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Anti-C1q Antibodies as Markers of Renal Involvement in Patients with Systemic Lupus Erythematosus, Bolivar City, Venezuela

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Abstract

Background and objectives: Lupus nephritis is one of the most common complications of Systemic Lupus Erythematosus, due to the accumulation of immunocomplexes of antigens and antibodies at the renal level. In the laboratory, serum anti-C1q antibody levels have become an important tool for monitoring and management of this disease. This study evidences the levels of anti-C1q as a marker of renal involvement in patients with SLE. **Patients and methods**: The study was descriptive and cross-sectional. The sample consisted of 44 patients who met the proposed inclusion criteria. **Results**: 90.91% of the patients were female and the remaining 9.09% were male. Regarding age, the predominant age group was 38 - 54 years 52.27%. 100% of the participants reported being Hispanic. The frequency of anti-C1q was 38.63%. The levels of anti-C1q antibodies were related to the results of C3, C4, anti-DNAs and urinary sediment which were statistically significant ($p < 0.05$) according to fisher's exact test. **Conclusions**: Anti-C1q antibodies are significant as markers of renal involvement in lupus patients, when performed in conjunction with complement fractions c3 and c4, anti-DNAs antibodies.

Subject Areas

Biochemistry, Dermatology, Immunology, Nephrology, Rheumatology

Keywords

Anti-C1q Antibodies, SLE, Complement, Urinary Sediment, Lupus Nephritis

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which

organs, tissues and cells are damaged by adhesion of various autoantibodies and immune complexes. In most patients there is involvement of organs such as kidney, brain, cardiovascular system, joints and skin. Clinical manifestations are highly variable and can range from very mild to severe forms [1].

Lupus nephritis, a form of glomerulonephritis, is one of the most frequent organ manifestations of SLE. Most lupus patients develop this nephropathy within 5 years of the diagnosis of SLE, and in many cases, lupus nephritis is the debut manifestation leading to the diagnosis of lupus, however, its diagnosis remains a challenge due to the absence of effective and sensitive biomarkers [2].

Homozygous deficiency of complement C1q, the first component of the classical complement pathway, is strongly associated with the development of (SLE), pointing to a primarily protective role of C1q. However, although most patients with (SLE) do not have hereditary C1q deficiency, there is indirect evidence for the importance of C1q in the inflammatory processes of the disease, including hypocomplementemia as a result of activation through the classical pathway, the deposition of C1q in the affected tissues, mainly kidneys due to their filtration process, and the appearance of autoantibodies against C1q, exacerbate the association between the presence of anti-C1q antibodies in the renal damage of SLE patients [3].

This is why the expert consensus of the European alliance of rheumatology associations (EULAR) has proposed the measurement of anti-C1q antibodies as a useful determination in the follow-up of patients with SLE and, above all; to establish the presence of renal involvement (supported by studies, proposed as a recommendation). The first study showing an association between anti-C1q autoantibodies and lupus nephritis included 35 patients with biopsy-proven diffuse proliferative or membranous lupus nephritis showing elevations of the solid phase C1q assay for immunocomplexes in all patients with diffuse proliferative nephritis and in 71.4% of patients with membranous nephritis [4].

The pathological activation of complement in renal tissue implies that there are molecular events that promote complement activation (immunocomplex deposition) and/or local phenomena that interact in complement regulation. Different renal compartments may be involved in complement regulation and in the genesis of different glomerular pathologies. Subendothelial deposits of immune complexes are common in pathologies such as lupus nephropathy, as are immunocomplexes deposited in the mesangium in different glomerular diseases including lupus nephropathy [5].

C1q is the first component of the classical complement activation pathway. Together with the enzymatically active fractions C1r and C1s, C1q forms the C1 complex. The main physiological function of C1q is its role in the removal of immune complexes and apoptotic bodies from the body. Disruption of this process can lead to the development of autoimmunity. It has been shown that C1q deficiencies result in an accumulation of apoptotic bodies in the kidneys. Also that C1q-deficient mouse and human macrophages have a reduced ability to clear

apoptotic bodies *in vitro* [6].

Some serum markers of SLE include: anti-double-stranded anti-DNA antibodies, and circulating levels of complement factors such as C3 and C4. These are diagnostically useful. Additionally, serum anti-C1q antibodies are also valuable non-invasive markers for predicting renal histopathology in patients with lupus nephritis. In fact, serum anti-C1q antibody levels can be used as a marker for renal activity with higher sensitivity and specificity than traditional markers of renal activity such as C3 and C4 consumption and anti-DNAs [7].

Existing anti-C1q antibody assays have been used in clinical studies, and a recent study showed a good correlation between a commercial kit with a clinically validated in-house enzyme-linked immunosorbent assay (ELISA). The results suggest the verification of this commercial assay in the detection of anti-C1q and confirm the association of anti-C1q with renal involvement in lupus nephropathy and the importance of introducing this parameter into the analytical panel for the evaluation of disease activity [8].

Renal biopsy is the gold standard for providing information on the histologic classes of lupus nephritis and the relative degree of activity and chronicity in the glomerulus. However, this procedure is invasive, expensive and impractical for disease monitoring. Therefore, new biomarkers that are able to discriminate renal lupus activity, its severity, predict renal relapses, and monitor response to treatment and disease progression are urgently needed. Anti-C1q antibodies are useful in the evaluation of active lupus nephritis, and could be implemented as a diagnostic and disease activity marker in SLE patients [9].

2. Materials and Methods

2.1. Patients and Study Design

A descriptive, cross-sectional study was carried out in which patients with a diagnosis of SLE were included, with requests for anti-dsDNA antibodies, C3 and C4, anti-C1q antibodies and general urine sample which were attended in a private laboratory in Ciuad Bolivar during the period from April to June 2022.

2.2. Ethical Aspects and Informed Consent

The study was conducted in accordance with the ethical principles for medical research on human beings of the Declaration of the Declaration of Helsinki [10], with the corresponding signed informed consent of all patients.

2.3. Instruments

Data such as name, surname, age, and laboratory results were collected with an instrument designed for this purpose, also presenting clinical epidemiological data, diagnostic impression: Systemic Lupus Erythematosus, among others.

2.4. Procedure

We proceeded to explain to the patients the reason and scope of the work in order

to obtain informed consent for their participation. The tubes and containers of general urine were previously identified with the patient's clinical history number, name and surname. Under the supervision of the bioanalyst in charge of the area, the patients' serum samples were processed using the technique to determine anti-C1q antibodies by the ELISA method, from the commercial company QUANTA lite, anti-DNA antibodies by the indirect immunofluorescence method (IFI) from the commercial company AESKULIDES, C3 and C4 by the radial immunodiffusion technique from the commercial company LTA. The reference values of the commercial company QUANTA lite were taken as cut-off points for anti-C1q antibodies Negative < 20, Low positive 20 - 39, Moderate positive 40 - 80 and Strong positive > 80 IU/ml, as well as the cut-off points for c3 and c4 were taken from the reference values of the commercial company LTA for C3 91 - 156 mg/dl and C4 20 - 50 mg/dl.

2.5. Statistical Analysis

The results were presented by means of frequency distribution tables and contingency tables using absolute and relative values; performed with the Microsoft Excel® 2010 program for the elaboration of the database and the IBM SPSS Windows version 23 statistical package for the analysis of the data. For the statistical analysis of the results, descriptive statistics and clinical percentage of patients were used. To compare the variables, Fisher's exact test (bilateral) was applied since these were qualitative variables, and the confidence margin was taken as results higher than 95% or when $p < 0.05$, which were considered statistically significant results.

3. Results

3.1. Patients According to Gender and Age

Of the 44 patients attended, 9.09% (n = 4) were male and 90.91% (n = 40) were female. The predominant age group was 38-54 years 52.27% (n = 23), followed by 21 - 37 years 20.45% (n = 9), 4 - 20 13.64% (n = 6), 55 - 71 years 9.09% (n = 4) and the least frequent group 72 - 88 4.55% (n = 2) (See Table 1).

Table 1. Patients according to gender and age, Bolivar City, Venezuela. April-June, 2022.

	Gender		
Age	Male	Female	Total
(years)	n (%)	n (%)	n (%)
Apr-20	1 (2.27)	5 (11.36)	6 (13.64)
21 - 37	-	9 (20.45)	9 (20.45)
38 - 54	3 (6.82)	20 (45.45)	23 (52.27)
55 - 71	-	4 (9.09)	4 (9.09)
72 - 88	-	2 (4.55)	2 (4.55)
Total	4 (9.09)	40 (90.91)	44 (100.00)

Source: data collection sheet.

3.2. Epidemiological Characteristics of the Population

In this variable only race was taken as the only criterion. 100% (n = 44) of the participants reported being Hispanic (See Table 2).

Table 2. Epidemiological characteristics of the patients. Bolivar City, Venezuela. April-June, 2022.

	Gender		
	Male	Female	Total
Race	n (%)	n (%)	n (%)
Hispanic	4 (9.09)	40 (90.91)	44 (100.00)
Total	4 (9.09)	40 (90.91)	44 (100.00)

Source: data collection sheet.

3.3. Frequency of Anti-C1q Antibodies

As for the frequency of anti-C1q antibodies, negative and positive results were considered according to the positivity scale provided by the QUANTA Lite anti-C1q ELISA insert, Negative < 20 IU/ml, Low positive 20 - 39 IU/ml, Moderate positive 40 - 80 IU/ml, Strong positive > 80 IU/ml. The majority of the results were negative 61.37% (n = 27) only 20.45% (n = 9) were strongly positive, followed by 11.37% (n = 5) with moderate positive and 6.81% (n = 3) with weak positive (See Table 3).

Table 3. Frequency of Anti-C1q antibodies in lupus patients, Bolívar City, Venezuela. April-June, 2022.

Anti-C1q	n (%)
Negative	27 (61.37)
Strong positive	9 (20.45)
Moderate positive	5 (11.37)
Weak positive	3 (6.81)
Total	44 (100.00)

Source: data collection sheet.

3.4. Relationship of Anti-C1q Antibodies with the Results of C3, C4, Anti-DNAs and Urinary Sediment

It is observed that negative anti-C1q values predominate, with normal C3 values (normal C3 56.82%, low C4 61.37%) with negative results of anti-DNAs and negative urinary sediment 61.37%. On the other hand, in the scale of strong positivity of anti-C1q antibodies, low values of C3 18.18%, and C4 20.45%, positive anti-DNAs 18.18%, active urinary sediment 15.91% and proteinuria 9.09%, which was statistically significant ($p < 0.05$) (See Table 4).

Table 4. Relationship of Anti-C1q antibody levels with C3, C4, anti-DNAs and urinalysis levels. Ciudad Bolivar, Venezuela. April-June, 2022.

	Anticuerpos Anti-C1q				
	Positive weak	Positive moderate	Positive strong	Negative	Total
C3	n (%)	n (%)	n (%)	n (%)	n (%)
Low	3 (6.81)	5 (11.37)	8 (18.18)	2 (4.55)	18 (40.91)
Normal	-	-	1 (2.27)	25 (56.82)	26 (59.09)
Subtotal	3 (6.81)	5 (11.37)	9 (20.45)	27 (61.37)	44 (100.00)
Fisher's exact test = 5.822×10^{-9}					
C4					
Low	-	-	9 (20.45)	27 (61.37)	36 (81.82)
Normal	3 (6.81)	3 (6.82)	-	-	6 (13.63)
High	-	2 (4.55)	-	-	2 (4.55)
Subtotal	3 (6.81)	5 (11.37)	9 (20.45)	27 (61.37)	44 (100.00)
Fisher's exact test = 2.59×10^{-15}					
Anti DNAs					
Positive	3 (6.81)	4 (9.00)	8 (18,18)	-	15 (34.09)
Negative	-	1 (2.27)	1 (2.27)	27 (61.37)	29 (65.91)
Subtotal	3 (6,81)	5 (11.37)	9 (20.45)	27 (61.37)	44 (100.00)
Fisher's exact test = 7.09×10^{-10}					
Urine					
Active sedim	-	3 (6.82)	6 (15.91)	-	14 (31.82)
Proteinuria	-	1 (2.27)	4 (9.09)	-	5 (11.36)
Negative	-	1 (2.27)	2 (4.54)	27 (61.37)	30 (68.18)
Subtotal	3 (6.81)	5 (11,37)	9 (20.45)	27 (61.37)	44 (100.00)
Fisher's exact test = 8.264×10^{-9}					

($p < 0.05$) Significant. Legend: Active urinary sediment: bacteria-free sediment with red blood cells, globules, and/or granular casts. Proteinuria: qualitative determined with sulfosalicylic acid 3.8%.

4. Discussion

The etiopathogenesis of lupus disease and its complications are related to hormonal factors not currently defined, in the present study of 44 patients attended 90.91% corresponded to the female gender, and 9.09% to the male gender, these results are similar to those obtained by Lopez et al, in their study "Anti-C1q antibodies as markers of renal involvement in patients with systemic lupus erythematosus" Colombia 2013 [11], in which they also obtained a predominance of 87% female gender over 13% male gender.

Lupus disease is common in reproductive age, which accentuates the hormonal involvement in the development of the same, of the population studied, the

predominant age range is comprised by the group of 38 - 54 years of age 52.27%, referring to this Condori and Melva [12], conducted a study entitled "Clinical Epidemiological Profile of Systemic Lupus Erythematosus—Carlos Monge Medrano Hospital of Juliaca 2015-2019" in Peru 2020, in which they also found a predominance of the age range between 31 - 50 years of age equivalent to (58.7%), which is similar to the results obtained in the present research.

The frequency of Anti-C1q antibodies in the patients attended corresponds to Weak Positive (6.81%), Moderate Positive (11.37%), Strong Positive (20.45%) and Negative (61.37%), in the study population a total of (38.63%) of positivity for Anti-C1q is observed, coinciding with the findings made by Kokuima *et al.* [13] in their study, Anti-C1q as a marker of lupus nephritis in which their results showed that the patients with (SLE) investigated for Anti-C1q had a repositivity (37.00%).

In the study, the relationship between anti-C1q levels and various clinical and immunological parameters in SLE patients was performed. A significant correlation ($p < 0.05$) was found between elevated anti-C1q levels and low C3 and C4 levels, as well as with anti-DNA antibody positivity, active urinary sediment and proteinuria. This suggests that patients with lupus may have difficulty clearing immunocomplexes, which are deposited in the kidneys causing obvious damage to these organs. Complement proteins act as opzonins to assist in the signaling of immune complexes to macrophage cells to clear their accumulation in the blood. The presence of anti-DNA antibodies is related to the formation of immunocomplexes that cannot be eliminated and thus remain in the kidney causing renal damage and increasing the local inflammatory response, the participation of anti-C1q antibodies is related as well as anti-DNA antibodies to increase the deposition of immunocomplexes at the renal level. This conclusion supports previous findings by Severiche and Vasquez, who observed an association between anti-C1q, hypocomplementemia, presence of anti-DNA antibodies and alterations in renal function tests in their study "One hundred and fifteen patients with Systemic Lupus Erythematosus: clinical and immunological characteristics" Medellin, Colombia 2014 [14].

In the present study, several limitations were identified that could affect the generalizability of the results. First, the small sample size limits the ability to make robust inferences and may not adequately represent the population studied. In addition, being a single-center design, the findings may be influenced by specific characteristics of the clinical setting and patients, making extrapolation to other contexts difficult. Finally, the lack of biopsy correlation in all cases raises questions about the validity of the results obtained, as no clear relationship between clinical findings and histopathologic results could be established in all participants. These limitations underscore the need for further studies with larger and multicenter samples to validate our conclusions.

5. Conclusion

In conclusion, although renal biopsy remains the gold standard for the diagnosis

of lupus nephritis, its limitations, such as invasiveness, the need for hospitalization, high cost and the scarcity of specialized centers in Venezuela, highlight the need for more accessible alternatives. This study proposes a paraclinical tool that, without substituting biopsy, seeks to guide the physician in making decisions based on the patient's manifestations, with the aim of optimizing therapeutic options and improving the quality of life of those suffering from SLE. This approach reflects an advance in evidence-based medicine by integrating the clinic with less invasive diagnostic methods.

Recommendations

It is advisable in lupus patients with urinary alterations other than infection, to perform the determination of anti-C1q antibodies together with anti-DNA antibodies and complement levels as follow-up tests of the course and treatment of the renal condition and not as a diagnosis since the confirmatory test for this is renal biopsy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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