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Original Article

Clinical importance of C1q antibodies in systemic lupus patients with and without nephritis

Clinical Pathology

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ABSTRACT

Background: Serological markers for lupus nephritis (LN) have recently been established in Systemic Lupus Erythematosus (SLE) cases with high levels of anti-C1q antibodies (SLE). We investigated serum level ofanti-C1q antibodies in Egyptian female SLE cases less than 25 years to detect if they could serve as a biomarker for nephritis activity.

Methodology: This hospital based case control study was conducted on 180 female subjects from Sept 2021 to March 2022. Patients were collected from rheumatology, nephrology and pediatrics departments of Alhusien and Bab Alsharia University hospitals, all female cases underwent follow-up. Their ages were less than 25 years old. They were divided into three groups. Group 1 included 60 female cases of SLE and active lupus nephritis. Group 2 included 60 female cases of SLE without active lupus nephritis. Group 3included 60age matched apparently healthy females as a control group.

Results: There was significant elevation in ESR and anti C1q in group 1 more than other two groups with decrease in C3,4. In group 1 Anti-C1q was significantly correlated with 24 h Protein, C3&4 and SLEDAI Score. In group 2 Anti C1q was significantly correlated with C3 only. ESR, C3, C4, Anti-C1q, ANA Titer and Anti dsDNA were considerable sensitive as positive markers for lupus nephritis in SLE cases.

Conclusion: Proteinuria, complement levels, and renal SLEDAI all correlate with renal disease activity and flare-ups, as do anti-Clq auto antibodies. Anti-C1q antibodies, instead of other validated disease activity markers, may be utilized to diagnose nephritis flare in pediatric and adolescent Egyptian females with SLE.

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INTRODUCTION

Lupus nephritis (LN) is a common major organ manifestation of SLE and a substantial cause of morbidity and mortality [1]. As a result, the presence of renal impairment is a considerable prognostic factor in Systemic Lupus Erythematosus (SLE) and identifying LN in SLE cases has a considerable therapeutic advantage in clinically guiding SLE medications. SLE cases produce abnormal auto antibodies. Autoantibody profiles and disease characteristics have helped identifying SLE cases at risk for certain problems, enabled physicians to start a successful therapy plan and minimize morbidity or death in SLE cases [2]. Nuclear (antinuclear antibodies, ANA), double-strand DNA (antidsDNA) and complement C1q (anti-C1q) antibodies are the most clinically relevant auto antibodies seen in patients with SLE. It would be extremely beneficial to have a non-invasive indicator of renal sickness, since kidney biopsies are rarely done during a flare [3]. Biomarkers that consistently predict SLE nephritis activity, pathology, and prognosis will be needed to guide pharmacological decisions as the treatment paradigm shifts from reactive to proactive.

Anti-dsDNA and anti-C1q antibodies have been demonstrated to be more strongly associated to clinical features of active SLE emphasizing the importance of

detecting these auto antibodies in SLE cases [4]. In SLE cases, anti-dsDNA and anti-C1q antibodies have been connected to renal disease, bad prognosis and a greater anti-C1q antibody concentration has been linked to a lower complement C1q level in cases with active LN. As a result, anti-C1q antibodies in the blood have been intensively researched as a biomarker for predicting renal flares in SLE cases. C1q, C3, and C4 complement levels in the blood are often reduced in SLE cases. As a consequence, auto antibodies against C1q, dsDNA, and chromatin/nucleosome have been identified as useful immunological markers for SLE diagnosis, particularly in LN disease [5]. It was previously considered that the presence of anti-C1q was essential for the start of lupus nephritis. Monitoring anti-C1q levels as a non-invasive biological marker of renal sickness, according to some study, may be effective in the therapeutic treatment of SLE cases [6]. Because immune complex deposition is the primary source of tissue damage, the complement system plays an important role in the pathogenesis of SLE. Hereditary classical complement component deficiencies are often linked to the development of SLE as a result of poor apoptotic debris clearance [7]. Homozygous C1q deficiency is the most common genetic risk factor for SLE, with 93% of C1q-deficient cases developing SLE or lupus-like symptoms. In the majority of SLE cases, anti-C1q antibodies cause secondary complement insufficiency [8]. The purpose of this research is to examine serum anti-C1q antibodies as a biomarker for nephritis activity in Egyptian female SLE cases, both pediatric and adolescent.

PATIENT AND METHODS

This was a hospital based case control study done from Sept 2021 to March 2022. The study was conducted on 180 female subjects less than 25 years. Patients were collected from rheumatology, nephrology and paediatrics departments of Alhusien and Bab Alsharia University hospitals, all female cases underwent follow-up. They were divided into three group: Group 1 included 60 female cases of SLE with active lupus nephritis (LN SLE). Group 2 included 60 female cases of SLE without active lupus nephritis (Non-LN SLE). Group 3 included 60 ages matched apparently healthy females (Non SLE).

Methods: A full clinical examination was performed on all cases, which included vital signs, body weight, lower limb edema and uremia symptoms. The disease activity was assessed using the SLE disease activity index renal (SLEDAI) [9]. A kidney SLEDAI score of more than 4 was arbitrarily regarded as lupus activity. Nephritis was diagnosed by evaluating the patient's proteinuria (more than 0.5 grams per 24 hours), cellular casts, hematuria (more than 10 red blood cells per urine sample), and renal insufficiency. The mean renal SLEDAI in group 1 was 12. The WHO classification was used to classify the renal histology [10].

The subjects were subjected to the following laboratory tests: 1) Complete blood count, 2) Erythrocyte sedimentation rate, 3) Sodium, potassium, urea and creatinine level in the blood, 4) Serum C3 and C4, 5) Antibodies correlated to SLE (Shown in Statistics tables), 6) Analysis of the urine, 7) 24-hour-protein of the urine, 8) Serum anti-C1q by ELISA, 9) All SLE cases in groups 1 and 2 had their kidneys biopsied. (When group 2 had active illness in the past, a kidney biopsy was conducted). Class IV to V histopathology was found in the kidneys of both groups (According to the WHO, diffuse proliferative and membranous glomerulonephritis).The renal biopsy and serum sample for antiC1q antibody detection were obtained at the same time in group 1 participants. Group 1 cases were also undergoing active treatment during this time. A kidney biopsy was conducted after each individual gave their consent.

Sample collection and treatment: Specimen: Three milliliters of blood were extracted through vein puncture and allowed to clot before being centrifuged at 2500 g for 10 minutes to separate the serum. The research did not include hemolyzed or lipemic serum. Specimen storage: Before being analysed, specimens were sealed and stored at -20oC for a few months. On a regular basis, thawing and freezing were avoided. Immunoassay of the test: Microwells of the Anti-C1q ELISA kit are coated with very pure human C1q. Antibodies against this antigen bind to the antigen when they are present in diluted serum. Removing serum from the microwells is accomplished by rinsing. Immunologically, antihuman IgG conjugated with horseradish peroxidase (HRP) detects binding patient antibodies, resulting in a conjugate/antibody/antigen combination. Washing the microwells removes any unbound conjugate. When hydrolyzed with bound conjugation, an enzyme substrate becomes blue. The process comes to a stop when an acid is injected, resulting in the creation of a yellow end product. The photometric wavelength of 450 nm is used to measure the intensity of the yellow color. The concentration of IgG antibodies present in the sample is reflected in the intensity of the color.

Ethical consideration: The protocol was approved by the local Ethics Committee of the Faculty of Medicine, Al-Azhar University, Cairo, Egypt. All participants signed a written consent form after being given a short and transparent explanation of the study's aim, procedure, and the chance to opt out.

Statistical analysis: SPSS version 22.0 was used to analyse computer-generated data. Percentages and numbers were employed to express qualitative data. Continuous data were presented as Mean ± Standard deviation. T. test was used for comparison continuous data between two groups and ANOVA test for more than two groups. For qualitative data we used Chi square test. Result is considered significant at P. Value < 0.05.

RESULTS

In the present study, the mean age of female patients with (LN SLE) (group1) was (17±1.9) years ranged between 12 to 24years. In group 2 (Non-LN SLE); their age ranged between 13 to 24years with mean (16.6 ±1.8) years. While, in healthy females (group3), their age ranged between 12 to 24 years with mean (16.5±1.8) years. There was considerable elevation in ESR and anti C1q in group 1 compared to other groups. Also, there was statistically significant decrease in C4in group 1 compared to other groups (P<0.05) (table 1).There was statistically significant elevation in disease duration, SLEDAI score, ANA titer and Anti-dsDNA in group 1 (table 2). In group 1 Anti C1q was statistically correlated with 24 h Protein, C3&4 and SLEDAI Score. In group 2 Anti C1q was significantly correlated with C3 only (table 3).ESR, C3, C4, Anti C1q, ANA Titer and Anti dsDNA were considerable sensitive as positive markers for lupus nephritis in SLE cases in group 1. (table 4 and figure 1).ESR, C3, C4, Anti C1q, ANA Titer and Anti dsDNA were considerable sensitive as positive markers for SLE in group 2 (table 5 and figure 2).

Table (1): The basic laboratory data of the studied subjects

Variables	LN SLE (n= 60)	Non-LN SLE (n= 60)	Non SLE (n= 60)	Stat. test	P-value
HB g/dl	9.47±2.31	9.73±1.32	10.98±1.5	F=1.30	0.2
TLC (103/ mm3)	9.11±1.38	7.25±1.42	6.88±1.3	F=1.43	0.16
Platelets (103/ mm^3)	198.6±48.05	164.69±45.99	196.49±37.98	F=0.41	0.62
ESR mm/h	89.42±7.35	51.29±6.81	12.69±2.19	F=5.06	< 0.05 *
Glucose random <140mg/dl	120.1±26.15	116.54±16.29	110.82±8.84	F=0.97	0.34
Urea mg/dl	53.2±18.3	31.55±13.64	20.36±6.46	F=0.93	0.36
Creatinine mg/dl	1.5±0.15	1.23±0.22	1.1±0.21	F=1.47	0.15
24h Protein in urine (gm/dl)	2.32±0.56	0.53±0.22	0.25±0.09	F=5.32	< 0.05*
C3 U/l	57.87±15.43	82.88±11.86	84.95±13.09	F=6.52	< 0.05*
C4 U/l	14.95±3.3	36.25±7.29	40.19±5.74	F=7.26	< 0.05*
Anti C1q U/l	123.84±39.09	20.74±3.8	8.43±5.62	F=12.32	< 0.05*

F: for ANOVA test , Hb: Hemoglobin | TLC: Total Leucocyte Count | ESR: Erythrocyte Sedimentation Rate, C3: Complement component 3, C4: Complement component 4, C1q: Complement Component C1q, *: Significant p value (<0.05)

Table (2): Disease duration, disease activity score and antibodies detected in groups 1 and 2

Variables	LN SLE (n= 60)	Non-LN SLE (n= 60)	Stat. test	P-Value
Disease duration (years) [mean ±SD]	6.29±0.39	5.39±0.57	t=9.21	< 0.05*
SLEDAI score [mean ±SD]	14.09±0.79	6.84±0.31	t=6.04	< 0.05*
ANA titer [mean ±SD]	2999.5±326.42	2514.78±307.27	t=2.73	< 0.05*
Anti-dsDNA (IU/mL) [mean ±SD]	67.86±8.48	48.44±5.37	t=4.98	< 0.05*
ACL Ab (+) (no, %)	43 (71.67%)	38 (63.33%)	X^2=0.99	0.33
Anti-dsDNA (+) (no, %)	60 (100%)	60 (100%)	X^2=0	1
ANA (+) (no, %)	59 (98.33%)	58 (96.67%)	X^2=0.59	0.56
Anti-Rib-P (+)(no, %)	12 (20%)	9 (15%)	t=0.73	0.47
Anti-Smith (Sm) (+) (no, %)	19 (31.67%)	12 (20%)	X^2=1.49	0.14
Anti-SSA Ab (+) (no, %)	29 (48.33%)	21 (35%)	X^2=1.51	0.14
Anti-SSB Ab (+) (no, %)	16 (26.67%)	8 (13.33%)	X^2=1.88	0.07
pANCA (+) number (no, %)	17 (28.33%)	18 (30%)	X^2=0.20	0.84
cANCA (+) number (no, %)	1 (1.67%)	0 (0%)	F=0.063	0.95

t: t-Test, f: Fischer Exact test, X^2: Chi square test, SELDAI: Systemic Lupus Erythematosus Disease Activity Index, ANA: Antinuclear antibodies, dsDNA: Double Stranded DNA, ACL Ab :Anticardiolipin antibodies | Anti-Rib-P: Anti-ribosomal P protein | Anti-SSA Ab: anti–Sjögren's-syndrome-related antigen A autoantibodies | Anti-SSB Ab: Anti-Sjögren's syndrome type B, ANCA: Anti-Neutrophilic Cytoplasmic Autoantibody, *: Significant p value (<0.05)

Table (3): Anti C1q univariant correlation with different parameters among the studied groups

Variables		LN SLE	Non-LN SLE	Non- SLE
Age	**r**	-0.148	0.120	0.095
	p	0.26	0.36	0.49
Hb	**r**	0.083	-0.201	0.030
	p	0.53	0.12	0.81
TLC	**r**	0.188	0.027	0.175
	p	0.15	0.84	0.17
Platelets	**r**	-0.141	-0.191	0.059
	p	0.28	0.14	0.65
ESR	**r**	0.037	0.091	0.029
	p	0.78	0.49	0.82
Random Glucose	**r**	0.169	0.159	0.113
	p	0.20	0.22	0.38
Urea	**r**	-0.062	-0.041	0.128
	p	0.64	0.75	0.32
Creatinine	**r**	0.014	0.066	0.347
	p	0.91	0.62	0.01*
24 h Protein	**r**	0.320	0.065	0.002
	p	0.04*	0.62	0.99
C3	**r**	-0.681	-0.322	0.061
	p	0.03*	0.01*	0.64
C4	**r**	-0.52	-0.017	0.135
	p	0.04*	0.90	0.30
Disease duration	**r**	-0.254	0.085	0.080
	p	0.05	0.52	0.54
SLEDAI Score	**r**	-0.63	0.077	-
	p	< 0.05*	0.56	-
ANA titer	**r**	0.219	-0.117	-
	p	0.09	0.37	-
Anti-dsDNA	**r**	0.099	0.128	-
	p	0.45	0.33	-

Test: Pearson correlation,* statistically significant |Hb: Hemoglobin, TLC: Total leucocyte count | ESR: Erythrocyte sedimentation rate, C3: Complement component 3, C4: Complement component 4,SELDAI: Systemic lupus erythematosus disease activity index, ANA: Antinuclear antibodies, dsDNA: Double stranded DNA, *: Significant p value (<0.05)

Table (4): Different parameters sensitivity and specificity in group SLE with active lupus nephritis

Variables	Cut off	AUC	95% CI	*P.* Value	Sensitivity	Specificity
ESR	49.1	0.856	0.784-0.928	< 0.05*	90%	70%
C3	33.48	0.200	0.118-0.283	< 0.05*	91%	96%
C4	11.33	0.165	0.083-0.248	< 0.05*	93%	95%
AntiC1q	17.1	0.854	0.783-0.925	< 0.05*	98.3%	83.3%
ANATiter	2540	0.795	0.716-0.874	< 0.05*	91.7%	58%
AntidsDNA	45	0.816	0.738-0.895	< 0.05*	95%	78%

AUC: area under curve, ESR: Erythrocyte sedimentation rate, C3: Complement component 3, C4: Complement component 4, C1q: Complement Component C1q, ANA: Antinuclear antibodies, dsDNA: Double stranded DNA, *: Significant p value (<0.05)

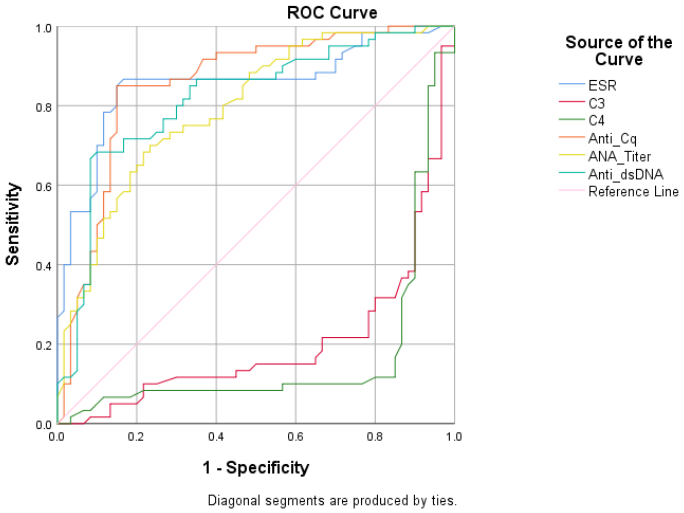

Figure (2): Roc curve analysis of ESR, C3, C4, Anti C1q, ANA Titer and Anti dsDNA in group 1

Table (5): Different parameters sensitivity and specificity in group 2

Variables	Cut off	AUC	95% CI	*P.* Value	Sensitivity	Specificity
ESR	44	0.144	0.07-0.22	< 0.05*	81.7%	98.3%
C3	31.8	0.800	0.72-0.88	< 0.05*	96.7%	91.7%
C4	11.7	0.835	0.75-0.92	< 0.05*	95%	93.3%
AntiC1q	17.1	0.146	0.07-0.22	< 0.05*	91.3%	98.3%
ANA Titer	2207	0.205	0.13-0.28	< 0.05*	88.3%	92.3%
AntidsDNA	42.76	0.184	0.11-0.26	< 0.05*	83.3%	95.3%

AUC: Area under curve, ESR: Erythrocyte sedimentation rate, C3: Complement component 3, C4: Complement component 4, C1q: Complement Component C1q, ANA: Antinuclear antibodies, dsDNA: Double stranded DNA, *: Significant p value (<0.05)

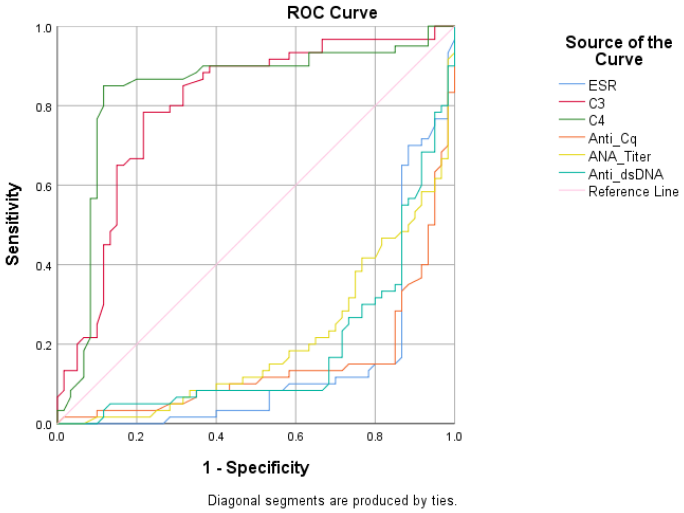

Figure (3): Roc curve analysis of ESR, C3, C4, Anti C1q, ANA titer and Anti dsDNA in group 2

DISCUSSION

SLE is a systemic autoimmune illness marked by the presence of many auto antibodies, elevation B-cell activity, and the formation of immune complexes (ICs)[11]. C1q, the first component of the traditional complement pathway, is thought to have a role in the development of SLE. This is based on the following assumptions: To begin, practically everyone with a C1q deficit has lupus-like symptoms, and the most frequent disease susceptibility gene for SLE is homozygous C1q deficiency [12]. Second, depletion of C1q and other classical complement system components induces hypocomplementemia in a considerable percentage of SLE cases [13], and C1q is deposited in afflicted tissues [14]. Glomerulonephritis is a frequent and often severe

complication of SLE, and it is associated with a poor prognosis. As a consequence, precise criteria for lupus nephritis diagnosis and monitoring are necessary.

Anti-Clq antibodies were detected in the kidneys of lupus nephritis cases, suggesting a link between anti-Clq antibodies and the disease [15]. Several clinical studies have raised the clinical relevance of anti-Clq antibodies in adult cases with active SLE nephritis [16,17], but Jesus et al.[18] discovered a lower frequency, but no clear difference in number, of anti-C1q antibodies with high specificity in cases with juvenile onset SLE.

Renal flare is a common consequence of SLE disorders, and early detection of LN would allow rheumatologists in a clinical environment to intervene sooner. Anti-dsDNA have been shown in studies to be helpful serological markers for diagnosing active SLE and LN activity [19]. Certain anti-dsDNA antibody tests, as well as complements C3 and C4, have a considerable influence in identifying SLE disease activity [20]. Changes in systemic disease activity measures like these may not adequately depict SLE activity. Although these symptoms have a strong negative predictive value in SLE, they are not always related with renal illness [21]. The existence of glomerular lesions may be associated with renal-specific hematuria and proteinuria; however, this may be due to glomerular damage rather than inflammation. Renal disease activity in SLE is typically confirmed by histological evaluation of recurrent biopsy specimens. LN and hypocomplementemia were linked to SLE cases who had C1q antibodies; individuals with SLE who these antibodies did not have were far less likely to experience active renal flares [22,23].

As anti-C1q levels rise, this could lead to elevated inflammatory mediators and the development of C1q-anti-C1q complexes, all of which could interfere with complement activation and the removal of immune complexes, ultimately leading to an elevation in the release of auto antigens, the production of auto antibodies, and the formation of immune complexes, which would then activate diseases and damage tissues [24]. Depending on the anti-C1q immunoglobulin class repertoire present in SLE cases' sera, anti-C1q may activate the classical and lectin complement pathways, but not the alternative complement pathway, giving evidence that anti-C1q plays a considerable role in SLE hypocomplementemia [25]. According to De Liso et al.[16] cases with active SLE and LN had higher levels of anti-C1q antibodies than healthy controls and those with inactive SLE with non-renal illness. Anti-Clq antibodies, alone or in conjunction with other serological markers, may be utilized to distinguish active SLE cases from those with LN [26, 27].

Cases with active lupus nephritis had considerable higher levels of anti-C1q antibodies than those without active nephritis in the Abdelnaby et al. [23] investigation. In group 1 of our investigation, anti C1q sensitivity was 98.3% and specificity was 83.3 %. Group 2 has a sensitivity of 91.3 % and a specificity of 98.3 %. For SLE nephritis activity, Moroni et al.[17] found that anti-C1q had a sensitivity of 87% and specificity of 92%. Also, Sinico et al. [28] found that anti-C1q antibodies were linked to active SLE nephritis, and the current findings were consistent to them. Thus, Anti-C1q was found to be a better predictor of active nephritis in a later experiment than C3/C4 intake or anti-dsDNA.

Due to the vast variety of clinical symptoms associated with SLE in children and adolescents, as well as the enormous number of associated auto antibodies, researchers are increasingly looking for "organ-specific" auto antibodies to help in diagnosis, prognosis, and maybe therapeutic intervention [29]. Although anti-C1q is unlikely to replace gold standard kidney biopsies, it may assist to minimize the frequency of needless invasive biopsies in this age range, particularly during follow-up therapy. Because of their relatively high sensitivity in our research, anti-C1q antibodies are a helpful screening test for SLE active nephritis [30].

CONCLUSION

Proteinuria, complement levels, renal SLEDAI, and anti-Clq auto antibodies are all linked to the activity and flare-ups of renal illness. Anti-C1q antibodies may be used to identify nephritis flare in pediatric and teenage Egyptians with SLE, instead of other recognized disease activity indicators.

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الملخص العربي

الأهمية السريرية للأجسام المضادة C1q في مرضى الذئبة الجهازية الذين يعانون من التهاب الكلية وبدونه

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ملخص البحث

الخلفية: تم مؤخرًا تحديد العلامات المصلية لالتهاب الكلي الذئبي (LN) في حالات الذئبة الحمراء ذات المستويات العالية من الأجسام المضادة C1q لقدمنا بفحص مستوي المصل للأجسام المضادة لـ C1q بالدم في المصابين بمرض الذئبة الحمراء عند النساء المصريات لمعرفة ما إذا كان يمكن أن تكون بمثابة علامة بيولوجية لنشاط التهاب الكلي.

الطرق: كانت هذه دراسة مقارنة أجريت في الفترة من سبتمبر 2021 إلى مارس 2022. أجريت الدراسة على 180 امرأة. تم جمع المرضى من أقسام الروماتيزم وأمراض الكلى وطب الأطفال بمستشفى الحسين الجامعي وباب الشعرية، وخضعت جميع الحالات النسائية للمتابعة. كانوا جميعًا من المراهقين. تم تقسيمهم إلى ثلاث مجموعات. تضمنت المجموعة الأولى 60 حالة من مرضى الذئبة الحمراء والتهاب الكلى الذئبي النشط. تضمنت المجموعة الثانية 60 حالة من مرضى الذئبة الحمراء ولكن بدون التهاب الكلي الذئبي النشط . تضمنت المجموعة 3 60 امرأة متطابقة كمجموعة ضابطة.

النتائج: كان هناك ارتفاع ملحوظ في معدل ترسيب كرات الدم الحمراء ومضاد C1q في المجموعة 1 أكثر من المجموعات الأخرى. أيضا، كان هناك انخفاض فيC3 و 4في المجموعة 1 أكثر من المجموعات الأخرى. في المجموعة 1، ارتبطت الاجسام المضادة Anti-C1q ارتباطًا وثيقًا بـ C3 و 4 ودرجة .SLEDAI في المجموعة 2، كان المضاد C1qمرتبطًا بشكل كبير بـ C3 فقط. كان معدل ترسيب كرات الدم الحمراء C3 و C4 و Anti-C1q و ANA Titer و Anti dsDNA حساسة بشكل كبير كعلامات إيجابية لالتهاب الكلي الذئبي في حالات الذئبة الحمراء.

الاستنتاجات: ترتبط كلا من البيلة البروتينية، ومستويات البروتينات التكميلية، و SLEDAI الكلوي بنشاط أمراض الكلى وتفاقمها، كذلك الأجسام المضادة الذاتية المضادة لـ .Clq وبالتالي يمكن استخدام الأجسام المضادة لـ C1q، بدلاً من علامات نشاط المرض الأخرى التي تم التحقق من صحتها، لتشخيص التهاب الكلية في الأطفال والمراهقات المصابات بمرض الذئبة الحمراء.

الكلمات المفتاحية: الاجسام المضادة Anti-C1q، مرقم حيوي، التهاب الكلية، مرض الذئبة الحمراء، مصريون.

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