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ORIGINAL ARTICLE

Correlation between various clinical parameters of systemic lupus erythematosus and levels of anti-histone and anti-chromatin antibodies

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KEYWORDS

Systemic lupus erythematosus (SLE);
Anti-chromatin;
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Clinical manifestations;
SLE Disease Activity Index (SLEDAI)

Abstract *Background:* Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of auto-antibodies leading to a spectrum of clinical findings. Among these auto-antibodies are anti-chromatin and anti-histone antibodies in which researches showed a renewed interest in the last few years.

Aim of the work: The aim of our study was to assess the serum levels of anti-chromatin and anti-histone antibodies in patients with SLE, and to correlate them with clinical features of the disease.

Patients and methods: The study included 60 female SLE patients and 13 normal females as controls. Patients were subjected to full history taking, clinical examination, and laboratory tests. Serum anti-chromatin and anti-histone antibodies were detected using enzyme linked immunosorbent assay (ELISA) in patients and controls.

Results: Anti-chromatin antibodies showed 100% sensitivity and 66.7% specificity, while anti-histone antibodies showed 100% sensitivity and 53.3% specificity. A statistically significant difference was elicited between SLE patients and controls regarding the serum levels of both antibodies. Serum levels of anti-chromatin antibodies in SLE patients were significantly correlated with the occurrence of hematological manifestations, duration of steroid therapy, and also dose and duration of hydroxychloroquine (HCQ) therapy. However, no significant correlation was found between anti-histone antibodies and other parameters.

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Conclusion: Anti-chromatin and anti-histone antibodies are both sensitive and specific for SLE and can be used not only for its diagnosis, but also for following therapeutic progress. Further studies on a large scale are needed to elucidate the effect of therapy on the serum levels of these antibodies in SLE patients.

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1. Introduction

Systemic Lupus Erythematosus (SLE) is often described as the classical systemic autoimmune disease due to its wide spectrum of clinical and immunological abnormalities [1]. It is the most diverse of the autoimmune diseases and it is characterized by the production of multiple auto-antibodies with a complex and wide spectrum [2,3]. Even though the presence of autoantibodies in SLE has been known, for more than 60 years, still nowadays a great effort is being made to understand the pathogenetic, diagnostic, and prognostic meaning of such autoantibodies [3]. The prominent feature of immunological defects in SLE is the production of autoantibodies to nuclear antigens including deoxyribonucleic acid (DNA), histones and ribonucleoprotein (RNP) [4].

Anti-double stranded DNA (anti-dsDNA) antibodies are considered useful for the diagnosis of SLE, to monitor the disease activity, and correlate with renal and central nervous involvements [3]; they are found only in 50% of SLE patients and do not always correlate with disease activity [5].

On the other hand, antinuclear antibodies (ANA), the most prevalent antibodies, have low specificity for the diagnosis of SLE because they are found in most systemic autoimmune diseases and even in healthy individuals. Thus, it is important to look for other auto-antibodies that may be useful in the diagnosis and assessment of the disease activity in SLE patients [6].

Autoantibodies directed to chromatin components date back to the discovery of the LE cell with subsequent evidence that major components were chromatin and histones in particular. Over time, immunoassays ranging from ELISA and line immunoassays to more modern bead-based assays incorporated histone and DNA mixtures, purified histones, and purified nucleosomes leading to a more thorough understanding of the genesis and pathogenetic relationships of antibodies to chromatin components in SLE and other autoimmune conditions [7]. Anti-nucleosome antibodies are an excellent marker for SLE and good predictors of flares in quiescent lupus and anti-histone antibodies characterize drug-induced lupus [3].

Methods to detect anti-nucleosome antibodies have been available for more than 10 years and the test has demonstrated its good sensitivity and high specificity in diagnosing SLE. Despite these data produced through clinical and laboratory research, the test is little used. Data from the metanalysis have shown that anti-nucleosome antibodies have equal specificity but higher sensitivity and prognostic value than anti-dsDNA antibodies in the diagnosis of SLE. The use of anti-nucleosome antibodies appears more efficacious than anti-dsDNA [8]. Anti-histones were associated with a higher proportion of proliferative renal disease and poorer outcome in lupus nephritis patients [9].

The aim of the present study was to assess the serum levels of anti-chromatin and anti-histone antibodies in SLE patients and to correlate their serum levels with various clinical features of SLE.

2. Patients and methods

2.1. Patients

The present study was carried out on 60 SLE patients fulfilling the 1982 American College of Rheumatology (ACR) revised criteria for the classification of SLE [10,11] in addition to 13 apparently healthy age and sex matched subjects as the control group. All patients were selected from the outpatient clinic of Rheumatology and Rehabilitation Department, Cairo University Hospitals. An Informed consent was obtained from all participants in the study, and the study was approved by the Institutional Review Board (IRB) of faculty of medicine, Cairo University.

2.2. Methods

All patients have been subjected to:

1. *Comprehensive history taking and thorough clinical examination:* general, cardiopulmonary, abdominal, neurological and musculoskeletal system.
2. *Routine laboratory investigations:* complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver and kidney functions and urine analysis, in addition to estimation of total albumin in 24 h urine, blood glucose, immunological assays as anti-nuclear antibodies (ANA), anti-double strand DNA (anti-dsDNA) antibodies, anti Ro, anti La, anticardiolipin (aCL) antibodies and serum complement levels (C3 and C4).
3. *Assessment of disease activity using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI):* Grading of disease activity to mild (1–10), moderate (11–20), severe (21–45), and very severe (>45) [12]. A final weight total SLEDAI score is then calculated with possible theoretic score of 105 [13].
4. *Radiological Investigations:* X-ray for any affected joint and Chest X-ray for detection of chest problems as pleural effusion, or interstitial lung disease.
5. *Electrocardiography (ECG):* for detection of ischemia, pericardial effusion, valvular abnormalities, pericarditis, myocarditis or endocarditis.
6. *Renal biopsy* and histopathological assessment in cases with renal involvement.

Serum anti-chromatin and anti-histone antibodies were detected in patients and controls as follows:

Determination of serum anti-chromatin (anti-nucleosome) and anti-histone antibodies using QUANTA-lite™ chromatin

and histone which are an enzyme linked immunosorbent assay (ELISA) for the semi quantitative detection of chromatin antibodies and histone antibodies in human serum.

Principle: Highly purified total histones and anti-chromatin are bound to microwells. Antibodies to these antigens, if present in diluted serum, bind in the microwells. Washing of the microwells removes unbound serum antibodies. Horseradish peroxidase (HRP) conjugated anti-human IgG immunologically binds to the bound patient antibodies forming a conjugate/antibody/antigen complex. Washing of the microwells removes unbound conjugate. An enzyme substrate in the presence of bound conjugate hydrolyzes to form a blue color. The addition of an acid stops the reaction forming a yellow end-product. The intensity of this yellow color is measured photometrically at 450 nm. The amount of color is directly proportional to the concentration of IgG antibodies present in the original sample.

Specimen collection, storage and handling: Whole blood specimens were collected using acceptable medical techniques to avoid hemolysis, then blood is allowed to clot and the serum is separated by centrifugation. Tested serum should be clear and non-hemolyzed. Specimens could be refrigerated at 2–8 °C for up to five days or stored at −20 °C up to six months. Repetitive freezing and thawing of serum samples should be avoided as it may result in variable loss of autoantibody activity. Also, testing of heat-inactivated sera is not recommended.

Quality control: This test is only valid if the optical density at 450 nm for Positive Control (1) and Negative Control (2) as well as for the Calibrators A and F complies with the respective range indicated on the Quality Control Certificate enclosed to each test kit. If any of these criteria is not met, the results are invalid and the test should be repeated.

Calculation of results: For anti-histone, anti-histone IgG a 4-Parameter-Fit with lin-log coordinates for optical density and concentration is the data reduction method of choice. Smoothed Spline Approximation and log–log coordinates are also suitable.

Interpretation of results: In a normal range study with serum samples from healthy blood donors the following ranges have been established with:

- The anti-histone test: anti-histone IgG, Cut-Off: 7.1 U/ml.
- The anti-nucleosome test: anti-nucleosome IgG, Cut-Off: 37.5 U/ml.

Data were statistically described in terms of mean ± standard deviation (SD), range (minimum–maximum), and percentage. Comparison between cases and control groups was done using Student's t test for independent samples. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables. p Values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS version 13 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA).

3. Results

The present study included 60 SLE female patients (Group A) as diagnosed according to the American College of Rheumatology (ACR) revised criteria for the classification of SLE with a mean age of 29.3 ± 7.5 years (age range 17–50 years). In addition, an age-matched group of 13 healthy females were included as the control group (Group B), with a mean age of 32 ± 6.4 years (age range from 22 to 48 years). The descriptive data of SLE Patients (Group A) are shown in Table 1.

The mean level of anti-chromatin antibodies (U/ml) in group A (SLE patients) was 103.02 ± 23.6 (38.1–142.5), elucidating a statistically significant difference as compared to 39.7 ± 18.4 (18.9–82.1) in group B (controls) ($p < 0.001$) (Fig. 1). Regarding anti-histone antibodies (U/ml), its mean level in SLE patients (Group A) was 17.8 ± 7.2 (7.4–42.1), as compared to 7.7 ± 3.4 (2.1–12.8) in group B (controls), which once again shows a statistically significant difference ($p < 0.001$) (Fig. 1).

On comparing between the mean levels of anti-chromatin and anti-histone antibodies among Group A (SLE patients) with different clinical manifestations, a statistically significant difference was found between the levels of anti-chromatin antibodies with hematological manifestations as compared to those without ($p = 0.01$) (Table 2). On comparing between the mean levels of anti-chromatin and anti-histone antibodies among Group A (SLE patients) with different variables, a statistically significant negative correlation was elucidated between the levels of anti-chromatin antibodies with the hemoglobin concentration ($r = -0.39$, $p = 0.002$) (Table 3).

Regarding drug intake, a statistically significant negative correlation was elucidated between anti-chromatin antibodies' level and the duration of steroid therapy ($r = -0.26$, $p = 0.04$), as well as with the hydroxychloroquine (HCQ) therapy regarding both dose ($r = -0.29$, $p = 0.037$), and duration ($r = -0.28$, $p = 0.049$) (Table 3).

Among Group A, 48 patients (80%) had lupus nephritis and 42 of them (70%) performed renal biopsy for grading of renal involvement. On comparing between serum levels of both anti-chromatin and anti-histone antibodies among patients with various grades of renal involvement, the highest mean level of anti-chromatin antibodies was in patients with grade III lupus nephritis, while the highest mean level of anti-histone antibodies was in patients with grade II lupus nephritis (Table 4).

Furthermore, an anti-chromatin antibody level of 37.5 U/L was postulated as a cutoff point with 100% sensitivity, and 66.7% specificity. Regarding anti-histone antibodies, a level of 7.1 U/L was the cutoff point that showed 100% sensitivity, and 53.3% specificity.

4. Discussion

Systemic lupus erythematosus is an autoimmune disease characterized by the production of antibodies against various cell components leading to a spectrum of clinical findings ranging from lesions confined to the skin to multisystem organ involvement [14]. The etiology of SLE remains largely unknown and is multifactorial. Several factors in the environment can contribute to onset and relapses of SLE. Mainly chemical and physical factors have been studied in SLE, whereas social and behavioral aspects have been less investigated [15].

Abnormalities in immune regulation are thought to be the consequence of a loss of self-tolerance in affected patients, leading to an autoimmune response with abnormal cellular

Table 1 Characteristics of systemic lupus erythematosus (SLE) patients (Group A).

Parameter		SLE patients (Group A) ($N = 60$)
Age (years), mean ± SD (range)		29.3 ± 7.5 (17–50)
Age of onset (years), mean ± SD (range)		23.4 ± 7.4 (16–49)
Disease duration (years), mean ± SD (range)		6.1 ± 3.9 (1–18)
Clinical manifestations		*N* (%)
Constitutional		
Fever		45 (75)
Fatigue		43 (71.7)
Weight loss		27 (45)
Musculoskeletal		
Arthralgia		46 (76.7)
Arthritis		51 (85)
Myositis		1 (1.7)
Mucocutaneous		
Photosensitivity		44 (73.3)
Malar rash		51 (85)
Alopecia		52 (86.7)
Oral ulcer		52 (86.7)
Discoid lesion		10 (16.7)
Cardiopulmonary		40 (66.7)
Pleurisy and pleural effusion		31 (51.7)
Pericarditis and pericardial effusion		14 (23.3)
Interstitial pneumonitis		1 (1.7)
Pulmonary hypertension		31 (51.7)
Gastrointestinal		
Hepatomegaly		4 (6.7)
Splenomegaly		1 (1.7)
Ascites		21 (35)
CNS manifestations		
Cognitive impairment		3 (5)
Seizures		9 (15)
Psychosis		5 (8.3)
Stroke		2 (3.3)
Mononeuritis multiplex		9 (15)
Transverse myelitis		2 (3.3)
Peripheral neuropathy		1 (1.7)
Renal affection		48 (80)
Vascular manifestations		
Vasculitis		21 (35)
Nail fold capillary vasculitis		2 (3.3)
Cutaneous vasculitis		2 (3.3)
Retinal vasculitis		2 (3.3)
Deep venous thrombosis		28 (46.7)
Hematologic		24 (40)
Anemia		9 (15)
Leukopenia		9 (15)
Thrombocytopenia		9 (15)
SLEDAI, mean ± SD (range)	26.8 ± 9.3	(9–47)
Laboratory characteristics	Mean ± SD	(range)
Erythrocyte sedimentation rate (mm/1st hour)	51.8 ± 37.95	(5–170)
Hemoglobin (g/dL)	11.4 ± 1.96	(6.8–16.6)
Total leukocytic count ($\times 10^3/mm^3$)	8.1 ± 3.7	(2.2–19.2)
Platelets ($\times 10^3/mm^3$)	262.3 ± 125.1	(76–941)
Alanine transaminase ALT (U/L)	25.2 ± 27.9	(6–202)
Aspartate transaminase AST (U/L)	23.8 ± 14.1	(6–85)
Urea (mg/dL)	49.4 ± 58.4	(7–136)
Creatinine (mg/dL)	1.4 ± 3.5	(0.2–6.5)
Immune profile, *N* (%)		
ANA positivity		60 (100)
Anti-dsDNA positivity		53 (87)
Anti-cardiolipin positivity		20 (32)
Anti-Sm positivity		11 (17)
Anti-Ro positivity		5 (8.3)
Anti-La positivity		3 (5)
C3, mean ± SD (range)	66.7 ± 44.95	(0.03–158)
C4, mean ± SD (range)	15.8 ± 11.8	(0.06–35)
Drug intake *N* (%)		
Steroids		60 (100)
Hydroxychloroquine (HCQ)		52 (86.7)
Azathioprine (Immuran®)		44 (73.3)
Cyclophosphamide (Endoxan®)		21 (35)
Mycophenolate mofetil (Cellcept®)		3 (5)

CNS, central nervous system; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; Anti-dsDNA, anti-double strand deoxyribonucleic acid; ANA, anti-nuclear antibodies; C3, complement factor 3; C4, complement factor 4.

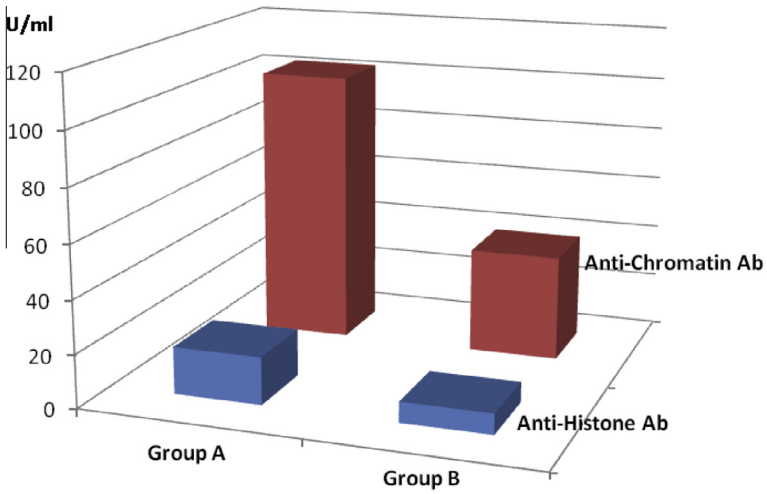

Figure 1 The mean levels of anti-chromatin and anti-histone antibodies in SLE patients (Group A) and healthy Controls (Group B).

Table 2 A comparison between the mean levels of anti-chromatin and anti-histone antibodies among Group (A) SLE patients with different manifestations.

Variable		No.	Anti-chromatin Abs		Anti-histone Abs	
			Mean ± SD	*p*	Mean ± SD	*p*
Arthritis	Yes	51	103.1 ± 24.96	0.62	17.96 ± 7.6	0.98
	No	9	102.5 ± 14.9		16.8 ± 5.2	
Vasculitis	Yes	27	99.4 ± 27.3	0.499	17.99 ± 7.6	0.99
	No	33	105.98 ± 20.1		17.6 ± 7.1	
Serositis	Yes	41	100.4 ± 22.3	0.07	17.4 ± 5.95	0.89
	No	19	108.7 ± 25.98		18.9 ± 9.6	
CNS	Yes	21	103.4 ± 30.02	0.57	17.9 ± 5.4	0.52
	No	39	102.8 ± 19.8		17.7 ± 8.1	
GIT	Yes	31	103.04 ± 22.8	0.96	18.8 ± 7.0	0.16
	No	29	103.0 ± 24.9		16.7 ± 7.4	
Hematological	Yes	28	110.98 ± 18.5	0.01*	18.5 ± 6.8	0.22
	No	32	96.1 ± 25.7		17.1 ± 7.7	
Renal	Yes	48	104.9 ± 21.7	0.39	18.6 ± 7.4	0.09
	No	12	95.6 ± 30.1		14.7 ± 5.6	

CNS, central nervous system; GIT, gastrointestinal tract.
* Statistically significant difference.

breakdown and the production of auto-antibodies [16]. Different auto-antibodies have been associated with SLE in the past, most notably anti-nuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies, the most relevant tests in diagnosing SLE. Patients with SLE have been shown to have elevated antibody levels in 50–80% of cases, correlating with disease activity [6]. In the present study the ANA antibodies were positive in 100% of the cases and the anti-dsDNA in 87%. In other studies on Egyptian SLE patients, the ANA was positive in 93–100% [17–19] while the anti-dsDNA was positive in 64–67% [17,18].

Additional antibodies with potential pathogenic and diagnostic relevance have been recognized in SLE [6]. Anti-chromatin antibodies, also referred to as antinucleosome antibodies, are directed against a major autoantigen in SLE, namely nucleosomes (nuclear histone-DNA complexes). Several studies have noted a prevalence of anti-chromatin antibodies in SLE patients of 48–80% [20]. Anti-histone antibodies have been detected in 18–53% of patients with SLE, and up to 95% of patients with drug-induced lupus [21].

In our study, SLE patients had a mean age of 29.3 ± 7.5 years, and mean disease duration of 6.1 ± 3.9 years. Shabana and coworkers studied SLE patients with a mean age of 25 ± 9.3 years which is close to the age of our patients; however they had shorter disease duration of 3.3 ± 3.2 years [22]. On the other hand, SLE patients studied by Souza et al. were older with a mean age of 35.1 ± 11.9 years [14]. Furthermore, our patients had a higher SLE Disease Activity Index (SLEDAI) with a mean of 26.8 ± 9.3 as compared to those of Souza et al. with a mean of 16.5 ± 9.6 [14].

In our study renal affection was present in 80% of patients, alopecia and oral ulcers in 86.7%, arthritis in 85%, and cardiopulmonary affection in 66.7%. However, Shabana and coworkers found renal affection in 36.9% of SLE patients, malar rash in 60.5%, alopecia in 57.9%, cardiac involvement in 5.3% and pulmonary affection in 18.4% [22]. Accordingly,

Table 3 Correlation between the mean levels of anti-chromatin and anti-histone antibodies among Group (A) SLE patients with various variables.

Variable			Antibodies	
			Anti-chromatin	Anti-histone
Age		*r*	0.04	0.07
		p	0.74	0.61
Age of onset		*r*	0.11	−0.001
		p	0.38	0.99
Duration		*r*	−0.14	0.08
		p	0.27	0.52
SLEDAI		*r*	0.06	0.02
		p	0.65	0.90
ESR		*r*	0.197	0.05
		p	0.13	0.71
Hemoglobin		*r*	−0.39	−0.09
		p	0.002*	0.49
TLC		*r*	−0.19	−0.11
		p	0.16	0.39
Platelets		*r*	−0.004	−0.09
		p	0.97	0.496
FBG		*r*	0.17	0.07
		p	0.20	0.58
ALT		*r*	−0.095	0.04
		p	0.47	0.75
AST		*r*	−0.13	0.13
		p	0.33	0.34
Albumin		*r*	−0.03	0.01
		p	0.83	0.97
Urea		*r*	0.10	0.20
		p	0.45	0.12
Creatinine		*r*	−0.04	−0.15
		p	0.74	0.26
24hr Urinary proteins		*r*	0.07	0.09
		p	0.59	0.49
C3		*r*	0.04	−0.08
		p	0.77	0.55
C4		*r*	−0.01	−0.10
		p	0.94	0.43
Drug intake				
Steroid	Dose	*r*	−0.16	0.06
		p	0.22	0.64
	Duration	*r*	−0.26	−0.14
		p	0.044*	0.27
HCQ	Dose	*r*	−0.29	−0.04
		p	0.037*	0.77
	Duration	*r*	−0.28	0.08
		p	0.049*	0.59
Azathioprine	Dose	*r*	−0.16	−0.15
		p	0.30	0.32
	Duration	*r*	−0.19	0.07
		p	0.23	0.67
Cyclophosphamide	Dose	*r*	−0.19	−0.09
		p	0.39	0.68
	Duration	*r*	−0.13	−0.02
		p	0.57	0.93

SLEDAI, systemic lupus erythematosus disease activity index; ESR, erythrocyte sedimentation rate; TLC, total leukocytic count; FBS, fasting blood sugar; ALT, alanine transaminase; AST, aspartate transaminase; C, complement; HCQ, hydroxychloroquine.
* Statistically significant difference.

Table 4 Comparison between serum levels of both anti-chromatin and anti-histone antibodies among SLE patients with various grades of renal involvement.

Grade of renal involvement	No.	Antibodies	
mean ± SD (range)		Anti-chromatin	Anti-histone
Grade II	8	101.5 ± 25.6 (65.3–142.5)	24.7 ± 12.7 (9.02–42.1)
Grade III	10	116.6 ± 12.4 (98.2–137.2)	16.9 ± 3.8 (10.7–24.3)
Grade IV	22	105.9 ± 21.5 (55.3–136.6)	16.9 ± 5.3 (8.6–28.4)
Grade V	2	104.5 ± 7.3 (99.3–109.6)	18.3 ± 14.1 (8.3–28.3)

our patients showed higher prevalence of cutaneous, musculoskeletal, renal and cardio-pulmonary manifestations than the study of Shabana et al. In another study on Egyptian SLE patients, renal involvement was present in 95%, mucocutaneous manifestations in 72.5%, arthritis in 67.5% and cardiopulmonary involvement in 30.5% [17].

Our data showed that the level of anti-chromatin antibodies was significantly higher in SLE patients with hematological manifestations as compared to those without ($p = 0.01$), while it did not show a statistically significant difference between those with arthritis, vasculitis, serositis, CNS, gastrointestinal, or renal affection and those without. On the contrary, the study of Shabana et al. showed that the levels of anti-chromatin antibody were significantly higher in SLE patients with arthritis, malar rash, oral ulcer and pulmonary affection than those without ($p < 0.05$) [22]. Additionally, Saisoong et al. showed a significantly higher level of anti-chromatin antibody patients with lupus nephritis ($p = 0.03$) [23]. In another study on Egyptian SLE patients, serum levels of anti-nucleosome antibodies were associated with active lupus disease and correlated with the degree of renal affection [24]. These discrepancies could be attributed either to the larger group of studied patients, different selection criteria, or different technique used for antibody detection. Regarding anti-histone antibody, our findings showed that its level did not differ significantly in SLE patients with arthritis, vasculitis, serositis, CNS, gastrointestinal, hematological manifestations, or renal affection as compared to those without. While Shabana et al. showed that the level of anti-histone antibodies was significantly higher in patients with fatigue only, and not with any other clinical manifestations [22].

Among all laboratory findings in our study, only hemoglobin concentration showed a statistically significant negative correlation with anti-chromatin antibodies ($r = -0.395$, $p = 0.002$).

In the study of Shabana and coworkers, SLEDAI scores of SLE patients positively correlated with serum levels of anti-chromatin antibodies ($p < 0.001$) but not with the serum levels of anti-histone antibodies; no significant correlations were observed between anti-chromatin and anti-histone antibodies and any of the hematological parameters in their SLE patients [22]. Also in disarrangement with our results Saisoong et al. showed a correlation between both anti-chromatin and anti-DNA antibody levels and disease activities ($r = 0.33$,

$p = 0.007$ and $r = 0.37$, $p = 0.002$ respectively) [23]. In our patients anti-chromatin and anti-histone antibodies did not correlate with SLEDAI, ESR or with platelets. This could be attributed to the effect of medications on disease activity of our patients. As we showed there was a significant negative correlation of anti-chromatin antibodies and steroid duration and HCQ dose and duration. This can have therapeutic implications on these antibodies.

Saisoong et al. reported that no correlation was observed between antinucleosome antibody activity and C4 levels [23]. Similarly, in our study we did not observe a correlation between anti-chromatin and anti-histone antibodies and C3 or C4 levels.

In our study 42 lupus nephritis patients performed renal biopsy (70%), the highest mean of anti-chromatin antibodies was in lupus nephritis grade III patients, while the highest mean of anti-histone antibodies was in lupus nephritis grade II patients. There was no statistical significant difference between the mean level of anti-chromatin and anti-histone antibodies in patients with and without renal affection ($p = 0.39$ and $p = 0.09$, respectively). In agreement with our results, Shabana et al., showed no significant statistical difference between serum levels of anti-histone antibodies in patients with and without renal involvement and no significant correlation between these antibodies and renal biopsy class. However, their results are different regarding anti-chromatin antibodies which were significantly higher ($p < 0.01$) in patients with, than in those without nephritis. Also in their study, there was a significant correlation between serum levels of anti-chromatin antibodies ($p < 0.01$) and World Health Organization (WHO) renal biopsy classes [22]. Contrary to our results, Putova et al. showed statistical significant higher serum levels of anti-nucleosome antibodies in patients with lupus nephritis. This could be related to the different patient selection and racial differences [25]. Similar to our results, many researchers failed to show association between both anti-chromatin and anti-histone antibodies and lupus nephritis [26–28].

In our study, anti-chromatin antibodies had 100% sensitivity and 66.7% specificity at the cutoff point of 37.5 U/L while anti-histone antibodies had a 100% sensitivity and 53.3% specificity at the cutoff point 7.1 U/L. The study of Schett et al. had a sensitivity of anti-chromatin antibodies of 48% and specificity of 95%, while sensitivity of anti-histone antibodies was 45% and specificity was 98% [27]. In the study of Bose et al. the anti-chromatin antibody sensitivity was 62.4% and the specificity was 91.5% [29]. A systematic review and metanalysis showed that the overall sensitivity of the anti-nucleosome assay was 61% and the specificity 94% [8]. In the present study the sensitivity was higher and the specificity lower than the other studies. In the study of Shabana et al., anti-chromatin antibody sensitivity was 89.5% and specificity 92.1%, while anti-histone antibodies showed a sensitivity of 80% and specificity of 82.2% [22]. These values were also similar to what was reported by Gómez-Puerta et al. [30]. Our results are close to these authors as regards sensitivity but not specificity. This could be attributed to the techniques and method used in our study to detect these antibodies and to the different cutoff points used.

The results of the present study emphasize the clinical benefits of anti-chromatin and anti-histone antibodies. Their detection could be more applicable for the diagnosis of SLE especially in cases with negative ANA, as they are highly sensitive and specific. The effect of drugs on the presence of anti-chromatin and anti-histone antibodies could be used for therapeutic purposes. Further large-scale studies are required for showing their effects.

In conclusion, the results of our study indicate that: anti-chromatin and anti-histone antibodies are both sensitive and specific for SLE and could be a useful addition to the laboratory tests that can help in the diagnosis of SLE. Determination of anti-chromatin antibodies could be a promising useful parameter to assess the effect of drugs on disease activity status. Furthermore, increased titer of anti-chromatin antibodies appears to be a sensitive marker for identifying patients with hematological manifestations.

Conflict of interest

The authors declared no conflict of interest.

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