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Hypogonadism and Erectile Dysfunction in Thai Men with Systemic Lupus Erythematosus

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Abstract

Objectives: To determine the prevalence of hypogonadism and erectile dysfunction (ED), along with associated factors in male SLE patients

Methods: A cross-sectional study of men with SLE conducted between January and December 2013. The demographic data, clinical parameters, sex chromosomes, testicular volume, and sex hormones (FSH, LH, and testosterone) were evaluated. We used Androgen Deficiency in the Aging Male (ADAM) screening questionnaires to determine androgen deficiency symptoms and the 5-item International Index for Erectile Function (IIEF-5) questionnaire to assess ED severity.

Results: The study included 26 male SLE patients with a mean ± SD age of 37.5 ± 15.4 and disease duration of 4.2 ± 4.5 years. The modified-SLE disease activity index (mSLEDAI) and SLE collaborating clinic (SLICC) damage score were 3.4 ± 5.5 and 0.7 ± 1.0, respectively. All patients had an XY chromosome. Seven patients (27%) had biochemical hypogonadism (testosterone ≤300 ng/dl). Patients with biochemical hypogonadism had a significantly higher prevalence of neuropsychiatric-SLE (NPSLE) than those without (57% vs. 5%, p=0.010). The prevalence of symptomatic hypogonadism and ED based on the ADAM and ED questionnaires were 62% and 76%, respectively. Patients with ED had smaller testicular volume (9.4 ± 2.4 vs. 12.4 ± 2.4 ml, p=0.046). Testicular volume correlated positively with testosterone level (r=0.525, p=0.010) and IIEF-5 score (r=0.476, p=0.046), but negatively with SLICC damage score (r=-0.435, p=0.038).

Conclusion: A substantial proportion of male SLE patients had symptomatic hypogonadism and ED. Patients with hypogonadotropic hypogonadism appeared to have higher proportion of NPSLE. ED by IIEF-5 score and testicular volume may be sensitive to predict hypogonadism in male SLE patients.

Keywords: Erectile dysfunction; Infertile; Hypogonadisn; Male SLE

Introduction

The incidence of systemic lupus erythematosus (SLE) peaks during the reproductive years in both sexes with higher frequency in females [1]. Most patients receive immunosuppressive therapy (i.e. glucocorticoid and cyclophosphamide) which affects the gonads and sexual function. Our previous study showed that male patients with SLE had a high prevalence of renal insufficiency indicating high disease activity and requiring glucocorticoid and immunosuppressive therapy [2]. Hence, we sought to study the effects of these treatments on the gonads and sexual functions of male patients with SLE.

In male hypogonadism, the testes fail to produce normal amounts of testosterone, which can result in androgen deficiency. Most studies in male SLE patients have compared sex hormone profiles with matched healthy controls [3-6]. Few studies have looked at the symptoms of androgen deficiency and the association between SLE-related factors and hypogonadism [5].

In male SLE patients receiving high dose glucocorticoid and immunosuppressive therapy, testosterone replacement therapy can be administered to increase testosterone levels and alleviate symptomatic hypogonadism in order to help preserve bone mineral density, muscle mass and strength, sexual function, and quality of life [7]. Therefore, it is essential to identify biochemical hypogonadism (low testosterone levels), along with signs and symptoms of androgen deficiency such as small testes, erectile dysfunction in these SLE patients.

The aims of this study were to determine the prevalence of biochemical hypogonadism, identify the signs and symptoms of androgen deficiency, and evaluate the association between SLE disease-related factors including treatments and hypogonadism in male SLE patients.

Patients and Methods

The study included Thai male SLE patients (older than 15 years) who fulfilled the American College of Rheumatology diagnostic criteria for SLE [8]. All patients were treated at the out-patient clinic of

the Division of Rheumatology, Chiang Mai University, between January and December 2013. Patients were invited to participate on a consecutive basis. Those who signed informed consent form to participate in this study were evaluated for demographic data, clinical features, disease activity determined by the modified-SLE disease activity index (mSLEDAI) [9], damage score determined by the systemic lupus erythematosus collaborating clinic (SLICC) [10], current treatment, sex hormones and sex chromosome study.

The sex hormones included follicle-stimulating hormone (FSH), luteinizing hormone (LH), and morning total testosterone level, which was detected by electro-chemi-luminescense immunoassay (ECLIA) using Roche Elecsys and MODULAR ANALYTICS E170 (Elecys module) immunoassay analyzers (Roche Diagnostics, Indianapolis, IN, USA). Total serum testosterone levels ≤300 ng/dL was the cutoff for defining hypogonadism [7] which is referred to as biochemical hypogonadism in this report.

The sex chromosome was extracted from peripheral blood lymphocytes using the synchronization method of Dutrillaux and Viegas-Pequignut [11] with only minor modifications. Analytical methods were determined by Giemsa banding techniques and Quinacrine banding techniques.

Consenting patients were evaluated using testicular ultrasound, the 5-item International Index for Erectile Function (IIEF-5) [12] (an index for screening erectile dysfunction severity, composed of 5 items, with a score range from 5 [worse] to 25 [best], and a cutoff score of ≤21 determining erectile dysfunction) and the Androgen Deficiency in the Aging Male (ADAM) questionnaire [13] (a screening tool for detecting men at risk for androgen deficiency composed of 10 questions about symptoms of hypogonadism). ADAM screening is positive when the patients answer "yes" to either question 1 or 2, or to any three other questions.

One experienced radiologist (N.P.) performed the high-frequency ultrasonography of the testes, using a high-resolution linear transducer at a frequency of 9-12 MHz (Aplio500, Toshiba Medical System, Tochigi, Japan). To avoid distorting testicular shape, only light pressure was applied during scans. At least three separate transverse and longitudinal images of each testis were obtained; electronic calipers were used to measure testicular length, width, and height. The mean value obtained for each testicular dimension was used to calculate the testicular volume according to the formula for a spheroid (length x width 2 x 0.52).

Our institutional research ethics board approved this study and prior informed consent was obtained according to the Declaration of Helsinki.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for Social Sciences Software (SPSS Inc., Chicago, IL, USA), version 17.0 for Windows XP. Mann-Whitney U test or Fisher exact tests were used to test the study characteristics between patients with and without hypogonadism and those with and without erectile dysfunction. Bivariate correlation analysis was performed using Spearman's rank correlation coefficient to reveal associations between continuous data and other factors.

Results

Of the 27 Thai male SLE patients treated at the clinic during the time of the study, 26 agreed to be included in this analysis. Their mean ± SD [range] age and disease duration were 37.5 ± 15.4 [17.5, 71.8], and 4.2 ± 4.5 [0.1, 20.6] years. Others disease parameters and treatments are shown in Table 1.

Variables**	
Prevalence of clinical manifestation and serologies	
Malar rash, n (%)	15 (55.6)
Oral ulcer, n (%)	6 (22.2)
Photosensitivity, n (%)	7 (25.9)
Discoid lupus erythematosus, n (%)	13 (48.1)
Arthritis, n (%)	8 (29.6)
Serositis, n (%)	5 (18.5)
NPSLE, n (%)	5 (18.5)
Nephritis, n (%)	13 (48.1)
Anti-ds DNA antibody, n (%)	13 (48.1)
Lupus anticoagulant*, n (%)	10 (55.5)
Anti-cardiolipin antibody, n (%)	3 (12.0)
mSLEDAI at study entry	3.4 ± 5.5 (2.0; 0.0, 24.0)
SLICC damage index at study entry	0.7 ± 1.0 (0.0; 0.0, 3.0)
Treatment	

Cumulative prednisolone dose (gm)	12.4 ± 10.4 (8.9; 0.2, 44.3)
Current dose of prednisolone (mg)	11.3 ± 11.0 (10.0; 1.2, 50.0)
Used cyclophosphamide, n (%)	13 (50.0)
Cumulative cyclophosphamide (gm)	5.5 ± 9.4 (0.4; 0.0, 40.0)
Profile of sex hormone and testicular volume	
FSH (mIU/ml)	10.3 ± 9.1 (6.0; 2.2, 37.8)
LH (mIU/ml)	8.1 ± 4.6 (6.8; 3.1, 24.6)
Total testosterone (ng/dl)	470.0 ± 250.0 (450.0; 010.0, 1060.0)
Testicular volume# (ml)	9.7 ± 3.2 (9.5; 3.3, 16.0)
Sexual function	
ADAM score	3.8 ± 2.9 (3.0; 0.0, 10.0)
IIEF-5 score	16.4 ± 5.2 (18 .0; 7.0, 24.0)
*from 18 patients, #from 46 testes, **continuous data presented as "mean ± SD (median; min, max)", NPSLE- Neuropsychiatric-SLE, mSLEDAI: modified-SLE Disease Activity Index, SLICC: SLE Collaborating Clinic, FSH: Follicular Stimulating Hormone, LH: Luteinizing Hormone, ADAM: Androgen Deficiency in the Aging Male, IIEF-5: the 5-Item International Index for Erectile Function	

Table 1: Clinical manifestation, treatment, testicular size, sex hormone and sexual function in 26 male lupus patients.

Five patients had additional co-morbidities; two with diabetes mellitus (DM), two with chronic renal failure, one with cirrhosis, and one with long-segment bowel dissection (1 patient had both cirrhosis and chronic renal failure). Eleven patients (42.3%) reported drinking alcohol (9 occasionally and 2 regularly) and six (23.1%) were current smoker. Two patients (7.6%) had a history of mumps. No patients had a history of orchitis or testicular trauma.

All patients had a 46, XY chromosome. Seventeen patients (65.4%) were married and four (23.5%) were divorced. Thirteen (76.5%) of the married patients fathered children before disease onset and two (11.8%) patients fathered children after SLE disease onset.

Assessment of hypogonadism

Sex hormones assessment for biochemical hypogonadism: All 26 patients agreed to a blood exam to study hormonal status. The level of FSH, LH, and total testosterone are shown in Table 1. Seven (26.7%) patients had biochemical hypogonadism (total testosterone level below 300 ng/dl) [7]. Of these seven, two (28.5%) patients had a high FSH level (FSH ≥15 mIU/ml) [7] which are consistent with a diagnosis of hypergonadotropic hypogonadism or primary hypogonadism. One of these two patients had a history of cyclophosphamide use with a cumulative dose of 6.4 grams. The remaining five patients had normal FSH and LH levels consistent with hypogonadotropic hypogonadism or secondary hypogonadism.

Patients with hypogonadism had a higher prevalence of neuropsychiatric SLE (NPSLE; defined by The American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature [14]), 57.1% vs. 5.3%, p=0.010 (Table 2). All patients with NPSLE and hypogonadism were hypogonadotropic. The patients with hypogonadism had shorter disease duration and higher disease activity (1.7 ± 2.0 vs. 5.1 ± 4.8 years, p=0.035 and mSLEDAI-2K 8.0 ± 9.0 vs. 1.6 ± 1.9, p=0.093, respectively). A negative correlation between testosterone level and disease activity score (mSLEDAI-2K) was present but not statistically significant (r=-0.37, p=0.061).

Risk factors@	Testosterone <300 ng/dl (N=7)	Testosterone ≥300 ng/dl (N=19)	P-value*
Age at diagnosis (years)	30.7 ± 16.9	34.2 ± 15.2	0.506
Age at study entry (years)	32.4 ± 16.2	39.4 ± 15.1	0.231
Alcohol, n (%)	5 (71.4)	6 (31.6)	0.095
Smoking, n (%)	2 (28.6)	4 (21.1)	1
Comorbidity, n (%)	2 (28.6)	3 (15.8)	0.588
Testicular volume (ml)	7.8 ± 2.0**	10.2 ± 3.3$	0.101
FSH (mIU/ml)	11.7 ± 9.9	9.7 ± 9.1	0.364

LH (mIU/ml)	10.0 ± 6.7	7.4 ± 3.4	0.285
Disease duration (years)	1.7 ± 2.0	5.1 ± 4.8	0.035
Prevalence of LN, n (%)	3 (42.9)	10 (52.6)	1
Prevalence of NPSLE, n (%)	4 (57.1)	1 (5.3)	0.01
Anti-ds DNA antibody positive, n (%)	3 (42.9)	10 (52.6)	1
Anti-cardiolipin antibody positive, n (%)	1 (16.7)	2 (11.1)	1
Lupus anticoagulant positive, n (%)	4 (80.0)[&]	6 (46.2)[&&]	0.314
Current mSLEDAI-2K	8.0 ± 9.0	1.6 ± 1.9	0.093
SLICC damage index	0.4 ± 0.8	0.7 ± 1.0	0.559
Cumulative prednisolone (gm)	7.1 ± 3.7	14.4 ± 11.4	0.214
Current dose of prednisolone (mg)	13.8 ± 10.4	10.3 ± 11.4	0.284
Cumulative cyclophosphamide (gm)	2.9 ± 2.7	6.5 ± 10.8	0.734

*P-value came from Fisher's exact test or Mann-Whitney test, [@]continuous data presented as "mean ± SD, **from 5 patients, [$]from- 18 patients, [&]from 4 from 5 patients, [&&]from 6 from 13 patients, **continuous data presented as"mean ± SD ", LH: Luteinizing Hormone, FSH: Follicular Stimulating Hormone, LN: Lupus Nephritis, NPSLE: Neuropsychiatric-SLE, mSLEDAI: modified-SLE disease Activity /index, SLICC: SLE Collaborating Clinic

Table 2: Compared associated factors between male lupus patients with and without biochemical hypoandrogenism.

Age at the time of SLE diagnosis and at study entry, alcohol use, smoking, co-morbidities, or BMI did not differ between the two groups. For the SLE-related factors, m-SLEDAI-2K at study entry, SLICC damage index, cumulative prevalence of clinical manifestations, and positive auto-antibodies (anti-ds DNA Antibody, anti-cardiolipin, and lupus anti-coagulant) did not differ between the two groups. For treatment factors, current use or cumulative dose of prednisolone and cyclophosphamide did not differ between the two groups.

Subgroup analyses excluded 5 old age patients (age > 50 year-old, 54.9, 58.8, 59.4, 61.5 and 71.8 year-old), one of which (59.4 year-old) had hypogonadism. The remaining 21 patients aged ≤50 years with hypogonadism had a higher prevalence of NPSLE (66.7% vs. 6.7%, p=0.011) and smaller testicular volume than those without hypogonadism (7.6 ± 2.2 vs. 11.3 ± 2.5 ml, p=0.019).

Screening tests for symptomatic hypogonadism and erectile dysfunction

In this study, two screening tests were used to determine symptoms of androgen deficiency: the ADAM questionnaire used to determine symptoms related to hypogonadism and the IIEF-5 questionnaire was used to determine erectile dysfunction. Twenty-one patients agreed to answer the ADAM and the IIEF-5 questionnaires.

Thirteen (62%) patients were positive for symptoms related to hypogonadism by ADAM questionnaire. Only one of the 13 patients had biochemical hypogonadism (242 ng/dl), while the other 12 patients had a total testosterone level above 300 ng/dl (606 ± 223 ng/dl).

The mean IIEF-5 score was 16.4 ± 5.2. Sixteen (76.2%) patients had an IIEF-5 score ≤21, which is considered erectile dysfunction. Three of sixteen (18.8%) patients had biochemical hypogonadism (159, 220 and 242 ng/dl) while other 13 patients passed criteria for biochemical hypogonadism (578 ± 223 ng/dl).

Testicular volume in patients with erectile dysfunction was significantly smaller than those without erectile dysfunction; Table 3 (9.4 ± 2.4 vs. 12.4 ± 2.4 ml, p=0.046). However, the total testosterone levels and other sex hormones did not differ between the two groups.

Age at the time of SLE diagnosis, age at study entry, alcohol use, smoking, co-morbidities and BMI did not differ between the two groups. For the SLE-related factors, disease duration, m-SLEDAI-2K at study entry, SLICC damage index, prevalence of NPSLE, lupus nephritis, and positive auto-antibodies (anti-ds DNA Antibody, anti-cardiolipin, and lupus anti-coagulant) did not differ between the two groups. Treatment did not differ between patients with and without erectile dysfunction (Table 3).

Risk factors**	**Erectile dysfunction (N=16)**	**Without Erectile dysfunction (N=5)**	**P-value***
Age at diagnosis (years)	33.5 ± 16.1	26.7 ± 11.2	0.495
Age at study entry (years)	38.6 ± 16.0	29.2 ± 10.0	0.354
Disease duration (years)	5.1 ± 5.1	2.6 ± 1.6	0.354
Alcohol, n (%)	5 (31.3)	2 (40.0)	0.557

Smoking, n (%)	3 (18.8)	1 (20.0)	0.696
Comorbidity, n (%)	3 (18.8)	0 (0.0)	0.421
Testicular volume (ml)	9.4 ± 2.4##	12.4 ± 2.4#	0.046
FSH (mIU/ml)	10.4 ± 10.5	6.0 ± 2.9	0.905
LH (mIU/ml)	8.4 ± 5.4	7.1 ± 2.4	1.000
Testosterone (ng/ml)	5.1 ± 2.5	4.7 ± 2.1	0.856
Prevalence of LN, n (%)	8 (50.0)	2 (40.0)	0.550
Prevalence of NPSLE, n (%)	3 (18.8)	2 (40.0)	0.338
Anti-ds DNA antibody positive, n (%)	6 (37.5)	2 (40.0)	0.656
Anti-cardiolipin antibody positive, n (%)	2 (14.3)	0 (00.0)	0.532
Lupus anticoagulant positive, n (%)	5 (50.0) %	2 (50.0) %%	0.720
Current mSLEDAI-2K	2.3 ± 3.6	3.8 ± 4.9	0.603
SLICC damage index	0.8 ± 1.0	0.0 ± 0.0	0.153
Cumulative prednisolone (gm)	14.3 ± 11.4	9.2 ± 5.6	0.495
Current dose of prednisolone (mg)	8.9 ± 7.1	14.2 ± 11.0	0.313
Cumulative cyclophosphamide (gm)	4.8 ± 6.8	5.4 ± 6.8	0.842

*P-value came from Fisher's exact test or Mann-Whitney test, ** continuous data presented as"mean ± SD, ##from 4 patients, #from 14 patients, %5 from 10 patients, 2 from 4 patiemt, LH: Luteinizing Hormone, FSH: Follicular Stimulating Hormone, LN: Lupus Nephritis, NPSLE: Neuropsychiatric-SLE, mSLEDAI: modified-SLE disease Activity /index, SLICC: SLE Collaborating Clinic

Table 3: Compared associated factors between male lupus patients with and without erectile dysfunction.

Testicular volume

Of the 26 patients, 23 consented to testicular volume analysis by ultrasound. In the 46 total testes, the mean testicular volume was 9.7 ± 3.2 ml. The mean testicular volume of the right and left testicles was 9.9 ± 3.4 ml and 9.4 ± 3.1 ml, respectively. The difference between the right and left testicles was 1.0 ± 0.7 ml. Two patients (8.7%) had a mean two-side testicular volume < 5 ml (shrinking testes) [15]. One patient was a 59-year-old male with DM (total testosterone level was 488.0 ng/dl, FSH 17.2 mIU/ml) and another patient was a 71-year-old male with cirrhosis and chronic renal failure (total testosterone level was 596.0 ng/dl, FSH 37.8 mIU/ml). Varicocele was found on the left side in three of 23 (13.0%) patients and on the right side in one of 23 (4.3%). One scrotal lipoma, one epididymal cyst and one hydrocele were found.

A significant negative correlation was found between testicular volume and the SLICC damage score (r=-0.435, p=0.038). In other words, the testicular volume decreased as the SLICC damage score increased. No significant correlation was observed between testicular volume and age at diagnosis, disease, BMI, disease duration, disease activity by mSLEDAI, and treatment (cumulative dose of prednisolone, cyclophosphamide, or anti-malarial drugs). For the sex hormones and sexual function, the testicular volume positively correlated with total testosterone level (r=0.525, p=0.010) and IIEF-5 score (r=0.476 and p=0.046).

Discussion

This study assessed hypogonadism by evaluating sex hormone levels, signs and symptoms of androgen deficiency. We used standard questionnaires (ADAM and IIEF-5) for detecting symptomatic hypogonadismd and erectile dysfunction [12,13], and measured testicular volume by high-frequency ultrasonography which was an accurate method [16] to detect signs of hypogonadism.

In our study sample, nearly one third of male SLE patients had low testosterone levels. A substantial proportion of patients had symptomatic androgen deficiency (62%) and erectile dysfunction (76%). None of the male SLE patients in this study had the genotype of Klinefelter's syndrome (46XY/47XXY), even though the prevalence of Klinefelter's syndrome is 14 times higher in men with SLE than without SLE [17]. Therefore, hypogonadism found in this study was not due to genetic abnormality.

Male SLE patients with chronic disease and receiving long-term glucocorticoid therapy may benefit from testosterone replacement therapy to improve bone mineral density, muscle mass and strength, sexual function, and quality of life. Moreover, it has been reported that testosterone replacement therapy induced clinical remission of SLE in patients with Klinefelter's syndrome [18]. However, in the general population, testosterone replacement therapy should be considered only in patients with signs and symptoms of hypogonadism and low testosterone levels [7]. Therefore, identifying male SLE patients with these conditions is crucial for additional testosterone replacement therapy.

The differences in total testosterone levels between male SLE patients and normal controls are uncertain. One previous study reported a significantly higher prevalence of low testosterone levels in male SLE patients compared with healthy controls [3], but other studies did not find differences [4,5,19]. One study reported normal testosterone among male SLE patients at onset of SLE before therapy [20]. These different outcomes may be explained by timing of sex hormone evaluation as well as varying disease durations, or treatment exposures. Another study showed that testosterone levels in male SLE patients were comparable to patients with other chronic diseases (i.e. rheumatoid arthritis, patients on long-term steroid therapy, and patients with renal failure on long-term haemodialysis) but lower than healthy controls [21].

In this study, we focused on the prevalence of hypogonadism among male SLE patients in order to identify the magnitude of hypogonadism problem in male SLE patients. We found that nearly one third of male SLE patients had total testosterone levels ≤300 ng/dl. Hypogonadism patients had shorter disease durations and tended to have higher disease activity (though not statistically significant), consistent with Mok et al. [5]. These findings suggest that the early-period, high activity disease state may influence testosterone levels. Therefore, follow-up testosterone level testing in these patients at low disease activity or remission may further support an association between disease activity and testosterone level.

In male SLE patients, the aging process may have considerable effect on sex hormone status. In this study, we defined “old age” as "any age after 50", according to World health organization (WHO) definition. Since only 1 in 5 old age patients in this study had biological hypogonadism, we did not find the aging process to associate with low testosterone level in these patients. Therefore, the biological hypogonadism found in our study is possible from the activity of SLE

Most biochemical hypogonadism SLE patients had normal or low levels of LH and FSH, compatible with hypogonadotrophic hypogonadism. Hypogonadotropic hypogonadism was demonstrated in other chronic diseases [21] suggesting the effects of illness to the hypothalamic-pituitary-gonal (HPG) axis. Interestingly, our study showed that biochemical hypogonadism had a significantly higher prevalence of NPSLE which was also consistent with the observation of Mok et al. [5]. Therefore, hypogonadotrophic hypogonadism may be partly secondary from the direct involvement of SLE to the brain. This issue remains to be further elucidated.

Due to the short disease duration among our study group (4.2 ± 4.5 years), we could not evaluate differences in current or cumulative doses of prednisolone, or cumulative dose of cyclophosphamide between patients with and without hypogonadism. The cumulative dose of cyclophosphamide may not have been high enough to suppress gonad function. This point was supported by the results that most of our patients with hypogonadism were hypogonadotropic hypogonadism, in contrast to the hypergonadotropic hypogonadism typically induced by cyclophosphamide. Since only this study and Mok et al. [5] studied associated factors of hypogonadism in male SLE patients, further studies are needed to confirm these findings.

More than one half (62%) of the male SLE patients in our study had symptomatic hypogonadism as defined by the ADAM questionnaire. However, only one of the patients with symptomatic hypogonadism had total testosterone lower than 300 ng/dl. This finding showed that symptomatic hypogonadism as defined by ADAM questionnaire did not correlate with biochemical hypogonadism in SLE patients. The clinical manifestations of hypogonadism are subtle, nonspecific, and modified by the severity and duration of androgen deficiency, the patient's age, co-morbidities, psychological status and variations in androgen sensitivity. It is difficult to identify patients with symptomatic androgen deficiency, particularly SLE patients, because some SLE patients have depression [22]. The ADAM questionnaire was developed for aging males; also, in some of the questions, it may be difficult to distinguish between symptoms of depression or hypogonadism. Therefore, the ADAM questionnaire may be too sensitive to identify patients with symptomatic hypogonadism because of other underlying conditions such as depression, particularly in young adult males with chronic disease.

In our study, three-fourths of the patients met erectile dysfunction criteria according to IIEF-5 questionnaire. This finding differed from a previous study by Vecchi et al. [19], which reported no SLE patients with erectile dysfunction. However, Vecchi et al. [19] evaluated erectile dysfunction via personal interviews by urologists, while our study used the self-report IIEF-5 questionnaire. Self-reported questionnaires may support honest answers to sensitive questions, since patients could not be individually identified.

Although, total testosterone levels were similar between patients with and without erectile dysfunction, those with erectile dysfunction had a statistically significant smaller testicular volume. This result may help explain why patients with IIEF-5 questionnaire defined erectile dysfunction also had other signs of hypogonadism. Therefore, the IIEF-5 questionnaire may also be helpful in detecting symptomatic hypogonadism.

The median [range] of testicular volume of male SLE patients by high-frequency ultrasonography in this study was 9.5 [3.3, 16.0] ml. Soares et al. [16] demonstrated that measuring testicular volume by high-frequency ultrasonography was more accurate than by Prader orchidometry; they also found that median testicular volumes were lower in male SLE patients with azoospermia than in control patients. Our study showed that testicular volume correlated with the total testosterone levels and IIEF-5 scores and a negatively correlated with the damage score (smaller testicular volume, higher damage score). These findings suggested that the testicular volume correlated well with both testosterone level and erectile dysfunction, some of the symptoms of hypogonadism.

Measuring serum testosterone levels in the general population to screen for hypogonadism is not recommended [7]. Instead, the Endocrine Society recommends to measure testosterone level in patients with symptoms and signs of androgen deficiency by using standard questionnaires such as the ADAM questionnaire. Since ADAM score did not correlate with testosterone levels found in our SLE patients, this questionnaire may not be a sensitive screen for hypogonadism in SLE male who may have multiple co-existing conditions especially depression. However, since our study showed that testicular volume had a good correlation with both IIEF-5 and testosterone level, testicular volume may be used as a surrogate marker for hypogonadism. Hence, we propose measuring testicular volume in male SLE patients along with administering the IIEF-5 questionnaire as a more adequate method for identifying patients at risk for hypogonadism than using the ADAM questionnaire alone, and then to consider measuring serum testosterone level.

Our study had some limitations. First, the sample size was small and underpowered to reach statistical significance for assessing some associated factors. Second, this study did not have a healthy control

group. However, the main aim of this study was to identify the prevalence of hypogoandism in male SLE patients, which did not require a control group. Third, we did not measure thyroid stimulating hormone (TSH) and prolactin level to exclude other causes of hypogonadism. Also, we did not measure free testosterone or serum hormone binding globulin (SHBG) and consequently cannot specify the bioavailable testosterone levels. In addition, many SLE conditions can influence hormone levels, particularly the free testosterone level and SHBG; therefore, measuring sex hormones or other hormones at one point in time may not accurate represent gonad function in male SLE patients. A prospective observational study with repeated hormone measurements is needed to assess the relationship between testosterone levels and gonad function in male SLE patients.

This study is the first to evaluate biochemical hypogonadism, symptomatic androgen deficiency by standard self-report questionnaires, and signs of hypogonadism by accurately measuring testicular volume. We also studied the association between hypogonadism and SLE-related parameters and found that NPSLE had tended to associate with hypogonadism in male SLE patients. Currently, no consensus exists as to practical guidelines for evaluating hypoganidism in male SLE patients, although testosterone replacement therapy may be of benefit. This study was an early step to suggest that an IIEF-5 questionnaire and testicular volume measurement by high-frequency ultrasonography are comparable in detecting the symptoms and signs of hypogonadism. Therefore, these two methods may guide physicians to identify male SLE patient candidates for testosterone level evaluation in clinical practice.

In conclusion, a substantial proportion of male SLE patients in this study had symptomatic hypogonadism and erectile dysfunction. Patients with biochemical hypogonadism had a significantly higher prevalence of NPSLE which need to be further confirmed. Testicular volume correlated with erectile dysfunction score by IIEF-5 questionnaire and testosterone level; therefore, these two methods may be sensitive and specific to predict sexual dysfunction in male SLE patients.

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References

1. D'Cruz DP, Khamashta MA, Hughes GR (2007) Systemic lupus erythematosus. Lancet 369: 587-596.
2. Mongkoltanatus J, Wangkaew S, Kasitanon N, Louthrenoo W (2008) Clinical features of Thai male lupus: an age-matched controlled study. Rheumatol Int 28: 339-344.
3. Sequeira JF, Keser G, Greenstein B, Wheeler MJ, Duarte PC, et al. (1993) Systemic lupus erythematosus: sex hormones in male patients. Lupus 2: 315-317.
4. Vilarinho ST, Costallat LT (1998) Evaluation of the hypothalamic-pituitary-gonadal axis in males with systemic lupus erythematosus. J Rheumatol 25: 1097-1103.
5. Mok CC, Lau CS (2000) Profile of sex hormones in male patients with systemic lupus erythematosus. Lupus 9: 252-257.
6. Köller MD, Templ E, Riedl M, Clodi M, Wagner O, et al. (2004) Pituitary function in patients with newly diagnosed untreated systemic lupus erythematosus. Ann Rheum Dis 63: 1677-1680.
7. Kazi M, Geraci SA, Koch CA (2007) Considerations for the diagnosis and treatment of testosterone deficiency in elderly men. Am J Med 120: 835-840.
8. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40: 1725.
9. Uribe AG, Vila LM, McGwin G, Jr., Sanchez ML, Reveille JD, et al. (2004) The Systemic Lupus Activity Measure-revised, the Mexican Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and a modified SLEDAI-2K are adequate instruments to measure disease activity in systemic lupus erythematosus. J Rheumatol 31: 1934-1940.
10. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, et al. (1996) The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 39: 363-369.
11. Dutrillaux B, Viegas-Pequignot E (1981) High resolution R- and G-banding on the same preparation. Hum Genet 57: 93-95.
12. Rosen RC1, Cappelleri JC, Smith MD, Lipsky J, Peña BM (1999) Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 11: 319-326.
13. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, et al. (2000) Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 49: 1239-1242.
14. [No authors listed] (1999) The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 42: 599-608.
15. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, et al. (2006) Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 91: 1995-2010.
16. Soares PM, Borba EF, Bonfa E, Hallak J, Corrêa AL, et al. (2007) Gonad evaluation in male systemic lupus erythematosus. Arthritis Rheum 56: 2352-2361.
17. Scofield RH, Bruner GR, Namjou B, Kimberly RP, Ramsey-Goldman R, et al. (2008) Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome. Arthritis Rheum 58: 2511-2517.
18. Bizzarro A, Valentini G, Di Martino G, DaPonte A, De Bellis A, et al. (1987) Influence of testosterone therapy on clinical and immunological features of autoimmune diseases associated with Klinefelter's syndrome. J Clin Endocrinol Metab 64: 32-36.
19. Vecchi AP, Borba EF, Bonfá E, Cocuzza M, Pieri P, et al. (2011) Penile anthropometry in systemic lupus erythematosus patients. Lupus 20: 512-518.
20. Chang DM, Chang CC, Kuo SY, Chu SJ, Chang ML (1999) Hormonal profiles and immunological studies of male lupus in Taiwan. Clin Rheumatol 18: 158-162.
21. Mackworth-Young CG, Parke AL, Morley KD, Fotherby K, Hughes GR (1983) Sex hormones in male patients with systemic lupus erythematosus: a comparison with other disease groups. Eur J Rheumatol Inflamm 6: 228-232.
22. Kasitanon N, Achsavalertsak U, Maneeton B, Wangkaew S, Puntana S, et al. (2013) Associated factors and psychotherapy on sleep disturbances in systemic lupus erythematosus. Lupus 22: 1353-1360.