23 (42)	62 (51)	0.32
Cumulative dose, lifelong, g	11.5 ± 6.20	10.9 ± 3.60	0.92
Nonimmunosuppressive treatment, n (%)	41 (75)	97 (80)	0.54
Antihypertensive	26 (48)	77 (64)	0.06
Antidepressant	3 (5)	6 (5)	1
Antidiabetic	2 (3)	5 (4)	1
Hypolipidemic	11 (20)	39 (32)	0.14
NSAID	15 (27)	36 (30)	0.85
Anticoagulation	8 (14)	29 (24)	0.22
Any comorbidities, n (%)	24 (44)	63 (52)	0.41
Type 2 diabetes mellitus	0 (0)	6 (5)	0.17
Hypertension	14 (25)	44 (36)	0.22
Renal replacement therapy	2 (3)	8 (6)	0.72
Postrenal transplantation	2 (3)	5 (4)	1
Major depressive disorder	3 (5)	5 (4)	0.69
Dyslipidemia[a]	12 (22)	33 (27)	0.57
Coronary heart disease[b]	0 (0)	5 (4)	0.32
Arterial and/or venous thrombosis	12 (22)	32 (26)	0.70
Peripheral arterial disease[c]	0 (0)	0 (0)	ND
Smoking[d]	11 (20)	32 (26)	0.90
Genitourinary surgery[e]	3 (5)	6 (5)	1

Table 3. Continued.

Variable	SLE without ED, n = 54, mean ± SEM	SLE with ED, n = 120, mean ± SEM	p
SLE (history), n (%)			
Hematological activity	14 (25)	33 (27)	1
Persistent lymphopenia	11 (20)	51 (42)	**0.006**
Neurological activity	4 (7)	15 (12)	0.43
Diffuse alveolar hemorrhage	2 (3)	7 (5)	0.72
Renal activity	23 (42)	68 (56)	0.13
APS serology	13 (24)	29 (24)	1

Values in bold face represent statistically significant p values. [a] Hypercholesterolemia ≥ 200 mg/dl (5.18 mmol/l) and/or hypertriglyceridemia ≥ 150 mg/dl (1.69 mmol/l). [b] Proven by angiography in the last 10 years. [c] Proven by angiography and/or Doppler ultrasound in the last 10 years. [d] Current or in the past 5 years. [e] Any urinary tract, prostate, penis, or testicle surgery, excluding circumcision. SLE: systemic lupus erythematosus; ED: erectile dysfunction; SEM: standard error of the mean; IIEF: Itemized International Index of Erectile Function; BMI: body mass index; SLEDAI: SLE Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; CYC: cyclophosphamide; NSAID: nonsteroidal antiinflammatory drugs; APS: antiphospholipid síndrome; ND: not determined.

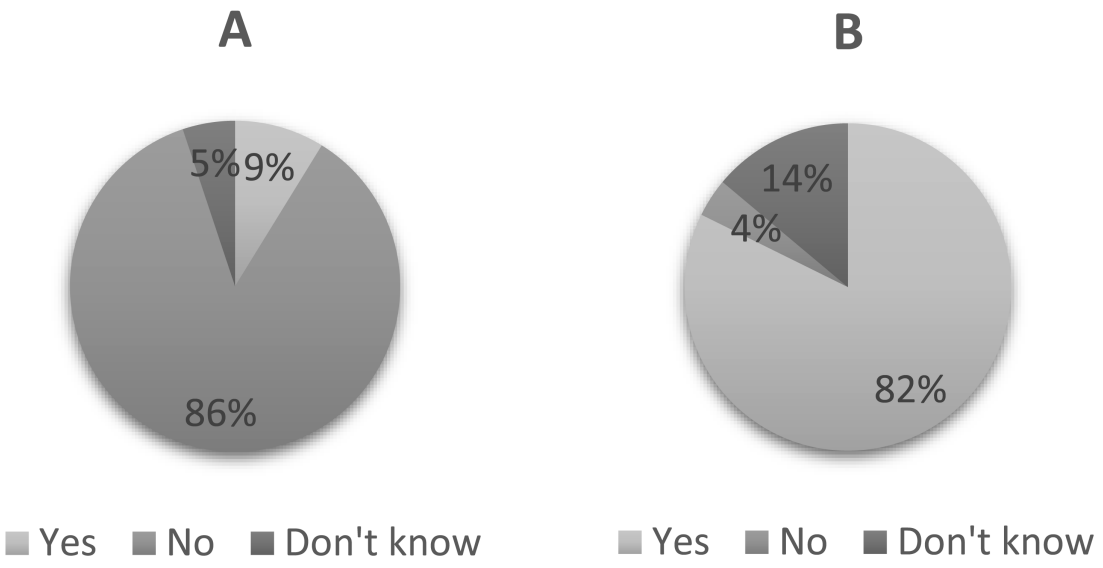

Figure 1. A. The distribution of responses of patients (n = 174) with SLE to this query: Have you been asked about your erectile function in your last 3 visits to the rheumatologist? B. The percentage of responses from patients with SLE regarding their likelihood of being questioned about their erectile function by their rheumatologists (i.e., would you like your rheumatologist to inquire about your erectile function during your regular visits?). SLE: systemic lupus erythematosus.

subclinical atherosclerosis in patients with SLE[38], and they are considered an additional risk factor for CV disease[39]. Along with their hormonal actions, their vascular effects could play an additional role in the development of ED in young patients with SLE. ED has been considered as an independent risk factor for major CV events in the general population[40]. Therefore, it will be relevant to identify SLE patients with ED, not only to offer adequate and timely treatment, but also to assess the presence of other CV risk factors and to begin an appropriate prevention strategy. Further, ED has been found to directly influence quality of life[41], which in the case of patients with SLE is already affected by the disease itself[42].

While it is widely known that cyclophosphamide may cause oligo/azoospermia, infertility, and alterations in the sex hormone profile in men with SLE[15,17], we did not find recent exposure or cumulative doses to be associated with ED.

Further, we also found persistent lymphopenia to be a risk factor for ED in these patients. This could also be related to vascular damage, and specifically to endothelial dysfunction. Low lymphocyte counts have been associated with accelerated atherosclerosis and CV disease[43,44]. Moreover, our

group has described different epidemiological associations between lymphopenia and other conditions related to endothelial dysfunction, such as thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and posterior reversible encephalopathy syndrome, in patients with SLE[45,46]. Additionally, it has been described that young men with ED have subclinical endothelial dysfunction, even without CV comorbidities[47]. Therefore, ED could be considered an early clinical sign of increased CV risk, with endothelial dysfunction potentially playing a key role[48].

Currently, there is no specific information regarding pharmacological therapies in men with SLE and ED. This should be studied to address their efficacy and safety in this population. However, lifestyle modifications (weight loss, an appropriate diet, and increased physical activity)[49] could be recommended for patients with ED, not only to improve erectile function, but also to reduce CV risk. Also, a prompt urology referral could help to individualize each case and the therapeutic options[50].

Our work has several limitations. First, it was a transversal study, which did not allow addressing whether there are changes according to disease activity and treatment throughout time. It was performed only in Latin Americans, so these findings may not apply to other populations. Also, there was no neuropsychological assessment at the time of the study, which could have helped to find other factors influencing erectile function. Prospective studies should be performed, with evaluations regarding health-related quality of life and disease perception, as well as functional studies of penile vasculature.

Men with SLE have a strikingly high prevalence of ED, regardless of their young age. Glucocorticoid use and lymphopenia, both of which may cause endothelial dysfunction and lead to vascular damage, are independent novel risk factors for ED in these patients. Men with SLE are rarely asked about sexual function in their regular outpatient visits, even though most of them would agree to such an assessment by their rheumatologist.

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