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Single anti-P ribosomal antibodies are not associated with lupus nephritis in patients suffering from active systemic lupus erythematosus

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ABSTRACT

Background: In clinical practice, it is sometimes difficult to diagnose a relapse in patients suffering from systemic lupus erythematosus (SLE) and lupus nephritis (LN) having potential complications, including renal failure and death. Some immunological markers can help to determine their association with LN and, therefore, diagnose the early onset of complications.
Objectives: Evaluating the association between systemic and/or kidney activity and anti-P ribosomal and anti-dsDNA antibodies in patients suffering from active SLE.
Methods: 389 patients were evaluated, 140 of whom were subsequently included in the study. The patients were divided into two groups by means of case–control studies, including Colombian patients having American College of Rheumatology (ACR) classification criteria for SLE (1997). The SLE disease activity index (SLEDAI) was applied and all patients presenting an increase of 5 or more compared to their last evaluation, as well as presenting renal manifestations, were considered to be cases; all patients had an activity score. An ELISA kit and the indirect immunofluorescence method with *Crithidia luciliae* were used for determining the presence of anti-P ribosomal and anti-dsDNA antibodies, respectively.
Results: No association was found between anti-P ribosomal antibodies and LN ($p=0.2971$) but anti-P ribosomal antibodies showed association with a >5 SLEDAI score (OR = 4.87; 1.32–17.98 95% CI; $p=0.008$). The coexistence of anti-P ribosomal and anti-dsDNA antibodies was associated with LN (OR = 3.52; 1.07–13.42 95% CI; $p=0.019$) and anti-dsDNA was associated with LN ($p=0.001$).
Conclusion: There was no association between anti-P ribosomal antibodies and LN but anti-P ribosomal antibodies coexisting with anti-dsDNA antibodies was associated with LN, thereby suggesting that the coexistence of two antibodies is nephritogenic to a greater extent. Additional studies are needed to evaluate the coexistence of kidney-specific antibodies in SLE to determine the biological nature of LN.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease having an unknown etiology (very probably multi-factorial, affecting multiple systems) and whose evolution is characterized by the appearance of remissions and relapses [1].

The involvement of the kidney is an important and worrying manifestation since it has a high prevalence and a potentially aggressive evolution if the appropriate measures are not taken in time. Much research has been undertaken to identify markers for predicting or indicating the presence of lupus nephritis (LN), within which anti-dsDNA and anti-Sm antibodies have been mentioned.

Abbreviations: SLE, systemic lupus erythematosus; LN, lupus nephritis; ALN, active LN; AZP, azathioprine; MPN, methylprednisolone; CYC, cyclophosphamide; MFM, mycophenolate mophetyl; CHQ, chloroquine; MTX, methotrexate; PDN, prednisolone; DFZ, deflazacort; HCQ, hydroxychloroquine; LFM, leflunomide; RTX, rituximab; dsDNA, double stranded anti-DNA; NPM, neuropsychiatric manifestation.

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More recent studies have shown the presence of the anti-P ribosomal protein antibody which has a potential role in expressing greater LN when associated with the anti-DNA antibodies, besides being a marker for the disease's systemic activity.

The association between systemic activity and LN with anti-P ribosomal and anti-dsDNA antibodies was thus evaluated (the so-called association cluster).

2. Materials and methods

2.1. Patients

A case/control study was carried out between February 2006 and August 2009 during which 389 patients were analyzed. The patients were selected through non-probabilistic sampling. They had to be older than 16, diagnosed as having SLE (ACR 1982 [2], modified in 1997 [3]) and needed to have signed the informed consent form to become part of the cohort. The cases were either incident cases and/or were identified during follow-up through the presence of activity (an increase of 5 on the SLE disease activity index (SLEDAI) [4] compared to the score obtained during their last evaluation) and LN. Patients who underwent renal biopsy were likely to present a histopathological finding in accordance with internationally accepted classification [5,6]. When a case was identified, a patient of the same gender and age from the control cohort without LN, but with some activity, was randomly chosen for the results to be compared. The protocol was approved by the Universidad Nacional de Colombia's ethics committee.

Patients who presented any other type of connective tissue disease were excluded from the study, as were those who were at risk of renal injury due to the medication they were receiving, who had the coexistence of any other autoimmune disease or pathology affecting the kidneys or in whom the histopathological findings discarded renal involvement for SLE and those who found it was impossible to present themselves for study follow-up.

Active LN (ALN) was defined as persistent proteinuria greater than 0.5 g during a 24-hour period, the presence of cellular cylinders, proteinuria and/or hematuria in urinalysis and/or high serum creatinine levels (30% increase above habitual value). Nephritis was attributed to SLE in all cases if no other cause was apparent. Cases were ideally subjected to renal biopsy to determine histopathological type and determine associations between such findings and the presence of anti-P ribosomal antibodies. Histopathology was reviewed by a nephropathologist who was familiar with the current classification (International Society of Nephrology/Renal Pathology Society: ISN/RPS) [5,6].

2.2. ELISA

A comercial ELISA kit (INOVA Diagnostics, Inc. San Diego, CA, USA) was used for measuring anti-P ribosomal antibody serum, following the manufacturer's protocol. Anti-nuclear antibodies (ANA) were detected by indirect immunofluorescence assay using HEp-2 cells (INOVA Diagnostics, Inc. San Diego, CA, USA) and anti-double stranded DNA (anti-dsDNA) was detected by using *Crithidia luciliae* substrate (Bio-Rad, Redmond WA, USA). ANA titres greater than 1:160 and anti-dsDNA titres greater than 1:20 were considered to be positive; each sample was tested twice. Sera were processed in groups to conclude the study. All samples were stored at −20 °C until processed.

2.3. Statistical analysis

STATA 9.0 software was used for statistical analysis. The Shapiro–Wilks test was used for evaluating data distribution. Clinical data and anti-P ribosomal serum values were compared by unpaired Student *t*-test or Mann–Whitney *U* test as appropriate. Fisher's exact test or Chi-2 test were used for determining the association between categorical variables. The odds ratios (OR) with 95% confidence interval (95% CI) were also reported. A correlation analysis was made between anti-P ribosomal antibody serum levels and creatinine and/or creatinine depuration.

Sample sized was determined with anti-P ribosomal antibody prevalence (22%) and in accordance with 1:1 case:control ratio. A 2.8 OR was considered to be clinically significant. Sixty-two patients were calculated to have 5% significance and 80% power. Each medication was analyzed to assess possible confounding or interaction factors meaning a decrease in antibodies and/or developing LN. Stratified analysis was undertaken and a homogeneity test applied showing crude OR (OR_{crude}) and/or Mantel and Haenszel OR (OR_{MH}) as appropriate. An association model was considered for active LN (dependent variable). The stepwise technique was used for including significant clinical variables; those having lower coefficients of partial correlation were then eliminated. The best coefficient of determination value was established as being the main factor for the final model. $p<0.05$ was considered significant for all analysis.

3. Results

Three hundred and eighty-nine patients were analyzed; 140 of them (131 women and 9 men, Table 1) were included (following inclusion and exclusion criteria) and divided into two groups of seventy (SLE and ALN: SLE–ALN and active SLE without ALN: SLE–nonALN). The principal demographic findings were not statistically different between both groups (Table 1).

The most frequent findings at the beginning of the disease showed the presence of positive ANAS in 100% of the cases, followed by arthritis (80%), immunological disorder (55%), hematological disorder (50.7%), photosensitivity (47.1%) and malar rash (45%). Renal involvement presented itself in 76% of the sample during the first five years of the disease, in 18.1% between 5 and 10 years and only 6% presented renal problems 10 years later (SLE–ALN).

The way in which SLE began was most frequently systemic, 71.2% SLE–ALN and 97.1% SLE–nonALN, having a significant statistical difference ($p<0.001$). Twenty-five (17.85%) patients had a personal history of another autoimmune disease. Antiphospholipid syndrome was the most common (5%), followed by rheumatoid arthritis and Sjögren's syndrome (4.3%). A family history of autoimmunity was observed in 25.7% of the patients, SLE being the most frequent (13.57%).

Hematological involvements at the start of the study were as follows: leucopenia (30%), neutropenia (2.31%), lymphopenia

Table 1
Demographic characteristics of the cases (Colombian patients suffering from SLE and active lupus nephritis) and the controls (Colombian patients having active lupus without active nephritis) followed-up from February 2006 until August 2009.

Characteristics	Active LN mean or median	LN absent Mean or median	*p*
Gender, female (%)	63	67	
Disease duration, years	4 Me	5 Me	0.256[a]
Current age, yrs	35 Me	37 Me	0.1425[a]
Age at onset, yrs	27 Me	30 Me	0.2838[a]
Malar rash (%)	40	50	0.234[b]
Discoid lupus (%)	5.71	5.71	0.999[c]
Photosensitive (%)	37.14	57.14	0.018[b]
Oral ulcerations (%)	17.14	34.29	0.20[b]
Arthritis (%)	68.57	91.43	0.001[b]
Serositis (%)	17.14	20.00	0.664[b]
Renal disorder (%)	58.57	17.14	0.000[b]
Neurological disorder (%)	7.14	2.86	0.441[c]
Immunological disorder (%)	50.00	60.00	0.234[b]
Acute onset (%)	25.76	13.04	0.061[b]

Me: median.
[a] Wilcoxon test (Mann–Whitney test).
[b] Pearson Chi-2.
[c] Fisher's test.

(58.14%) and thrombocytopenia (2.1%) with no significant statistical difference between both groups. Fifty biopsies were taken in SLE–ALN (71.4%); the distribution in each LN group was as follows: I. 2.04%, II: 12.24%, III: 8.16%, IV: 59.18% and V: 18.37%.

There was no correlation between the levels of hematuria, proteinuria and/or creatinine depuration and the antibodies studied. The most frequently occurring ANAS pattern was homogeneous (51.18%), followed by speckled (43.1%). The most commonly reported dilution was 1/1280 (24.81%), followed by 1/2560 (21.71%). Possible association between the homogeneous pattern, another pattern and ALN was not statistically significant ($p=0.0895$).

The median for anti-dsDNA dilutions for SLE–ALN was 1/40 (P-25% 1/10 and P-75% 1/320) and 0 for SLE–nonALN (P-25% 0 and P-75% 1/40), without being statistically different (Fig. 1). Positive anti-dsDNA was associated with ALN (OR = 3.542; 1.567–8.067 95% CI; $p=0.0008$) and an association was recorded with ALN (OR = 2.67; 1.121–6.437 95% CI; $p=0.0143$) in a stratified analysis of medium and high titres (anti-dsDNA > 1:80). ALN-related findings were presented regarding C3 and C4 levels (Table 2). SLEDAI values had a non-parametric distribution (Table 2) (Fig. 2).

Twenty-nine (21%) of the 140 patients presented positive anti-P ribosomal antibody, 17 in SLE–ALN and 12 in SLE–nonALN (Table 2) (Fig. 3). There was no association between anti-P ribosomal antibody presence and ALN (OR = 1.55; 0.62–3.90 95% CI; $p=0.29$); however, an association was found between anti-P ribosomal antibody presence and a SLEDAI score over 5 (OR = 4.87; 1.32–17.98 95% CI; $p=0.008$). A correlation between anti-P ribosomal antibody positive and SLEDAI was found ($r=0.36$) in SLE–nonALN and an association was found between anti-P ribosomal and anti-dsDNA antibodies ($p=0.050$). An association was found between composed factor anti-P ribosomal and positive anti-dsDNA antibodies for ALN (OR = 3.52; 1.07–13.42 95% CI; $p=0.019$). A possible confounding $OR_{MH}=1.15$ (0.35–3.74 95% CI) and ORcrude = 1.77 (0.54–6.31 95% CI) with non-significant clinical differentiation or interaction ($p>0.05$ homogeneity test) factor was ruled out for anti-dsDNA antibodies.

There were 50 renal biopsies in SLE–ALN and 12 in SLE–nonALN (previously undertaken). Type IV was the most frequently found (50%, diffuse proliferative glomerulonephritis) in the SLE–ALN group. Most patients presented an activity score of less than 7 in 60% of the sample and chronicity scores were under 4 in 84.78% of the patients, showing early diagnosis in most patients. No association was discovered between the anti-P ribosomal antibody and some specific histopathological types.

Some differences were reported regarding medication use. Azathioprine (AZP) ($p=0.004$), methylprednisolone (MPN) ($p<0.001$), cyclophosphamide (CYC) ($p=0.001$) and mycophenolate mophetyl (MFM) ($p=0.004$) were more frequently used in SLE–ALN and chloroquine (CHQ) ($p<0.001$) and methotrexate (MTX) ($p=0.001$) in SLE–nonALN. There was no statistically significant difference for prednisolone (PDN) ($p=0.353$), deflazacort (DFZ) ($p=0.494$), hydroxychloroquine (HCQ) ($p=0.820$), leflunomide (LFM) ($p=0.496$) or rituximab (RTX) ($p=0.055$). The most frequently used combinations were analyzed, no difference being found between both groups for PDN and AZP ($p=0.090$), AZP and CHQ ($p=0.835$) or PDN, AZP and CYC ($p=0.274$). A difference was noted in the use of PDN–CYC in SLE–ALN ($p=0.035$).

A possible confounding or interaction factor was thus analyzed for the medications used in both groups. An interaction with AZP was ruled out ($p>0.05$ homogeneity test) with ORMH = 1.75 (0.73–4.21 95% CI) and ORcrude = 1.55 (0.62–3.90 95% CI), having a non-significant clinical differentiation, thus ruling out a confusion factor. An interaction factor was ruled out for MPN ($p=0.6394$) with ORMH = 1.56 (0.64–3.81 95% CI); likewise, confusion was ruled out on comparing it with the crude OR. There was no interaction for CYC ($p=0.9406$) or confusion (ORMH = 1.80; 0.76–4.30 95% CI); these characteristics were also ruled out for MFM ($p=0.5324$; ORMH = 1.59; 0.67–3.75 95% CI). The results for the most frequently used medications in SLE–nonALN were: CHQ ruling out the presence of interaction ($p=0.3178$) or confusion, with ORMH = 1.43 (0.58–3.48 95% CI) and for MTX ($p=0.6257$; ORMH = 1.25; 0.53–2.95 95% CI). The presence of interaction or confusion was also ruled out

Table 2
Main laboratory findings regarding Colombian patients having SLE according to renal involvement, followed-up from February 2006 to August 2009.

Characteristics	LN present Mean or median	LN absent Mean or median	p
Leucocytes	4900 Me	5300 Me	0.4958[a]
Neutrophils	3420 Me	3550 Me	0.8298[a]
Lymphocytes	1261 Me	1435 Me	0.4965[a]
Hemoglobin	12.2 Me	13.65 Me	0.0004[a]
CRP	2 Me	2 Me	0.8652[a]
Creatinine	0.915 Me	0.81 Me	0.0116[a]
Hematuria	7 Me	0 Me	<0.0001[a]
Proteinuria	1535 Me P-25% 840, P-75% 3,250	99.7 Me P-25% 7.4, P-75% 210	<0.0001[a]
Homogeneous ANA%	59.02	43.9	0.0895[b]
Anti-dsDNA (%)	65.5	34.85	0.0008[b]
C3	61 Me	99.3 Me	<0.0001[a]
C4	9.5 Me	18 Me	0.0001[a]
Sm	11 Me	5 Me	0.2761[a]
Ro	6.9 Me	6.6 Me	0.6068[a]
La	2 Me	6.6 Me	0.0450[a]
SLEDAI	16 Me P-25% 12, P-75% 20	4 Me P-25% 2, P-75% 6	<0.0001[a]
Anti-P ribosomal	4.9 Me P-25% 3.7, P-75% 7.95	4.33 Me P-25% 3.7, P-75% 15.25	0.3548[a]
P ribosomal-DNA	13	5	0.0193[b]

C-reactive protein (CRP), Me: Median.
[a] Wilcoxon test (Mann–Whitney test).
[b] Pearson Chi-2.

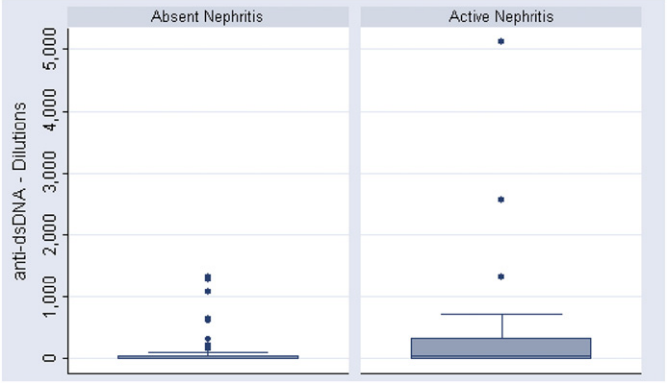

Fig. 1. Anti-dsDNA antibody in Colombian patients suffering from SLE according to renal involvement.

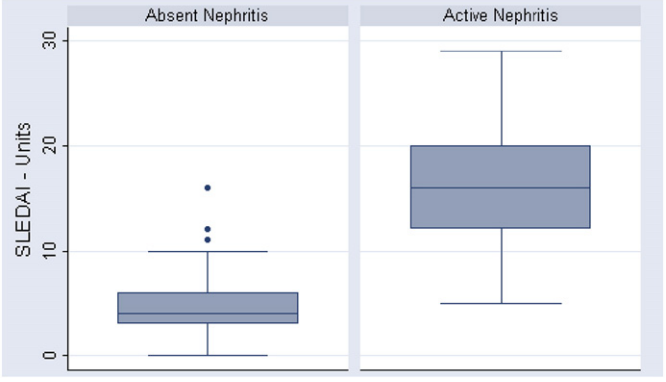

Fig. 2. SLEDAI scores for Colombian patients suffering from SLE.

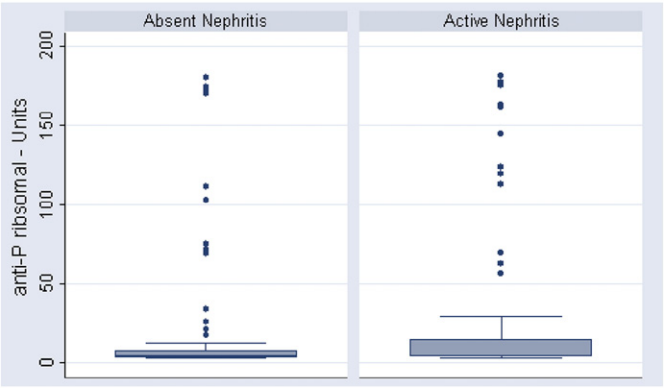

Fig. 3. Anti-P ribosomal antibody in Colombian SLE patients according to renal involvement.

($p = 0.9171$; ORMH = 1.69; 0.72–3.92 95% CI) for the only combination having differences between both groups (PDN–CYC).

Logistic regression analysis was undertaken to determine which variables were associated with the appearance of LN to obtain a model of association from the following variables: SLE evolution, age at beginning, BUN, creatinine, leukocytes, lymphocytes, hemoglobin, ESR, CRP, platelets, proteinuria, hematuria, anti-dsDNA, C3, C4, anti-Sm, anti-Ro, anti-La, anti-RNP, anti-cardiolipin IgG, anti-cardiolipin IgM, SLEDAI and anti-P ribosomal. Hematur, proteinuria, anti-dsDNA antibodies and SLEDAI score were associated with the onset of LN (Table 3). Interaction and/or confusion factors were ruled out through verisimilitudes quotient logarithm and Wald test.

4. Discussion

Alanine-rich ribosomal phosphoproteins ("P" proteins) P0, P1 and P2 (38, 19 and 17 kDa respectively) are located in the 60 subunits of the eukaryotic ribosome and are the main target for anti-P ribosomal antibodies [7,8]. These antibodies recognize a number of epitopes, including a 22 amino acid-long determinant lineal antigen in the common terminal carboxyl group of these three ribosomal proteins. Such antibodies can be detected through immunofluorescence; however, Bonfa et al. [9] have used quantitative radioimmunoassay to do so. Other methods include ELISA and immunoblotting of purified ribosome proteins. The ELISA test using purified human antigens is very sensitive and specific (97%) [10].

Anti-P ribosomal antibodies are found almost exclusively in patients with SLE. They are present in 13%–20% of Caucasian patients and in more than 36% of Chinese patients suffering from the disease [11,12]. The ribosomal epitope has been found in human neuroblastoma cells and, to a lesser extent, in human fibroblasts [13]. Yoshio et al. [14] have shown that these autoantibodies can be linked to endothelial cell surface. There is evidence to show that double stranded anti-DNA antibodies (dsDNA) can sometimes have cross-reactivity with anti-P ribosomal antibodies [15]. Sun et al. [16] have reported that proteins from the ribosomal region hydrophobic terminal C group are essential for their cross-reactivity with anti-dsDNA antibodies.

Table 3
Logistic regression model for lupus nephritis.

Variable	OR	95% CI	*p*
Hematuria	1.71	1.014–2.89	0.044
Proteinuria	1.00075	1.000035–1.00146	0.040
DNA	1.0012	1.000088–1.0023	0.034
SLEDAI	1.52	1.16–1.99	0.002

The association between anti-P ribosomal antibodies and psychosis by SLE was first reported by Bonfa et al. [9]. They found that 18 out of 20 patients (90%) with psychosis by SLE had anti-P ribosomal antibodies. These observations were reproduced by Schneebaum et al., [17] but refuted in the studies of Teh et al. [18] and Inverson [19]. These differences have been attributed to methodological differences and in reporting and analysing results. A number of subsequent studies have supported the association between anti-P ribosomal antibodies and neuropsychiatric manifestations (NPM) by lupus [20–23]. For example, Tzioufas et al. [22] found that 11 out of 28 patients (39.3%) with SLE and neurological involvement (psychiatric 71%, epilepsy 75%) had anti-P antibodies.

Nevertheless, in view of the previous contradictory reports, the controversy about antibody association with NPM due to lupus still remains. Recent studies have supported the association between antibodies and active lupus and/or with nephritis [23,24], generally accompanied by anti-dsDNA antibodies, observing that nephritis activity is closely related to these autoantibodies, suggesting that the presence of two antibodies is more nephritogenic than when there is only one. Nevertheless, it should be born in mind that the coexistence of both autoantibodies with nephritogenicity is not ideal, since they can be present without any involvement, suggesting that pertinent pathogenic mechanisms are heterogeneous. Some anti-dsDNA antibodies join with the membrane but do not penetrate the cell (*in vitro*); others penetrate and emigrate to the nucleus and a third variety penetrates the cell membrane and resides in the cytoplasm, even after 24 h [25]. Anti-P ribosomal antibodies consistently link to the cells, penetrate them and are able to inhibit protein synthesis [26,27]. Anti-dsDNA antibodies are also very efficient in inhibiting *in vitro* translation [28,29]. All such properties (anti-dsDNA and anti-P ribosomal antibodies) may be partly responsible due to their *in vivo* pathogenicity. Other studies have found a greater probability of cutaneous [30] and liver involvement and it has been reported that anti-P ribosomal antibodies are pathogenic for hepatocytes [30,31].

Such marked differences related to clinical significance can be attributed to various factors; populations have ethnic differences, different methods are used for measuring antibodies, NPM measurement varies and there are heterogeneous occurrences in other autoantibody populations different to anti-P ribosomal antibodies which are able to affect the neural function of patients suffering from SLE [32]. A recently published meta-analysis has illustrated poor anti-P ribosomal antibody sensitivity (around 26%) for NPM diagnosis by SLE; the study also reported that specificity was around 80%, concluding that anti-P ribosomal antibody had poor diagnostic use for NPM in SLE [33].

Many studies have found high anti-P ribosomal antibody specificity for SLE [30,34,35], having extremely low prevalence amongst patients suffering other types of illness [36,37]. These antibodies are thus considered diagnostic markers for SLE when found in patients' serum; in spite of their fluctuating levels, they seem to be related to illness activity level [22,38,39], but it is not clear whether these antibodies are associated with greater illness severity.

Reichlin [40] recently adopted a statistical approach to OR values between different nephritogenic antibodies and LN. The most representative values were represented by composed factors such as anti-P ribosomal antibody and anti-lipoprotein lipase (OR = 17.11), anti-P ribosomal and anti-DNA (OR = 5.08) and anti-lipoprotein lipase and anti-DNA (OR = 4.23) and individually, anti-lipoprotein lipase (OR = 5.28) and anti-P ribosomal antibody (OR = 3.47). Unfortunately, these calculations were made by reviewing the literature and data capture from original studies.

Nascimento et al. [41] found an association between anti-P ribosomal antibody and specific histopathologic type (proliferative glomerulonephritis — Type V), but this study's methodology has been questioned by Bertolaccini et al. [42] who argued that no positive

results were found in a study specifically designed to seek such association.

The present study's prominent findings showed no association between ALN and anti-P ribosomal, antibody but an association was found between anti-dsDNA antibody and the outcome mentioned. The association of both anti-P ribosomal and anti-dsDNA antibodies (association cluster) and the presence of ALN was more striking. These findings reaffirmed greater nephritogenicity during the coexistence of nephrophilic antibodies. Anti-P ribosomal antibody presence in some patients in SLE–nonALN was also relevant. This antibody might be an indicator of systemic activity, with or without LN, based on the association between anti-P ribosomal antibody and SLEDAI score, meaning that previous studies' findings should be taken with a certain degree of reserve. No association between anti-P ribosomal antibody and specific histopathologic types could be established in renal biopsy, thereby coinciding with comments made the group at St Thomas Hospital in London. It is also important to determine the variables in the model which are associated with ALN development, leading to early detection of this outcome and, therefore, the chance to undertake opportune measures to avoid LN development in each potentially affected patient. Nevertheless, the model's capacity needs to be validated with a different population.

There were a few differences between the two groups, except among renal activity-related variables and some considered within the context of complications inherent to high degrees of systemic activity. The demographic data illustrated a greater presence of arthritis (91.43% *cf* 68.57%, $p = 0.001$) and photosensitivity (57.14% *cf* 37.14%, $p = 0.018$) in SLE–nonALN, perhaps as possible protective factors of renal involvement in the population studied. Unfortunately, no differential reports in relation to renal involvement and these variables were found; however, relative frequencies were similar to those found in studies undertaken in Latin-America [43].

It should be clarified that most cases were incidental, meaning that medication use in these patients was stable relating to dose and the type of medicine. The presence of confusion or interaction was ruled out according to the presence or absence of antibodies or ALN.

When different patient cohorts were reviewed it was found that most variables coincided with the ranks expected, particularly for Latin-America studies [43]. In fact, there was greater illness aggressiveness represented by a large percentage of LN type IV, pleuri-pericarditis, whereby a greater number of medications were needed. Differences were observed when comparing this study's data with other cohorts, predominantly in the SLE–ALN group. Reduced C3 and C4 levels and greater anti-dsDNA dilutions could be attributed to the same condition (ALN) and were related to greater anti-dsDNA generation, deposited at glomerular membrane level, and subsequent complement consumption. There was greater positive anti-La value in SLE–nonALN (27.12% *cf* 6.9%; $p = 0.027$), agreeing with this autoantibody's protective factor for renal involvement [44,45]. This study's results can thus be compared to most ethnic groups, according to already published studies [46,47].

The study's limitations involved renal biopsies not being undertaken on a minority of patients from the SLE–ALN group which may represent a small classification error regarding a “case” patient who could in fact have been a “control” patient. There was difficulty in obtaining antibodies against extractable nuclear antigens and levels of complement in all patients. The ELISA test for anti-lipoprotein lipase was not undertaken on patients (developed within an immunological framework associated with LN) as the test is not available in Colombia and has not yet been standardized.

5. Conclusion

No association was found between anti-P ribosomal antibody and LN; however, a positive association was shown for the coexistence of anti-P ribosomal and anti-dsDNA antibodies. This suggested that the coexistence of two antibodies is more nephritogenic. Additional studies are needed to evaluate the coexistence of kidney-specific antibodies in SLE to determine the biological nature of LN.

Authors' contributions

GQ had full access to all study data and takes responsibility for its integrity and data analysis accuracy. GQ, AIR and RC designed the study. GQ, PC, PM, PC, GA and AI participated in data acquisition. GQ, PC and RC analyzed and interpreted data and prepared the manuscript. GQ performed the statistical analysis and participated in study supervision. All authors read and approved the final manuscript.

Take-home messages

- Anti-P ribosomal antibodies are found almost exclusively in patients with SLE and recent studies have supported their association with lupus nephritis.
- This study showed no association between ALN and anti-P ribosomal, but a positive association was shown for the coexistence of anti-P ribosomal and anti-dsDNA antibodies.
- These findings reaffirmed greater nephritogenicity during the coexistence of nephrophilic antibodies.
- This antibody might be an indicator of systemic activity, with or without LN.

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Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection

The aim of this prospective study was to examine the safety of anti-tumor necrosis factor (TNF) therapy in patients with rheumatic disease and hepatitis B virus (HBV) infection. The study included 14 patients with chronic HBV infection, 19 HBV-vaccinated patients and 19 patients with resolved HBV infection. **Vassilopoulos D. et al. (Ann Rheum Dis 2010; 69:1352–5)**. All HBV-infected patients received combination therapy with oral antivirals and anti-TNF agents. During treatment the levels of hepatitis B surface antibodies (anti-HBs) in HBV-vaccinated patients and of serum HBV DNA in patients with chronic or resolved HBV infection were monitored. No viral reactivation was observed in patients with resolved HBV infection while anti-HBs titers decreased during anti-TNF treatment in vaccinated patients, similarly to patients treated with methotrexate alone. None of the HBV-infected patients developed liver decompensation or a significant increase in alanine aminotransferase levels. One patient (7%) treated with lamivudine and etanercept showed viral reactivation due to the emergence of a lamivudine-resistant mutant strain. Thus, anti-TNF agents represent a safe option for patients with chronic HBB infection when combined with antiviral therapy, as well as in patients previously exposed to HBV receiving no HBV prophylaxis. Resistant HBV strains may arise in patients with chronic hepatitis B, necessitating the initial use of ant-HBV agents with a low risk of resistance.

T cell and APC dynamics in situ control the outcome of vaccination

The factors controlling the progression of an immune response to generation of protective memory are poorly understood. Here, **Khanna KM. et al. (J Immunol 2010; 185: 239–52)** compared the in situ and ex vivo characteristics of CD8 T cells responding to different forms of the same immunogen. Immunization with live Listeria moncytogenes, irradiated L. monocytogenes (IRL), or heat-killed L. monocytogenes (HKL) induced rapid activation of CD8 T cells. However, only IRL and live L. monocytogenes inoculation induced sustained proliferation and supported memory development. Gene and protein expression analysis revealed that the three forms of immunization led to three distinct tranascriptional and translational programs. Prior to cell division, CD8 T cell-dendritic cell clusters formed in the spleen after live L. monocytogenes and IRL but not after HKL immunization. Furthermore, HKL immunization induced rapid remodeling of splenic architecture, including loss of marginal zone macrophages, which resulted in impaired bacterial clearance. These results identify initial characteristics of a protective T cell response that have implications for the development of more effective vaccination strategies.