Aswan University Medical Journal, volume 4 / No.2/ September 2024 (37-45) Online ISSN: **2735-3117**

ORIGINAL ARTICLE

Antibodies against monomeric C-reactive protein as a promising biomarker of lupus nephritis

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ABSTRACT

Keyword: C-reactive protein antibodies, Early diagnosis, Lupus nephritis.

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Background: Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus. Conventional clinical parameters are not sensitive or specific enough for early detection of LN. **Objective**: This research goals to estimation the possibility of utilizing antibodies to monomeric CRP as an early marker of renal involvement in cases with SLE. **Methodology**: This research was performed at the Department of Clinical Pathology and Rheumatology, at Aswan University Hospital. It involved 30 (four male and twenty-six female) outpatients complaining of SLE and 15 age-matching healthy controls (two male and thirteen female). They were grouped into three case groups and a healthy control group: Group 1: healthy control group. Group 2: patients with microalbuminuria and urinary sediment. Group 3: patients with microalbuminuria without urinary sediment. Group 4: patients with macroalbuminuria. A full workup including history taking, clinical examination, and another related laboratory investigation was performed. **Results**: A statistically significant variance was observed among the groups (p-value=0.001) in the median concentrations of anti-mCRP -Ab. All groups significantly differ from the control group in the median concentrations of anti-mCRP-Ab (p-value=0.014, 0.026, 0.001, respectively). **Conclusion**: anti-mCRP-Ab may be an early biomarker of lupus nephritis with a high level of specificity and accuracy.

INTRODUCTION:

Systemic lupus erythematosus (SLE) defined as an autoimmune, inflammatory chronic condition which may impact on any organ in the body (1). Serologic testing for systemic lupus erythematosus is primarily based on anti-nuclear antibody (ANA) testing and its subtypes, which include anti-extractable nuclear antigen (anti-ENA), anti-histone antibodies, anti-double-stranded DNA (ds DNA) and anti-smith antibodies (2).

Glomerulonephritis defined as one of the commonest and most serious manifestations of SLE. In adults who have lupus, as many as 5 out of 10 will have kidney disease (3). Blood or protein passing through the urine without pain is a frequent sign of kidney involvement.

Therefore, all patients with SLE should be evaluated for kidney involvement even if they don't have symptoms. Laboratory tests that will help doctors diagnose are blood tests like urea and creatinine, twenty-four-hour urine collection for protein excretion, urinalysis and creatinine clearance (to check

for protein, red blood cells, and cellular casts). Kidney biopsies are the most accurate but also the most invasive way to diagnose (4).

Although there have been advancements in the treatment of systemic lupus erythematosus over the last twenty years, the outlook for LN is still not satisfactory, because up to twenty-five percent of cases continue developing end-stage kidney failure. ten years following the start of kidney illness. It has been well established that early diagnosis and treatment of LN improves prognosis (5). In an effort to optimize the effectiveness of current treatments and reduce treatment-related complications, it may be necessary to establish more sensitive and specific clinical indicators for the first signs or relapse of kidney illness.

C-reactive protein (CRP) defined as a liver-derived acute-phase protein which is composed of 5 identical 23 Da globular subunits found in blood plasma, whose levels rise in response to inflammation (6). It's found as 2 forms: the circulating native, the monomeric or modified CRP (mCRP), and pentameric CRP (PCRP) formed because of a dissociation process of PCRP (7). The method of pentameric CRP dissociation to modified CRP includes numerous steps (8). The initial step involves the enzyme phospholipase A2 (PLA2) facilitating the exposure of phosphocholine (PC) to the cell surface. Subsequently, pentameric CRP interacts with phosphocholine to bind to the cell surface. Dissociation from modified CRP is the result of a conformational change that cell-bound pentameric CRP undergoes in the final step.

Several investigations demonstrate that modified CRP has potent proinflammatory properties (9). modified CRP activates leukocytes, endothelial cells and platelets as well as activating the complement system (10). Opsonization, immune complex elimination, and apoptotic cell clearance represent the physiological functions of modified CRP. This occurs through the interaction of modified CRP with complement factor H and CIq (11).

CRP is generally a highly effective indicator of inflammation and tissue damage because of its significant rise concentrations on induction of interlukin-6; however, it isn't applicable to all inflammatory conditions. Systemic lupus erythematosus is an exception because the concentrations of C-reactive protein rarely reflect the activity of the illness (12).

Antibodies that interfere with the function of modified CRP, such as IgG autoantibodies against modified CRP (anti-CRP-Ab), may result in a changed clearance of apoptotic cells and may be included in the pathogenic mechanisms of lupus nephritis (11). Sjowall et al., (2009)(13) research demonstrated that the level of anti-C-reactive protein antibody associated with the kidney biopsy activity index, and might be used to predict an insufficient response to treatment during a follow-up period of eight months. Therefore, suppression of the modified CRP pathway is a promising therapeutic approach to the therapy of a variety of illnesses, including cardiovascular illness and Alzheimer's illness, in addition to inflammation-related illnesses.

This research goals to correlated anti-CRP-Ab with LN as a risk biomarker and predictor of early renal involvement.

PATIENTS AND METHODS

This is retrospective case-control research, which has been achieved from January 2020 to December 2021 at the Department of Clinical Pathology and Rheumatology, at Aswan University Hospital. We included 30 (4 male and 26 female) patients complaining of SLE with an age range from 20-60 years old, and 15 age-matching healthy controls (2 male and 13 female). They were grouped into four groups:

Group I: formed of 15 healthy controls.

Group II: formed of 7 LN patients with microalbuminuria with urinary sediment.

Group III: formed of 9 LN patients with microalbuminuria without urinary sediment.

Group IV: formed of 14 LN patients with macroalbuminuria.

Any patients with renal failure, diabetes, or hypertension were excluded.

The research procedure has been accepted by the local ethics committee of scientific research and all cases provided their agreement prior to the research according to Helsinki Declaration. They have been exposed to case history, clinical investigation, and other related laboratory examinations including urea, complete blood count, creatinine, sodium, potassium, and (eGFR) calculated by the Cockcroft-Gault formula (14). Also, urine tests (complete with microscopic urinalysis, and 24-hour urine collection for protein estimation) were done. We use ANA, Anti-dsDNA which were found with patients in our statistical analysis. Anti-mCRP-Ab has been estimated by the sandwich ELISA technique.

STATISTICAL ANALYSIS

Data have been coded, collected, entered and revised into the Statistical Package for Social Science SPSS version 24. The data have been described as numbers and descriptive statistics; means, SD, medians, and percentages have been evaluated.

Tests of significance; ANOVA test, post-hoc test, Chi-square test, Kruskal-Wallis test with Bonferroni correction. The confidence interval (CI) has been set to ninety-five percent and the standard of error (SE) known has been set to five percent. The receiver operating characteristic curve (ROC) was used to assess the best cut-off point. Consequently, the P-value of less than 0.05 has been defined statistically significant.

RESULT

Our research has been performed at the Department of Clinical Pathology and Rheumatology department, at Aswan University Hospital. It includes 30 cases with an average age of 32.7 ± 11.4 with a variety of 40 years. 26 patients (86.7%) were women and 4 patients (13.3%) were men. 15 healthy volunteers were also used as a control group.

Table 1: General characteristic Variances among the examined groups.

	Group I (Number=15)	**Group II (Number=7)**	**Group III (Number=9)**	**Group IV (Number=14)**	**P-Value**
Age/year	**32.47± 4.4**	**34.57 ± 3.9**	**29.33 ± 4.8**	**33.57 ± 7.6**	**=0.604***
P-Value**	**I vs II = 0.185 I vs III = 0.895**	**II vs III = 0.290 II vs IV = 0.825**	**III vs IV = 0.312**	**I vs IV = 0.587**	
Sex Female Male	 **13 (86.7%) 2 (13.3%)**	 **5 (71.4%) 2 (28.6%)**	 **7 (77.8%) 2 (22.2%)**	 **14 (100%) 0**	**=0.130*****

*** The Chi-square test has been used to compare proportions among groups.

**Post-hoc test with Bonferroni corrections has been used for Pairwise comparisons.

*ANOVA test has been used to compare the mean variance among groups.

Table 1 demonstrates the general characteristic of the examined groups. Regarding age, Insignificant variance was observed in the average age among groups (p-value is higher than 0.05) Also, the sex was statistically insignificant (p-value is higher than 0.05).

The CBC and Serum electrolytes found differences between the s20led groups; regarding hemoglobin level, a significant variance was observed in the mean concentration among groups (p-value is less than 0.032). A statistically insignificant variance was observed among the groups regarding mean platelet count, WBC count, serum sodium, and potassium (p-value is higher than 0.05).

The outcomes of the ANA examination of the examined case groups were as follows; the positive results were 28.6% in group II, 11.1% in group III, and 42.9% in group IV. These variances were statistically insignificant (p-value is higher than 0.05).

Table 2: Renal Function Parameter Differences of the studied case groups.

	Group II Number=7	**Group III Number=9**	**Group IV Number=14**	**P-Value**
B. Urea P-Value**	**22.39 ± 2.3 I vs II = 0.733**	**26.18 ± 3.2 II vs III = 0.453**	**32.50 ± 4.8 I vs III = 0.278**	**= 0.479***
S. Creatinine P-Value**	**0.94 ± 0.1 I vs II = 0.658**	**0.82 ± 0.1 II vs III = 0.356**	**1.02 ± 0.1 I vs III = 0.724**	**= 0.641***
eGFR P-Value**	**98.83 ± 12.2 I vs II = 0.883**	**99.94 ± 11.9 II vs III = 0.713**	**97.85 ± 16.0 I vs III = 0.875**	**= 0.931***
Albuminuria P-Value**	**212.46 ± 23.9 I vs II = 0.460**	**166.11 ± 25.7 II vs III < 0.001**	**471.78 ± 42.9 I vs III < 0.001**	**= 0.001***

**Post-hoc test with Bonferroni corrections has been used for Pairwise comparison.

Table 2 depicts the renal function parameter variances of the examined case groups. A statistically insignificant variance among the case groups regarding the mean concentrations of the kidney function test parameters (blood urea and serum creatinine) or the mean concentrations of the estimated glomerular filtration rate (eGFR) (p-value is higher than 0.05).

On the other hand, a statistically significant variance was observed among the case groups (p-value = 0.001) in the mean concentrations of albumin in urine (albuminuria) (table 3).

The variances in the concentration of anti-mCRP-Ab between the studied groups were summarized in Table 3 and Fig 1. A statistically significant variance was observed among the groups (p-value = 0.001) in the median concentrations of anti-mCRP-Ab. All case groups had significant differences in comparison to the control group in the median concentrations of anti-mCRP-Ab (p = 0.014, 0.026, 0.001, respectively). For pairwise comparisons, patients with macro-albuminuria (group IV) had significantly higher median anti-mCRP- Ab levels (44 (15 - 138)) compared with the control group (group 1) (0 (0 - 50)) and patients with microalbuminuria without urinary sediment (group III) (20 (0 - 39)), (p < 0.001 and = 0.002, respectively). Likewise, patients with microalbuminuria with urinary sediment (group II) had significantly higher median anti-mCRP-Ab concentrations (41 (0-76)) compared with the control group (group 1) (0 (0 - 50)) and patients with microalbuminuria without urinary sediment (group III) (20 (0 - 39)). (p = 0.014 and = 0.022, respectively). Also, patients with microalbuminuria without urinary sediment (group III) had significantly higher median anti-mCRP-Ab levels (20 (0 - 39)) compared with the control group (I) (0 (0 - 50)) (p = 0.026). Contradictory, the median anti-mCRP-Ab level for patients in the macro-albuminuria group (IV) was insignificantly higher compared with that of the patients with microalbuminuria with the urinary sediment group (II) (p = 0.187).

Table 3: Level of anti-mCRP-Ab variances among the studied groups.

	Control gp (I) Number=15	**Group II Number=7**	**Group III Number=9**	**Group IV Number=14**	**P-Value***
Mean ± SD	**13.74 ± 4.8**	**37.78 ± 22.1**	**15.84 ± 5.8**	**54.88 ± 37.2**	
Median (Range)	**0 (0 - 50)**	**41 (0 - 76)**	**20 (0 - 39)**	**44 (15 - 138)**	**=0.001**
P-Value**	**I vs II =0.014 I vs III=0.026**	**II vs III =0.022 II vs IV= 0.187**	**III vs IV=0.002**	**I vs IV < 0.001**	

*Kruskal Wallis test was used to compare the median difference between groups,

Diagnostic performance criteria of the anti-mCRP-Ab for the prediction of renal affection in SLE cases were illustrated in Figure 2. The findings showed that AUC for anti-mCRP-Ab was high (0.724; ninety-five percent confidence interval: 0.566-0.981, p-value is less than 0.001) in the prediction of microalbuminuria with the urinary sediment group (II). Likewise, AUC for anti-m-CRP was very high (0.857; ninety-five percent confidence interval: 0.723-0.992, p-value less than 0.001) in the prediction of macroalbuminuria group (IV). However, AUC for anti-mCRP-Ab insignificantly fair (0.541; ninety-five percent confidence interval: 0.298 0.784, p-value higher than 0.001) in the prediction of microalbuminuria without urinary sediment (group III).

For the control group vs. microalbuminuria with urinary sediment, using a cut-off of 18, the accuracy was 69% which means the ability of the test to diagnose accurately cases and controls, sensitivity that means the ability of the test to pick up true positives between all cases was 71.4%, specificity, which means the ability to determine negatives between all control was 66.7% Also. positive predictive value (PPV) was 68% which means the ability of the test to predict positives among all test positives, and negative predictive value (NPV) which means the ability of the test to predict true negatives among all test negatives was 70%.

For the control group vs. microalbuminuria without urinary sediment; use a cut-off of 20, the accuracy was 65%, sensitivity was 56%, and specificity was 73%. Likewise, PPV was 67.5%, and NPV was 62.5%.

For the control group vs. macroalbuminuria, using a cut-off of 17, the accuracy was 83.5, sensitivity was 93%, and specificity was 74%. Similarly, the positive predictive value was 78%, and the negative predictive value was 91%.

Correlation between anti-mCRP-Ab, microalbuminuria, and urinary sediment showed that, a significant moderated positive association was observed between anti-mCRP-Ab and microalbuminuria (r-value = 0.533, p-value = 0.001) . Likewise, a significant moderate positive association was observed among anti-mCRP-Ab and urinary sediment (r = 0.550 , p-value = 0.001) . Lastly, a significant moderate positive association was observed among microalbuminuria and urinary sediment.

DISCUSSION

The pathogenesis of SLE is only partially known. Anti-double-stranded DNA antibodies (anti-dsDNA-Ab), anti-nucleosome antibodies, and anti-Clq antibodies (anti-Clq-Ab) are among the numerous potentially pathogenic autoantibodies that have been identified in systemic lupus erythematosus. Some of them are used in routine clinical practice for diagnostic purposes and are associated with systemic lupus erythematosus and/or lupus nephritis activity (15).

Multiple studies demonstrate that modified CRP exhibits potent proinflammatory properties (9). Under specific conditions, pentameric C-reactive protein irreversibly dissociates into monomers CRP and reveals new epitopes. Platelets, leukocytes, and endothelial cells are activated by modified CRP, as well as to the complement system (10). Opsonization, immune complex elimination, and apoptotic cell clearance represent the physiological functions of modified CRP. This occurs through the interaction of modified CRP with complement factor H and Clq (11).

The search for novel indicators of illness activity is supported by the significant frequency of systemic lupus erythematosus, the varying responses to therapy and the severity of LN (16).

The primary pathomechanism in systemic lupus erythematosus is the accumulation of undegraded cellular material as a result of the immune cells' dysfunction and impaired apoptosis (17).

SLE Although there are increased concentrations of interleukin 6, there is a lack of C-reactive protein and other pentraxins. Multiple mechanisms have been discovered that explain the lack of pentraxin in systemic lupus erythematosus. These mechanisms include mutations in genes that cause impaired synthesis of C-reactive protein, inhibition of gene expression by interferon-alpha, and removal of C-reactive protein by autoantibodies (18).

Antibodies that interfere with the function of modified CRP, which include IgG autoantibodies against modified CRP, may result in a changed clearance of apoptotic cells and be included in the pathogenic mechanisms of lupus nephritis (11).

Our result reveals that there was a rise in the mean value of anti- modified CRP antibodies in the systemic lupus group in comparing to the healthy control group and this increase is statistically significant. Several research results have found that circulating autoantibodies against mCRP are commonly found in SLE (19).

In concomitant with our results Jakuszko et al. (2017) (16) found that the All-systemic lupus erythematosus cases' anti- modified CRP-positive sera exhibited elevated levels of the antibodies in comparison to healthy controls. Also, they detected that anti- modified CRP antibody more frequently in cases with LN as comparing to cases without lupus nephritis, healthy volunteers, and primary glomerulonephritis (GN) cases.

Pesickova et al. (2015) (19) found that the level of anti-C-reactive protein antibody was significantly greater in cases with active lupus nephritis than in cases with inactive lupus nephritis and associated with the overall activity of systemic lupus erythematosus as evaluated by the SLE Disease Activity Index (SLEDAI).

Also, the results of our research are in agreement with other reports, demonstrating that the secretion of anti- modified CRP antibodies is a defining feature of cases with renal involvement as a manifestation of systemic lupus erythematosus (20).

It is our understanding that, this is the 1st research to correlate the level of anti-mCRP antibody with the concentration of proteinuria (microalbuminuria (from thirty to three hundred milligram per day), or macroalbuminuria (higher than three hundred milligram per day) and its association with the presence of urinary sediments as a marker of severity of renal affection.

However, Jakuszko et al. (2017) (16) and his colleagues found that the frequency of elevated anti-modified CRP increased along with the bwth of the proteinuria; nevertheless, this trend was not sustained in the nephrotic samples. The researchers discovered that there was no correlation among the anti- modified CRP concentration and the severity of nephropathy, determined by the size of daily proteinuria.

Our results, comparing the level of proteinuria (micro or macro) with the level anti-mCRP-Ab as a new early marker of LN, reveal that there was a significantly higher level of anti-modified CRP antibody in cases with microalbuminuria in comparison to healthy volunteers.

Also, our data shows a significantly higher level of anti-mCRP-Ab in patients with macroalbuminuria in comparison to patients with microalbuminuria.

The interestingly statistically significant increase in anti-C-reactive protein antibody in cases with urinary sediment in comparing to cases without urinary sediment in cases with microalbuminuria supports our recommendations for the usage of anti-mCRP-Ab as an early marker of nephropathy for cases with SLE.

Our findings showed that AUC for anti-mCRP-Ab was high (0.724; ninety-five percent confidence interval: 0.566 - 0.981, p-value less than 0.001) in the prediction of microalbuminuria with urinary sediment. Likewise, the AUC for anti-mCRP-Ab was very high (0.857; 95% CI: 0.723 - 0.992, $p < 0.001$) in the prediction of macroalbuminuria.

Also, our results reveal a positive association among anti-mCRP-Ab and microalbuminuria (0.533, p-value = (0.001). In addition, a significant moderate positive association was observed among anti-mCRP-Ab and the urinary sediment (r-value = 0.550, p-value=0.001). Namely, with an increase in anti-mCRP-Ab level, there was an increase in the positive results of the urinary sediment.

Our results reveal no significant association between the positive or negative cases of ANA, anti-double-stranded DNA antibodies, and the concentration of anti-C-reactive protein antibody. In agreement with our results, Sjöwail et al. (2013) (20) revealed that insignificant association was observed among anti-double-stranded DNA antibodies and the level of anti- mCRP-Abs.

On the other side, Pesickova et al. (2015) (19) results revealed that anti-double-stranded DNA antibodies positive cases had significantly greater concentrations of anti-CRP-Ab as comparing with anti-double-stranded DNA antibodies negative cases. They explained this diverse result by the difference in the method of estimation. Also, Jakuszko et al. (2017) (16) found that in sera with increased anti-mCRP-Ab, significantly greater titers of ANA and anti-dsDNA were observed. Statistical analysis of the renal function (serum urea, serum creatinine, and eGFR) of anti-C-reactive protein antibody reveals no significant associations. Our results are in agree with Jakuszko et al. (2017) (16) who discovered insignificant association among the concentrations of anti-C-reactive protein antibody and the serum creatinine concentration.

Tan et al (2008) (21) postulate that modified CRP autoantibodies may be not only a indicator for illness activity but also an important contributor to the pathogenesis of systemic lupus erythematosus, specially LN. This makes the anti- modified CRP Abs a possible target for therapy or delaying the development of lupus nephritis in SLE cases.

These findings suggest that both the presence and concentrations of anti- modified CRP may be a prognostic indicator of lupus nephrites. Also, anti- modified CRP antibodies were a better indicator of nephritis than the classical markers of systemic lupus erythematosus disease activity (such as ANA, and anti-dsDNA).

Limitations of our study:

In this study, the sample size was small in number and there was no multiple centers study. It lacked evaluation response to treatment and lacked histological classification of LN of the cases.

CONCLUTION:

The concentration of monomeric CRP antibodies was significantly elevated in cases with lupus nephritis than in cases with SLE without clinical evidence of kidney involvement. These data

recommend that anti-mCRP antibodies can be a promising biomarker of LN with a high level of specificity and accuracy. Also, they can be used as an firstly marker of renal affection in cases with systemic lupus erythematosus.

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