Review about Anti C1q Antibodies and its Possible Correlation with Lupus Nephritis

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Abstract

Background: A biomarker refers to a biologic, biochemical, or molecular event that can be assayed qualitatively and quantitatively by laboratory techniques. The levels of biomarkers should correlate with disease pathogenesis or activity in different organ systems. An ideal biomarker for lupus nephritis should possess the following properties: (1) good correlation with renal activity as reflected by the degree of proteinuria and urine sediments, (2) ability to predict renal activity/flares before an obvious change in conventional clinical parameters occurs so that early treatment/preventive strategies can be considered, (3) specific to nephritis among patients with SLE, and (4) specific to SLE for aiding early diagnosis of lupus nephritis. In addition, a useful biomarker should be easy to assay, simple to interpret, and readily available in most laboratories with a reasonable cost. SLE being a rare disease, efforts have to be collaborative in a multi-centric fashion to ensure cost-effective utilization of resources. Conventional serum and urine biomarkers continue to be the most widely used. Renal biopsy is still the gold standard for deciding therapy in LN but its invasive nature prevents it from being used repetitively. What seems achievable and more practical at this point in time is to utilize the most beneficial property of each biomarker and to develop a combination test that could predict the various aspects of treatment of LN, such as chronicity and activity changes, response to treatment and prediction of flare. The prevalence of anti-C1q antibodies was 54.4%, and the presence of anti-C1q antibodies was closely correlated with acute injury indices of renal histopathology, with a better correlation compared with anti-dsDNA antibodies, such as endocapillary hypercellularity, karyorrhexis/fibrinoid necrosis, subendothelial hyaline deposits and leukocyte infiltration. However, similar to anti-dsDNA antibodies, the presence of the autoantibodies was not a risk factor of the renal survival. anti-C1q antibodies are more closely correlated with renal disease activity than other autoantibodies.

Keywords: Anti C1q Antibodies, Lupus Nephritis

DOI Number: 10.14704/nq.2022.20.10.NQ55863

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder where interplay of environmental and genetic risk factors leads to progressive loss of tolerance to nuclear antigens over time, finally culminating in clinical disease (1). Systemic lupus erythematosus (SLE) is a disease that can affect persons of all ages and ethnic groups and both sexes, but more than 90% of new patients presenting with SLE are women in the childbearing years. SLE is a disease that affects multiple systems (2).
Systemic lupus erythematosus (SLE) is associated with a broad spectrum of clinical and immunologic manifestations, of which lupus nephritis is the most common cause of morbidity and mortality. The development of nephritis in patients with SLE involves multiple pathogenic pathways including aberrant apoptosis, autoantibody production, immune complex deposition and complement activation. Some additional lesions that contribute to disease presentation, including glomerular crescents, podocyte injury, tubulointerstitial lesions and vascular injury, should be recognized. Although outcomes for patients with lupus nephritis have improved over the past 30 years, treatment of this disease remains challenging and is best approached on the basis of the underlying pathogenesis, which is only partially represented by the various pathological phenotypes defined by the ISN/RPS classification (3).

Lupus nephritis (LN) refers to inflammation of the kidney that encompasses diverse patterns of renal disease including glomerular, tubulointerstitial and vascular pathology. Renal involvement in SLE may be present in approximately 60 % of adults, with 25–50 % of patients presenting with clinical renal disease at the time of diagnosis. Most patients affected are female, and younger than 50 years of age. However, male patients tend to have more frequent renal involvement and greater severity of disease (4).

**Anti C1q Antibodies**

A biomarker refers to a biologic, biochemical, or molecular event that can be assayed qualitatively and quantitatively by laboratory techniques. The levels of biomarkers should correlate with disease pathogenesis or activity in different organ systems. An ideal biomarker for lupus nephritis should possess the following properties: (1) good correlation with renal activity as reflected by the degree of proteinuria and urine sediments, (2) ability to predict renal activity/flares before an obvious change in conventional clinical parameters occurs so that early treatment/preventive strategies can be considered, (3) specific to nephritis among patients with SLE, and (4) specific to SLE for aiding early diagnosis of lupus nephritis. In addition, a useful biomarker should be easy to assay, simple to interpret, and readily available in most laboratories with a reasonable cost (5).

SLE being a rare disease, efforts have to be collaborative in a multi-centric fashion to ensure cost-effective utilization of resources. Conventional serum and urine biomarkers continue to be the most widely used. Renal biopsy is still the gold standard for deciding therapy in LN but its invasive nature prevents it from being used repetitively. What seems achievable and more practical at this point in time is to utilize the most beneficial property of each biomarker and to develop a combination test that could predict the various aspects of treatment of LN, such as chronicity and activity changes, response to treatment and prediction of flare. (6).

**The complement system**

The complement system is an important part of the innate immune system, functioning as an immune surveillance system to distinguish between healthy tissue, cellular debris, apoptotic cells, and foreign intruders (6). When complement-mediated clearance mechanisms are not available, production of immune complexes composed of nucleic acids/nuclear material and autoantibodies can lead to auto-antigen presentation, loss of tolerance and production of both type I and type II IFN.

The classical pathway of complement activation is activated following binding of the recognition molecule C1q to ligands such as immune complexes. The lectin pathway is activated following binding of recognition molecules, such as mannos-binding lectin (MBL), collectins or ficolins, to their ligands, which include carbohydrate structures. Although the alternative pathway is initiated spontaneously, properdin might also serve as a recognition
molecule for directing activation of this pathway. Following activation via the initiating molecules a cascade of proteolytic activation steps leads to the formation of C3-convertases that cleave C3 into the anaphylatoxin C3a and the opsonin C3b. Next, C5-convertases generate the potent pro-inflammatory anaphylatoxins C5a and C5b, the latter of which, together with C6–C9, forms the membrane attack complex (MAC) (7).

Complement factor 1q (C1q) is part of the C1 complex which is the first protein in the classical pathway of the complement system. It is a 460 kDa glycoprotein consisting of 18 polypeptide chains that have an N-terminal collagen-like domain. These chains form six triple helices assembling to a structure that resembles a bouquet of tulips with the stalks being formed by the collagen-like regions while the C-terminal parts form the flower-like globular head regions of the molecule, which primarily mediate the binding of C1q (8).

C1q deficiency is a strong risk factor for SLE, with individuals carrying homozygous mutations in the C1q genes being at a high risk (~90%) of developing the disease. C1q deficiency is rare, and less than 100 cases have been reported. In addition to C1q, mutations in genes encoding complement factors C2 and C4 and mutations in complement inhibitors, for example CD46 and complement factor H, have also been associated with SLE. A far more common cause of decreased C1q levels is the presence of autoantibodies (anti-C1q antibodies) (8).
between the globular part of C1q and the Fc region of IgG in immune complexes (11).

**Pathogenic role of anti-C1q antibodies**

Anti-C1q are mostly IgG with a predominance of the IgG1 and IgG2 subclasses. In contrast to immune complexes, that bind to the globular heads of C1q, anti-C1q mostly bind to the collagen-like region of the molecule (12).

Their binding is mediated via the antigen-binding fragments (Fab) and of high affinity. Interestingly, anti-C1q do not or only weakly bind to unbound (soluble) C1q or to C1q within the C1 complex which consists of the three subcomponents C1q, C1r and C1s. Thus, a possible pathogenic role might be limited to tissues or organs in which C1q is deposited and not associated with the serine proteases C1r and C1s. In contrast to plasma C1q, which mainly assembles with C1r/s to form the C1 complex, free C1q is locally synthesised in tissues, mainly by dendritic cells and macrophages (8).

Consequently, anti-C1q cannot be regarded as a diagnostic marker of SLE, even though the highest titres of anti-C1q were described in SLE patients and patients with the closely related HUVS. However, anti-C1q have been found to be a useful marker of disease activity in SLE. In particular, anti-C1q levels and the percentage of SLE patients being positive for anti-C1q strongly dependent on the presence of active lupus nephritis at the time of sampling (13).

As a biomarker for the occurrence of proliferative lupus nephritis in patients with SLE, anti-C1q seem to be superior to determining classical parameters such as anti-dsDNA or complement (C3, C4) (8).
bacteria was the explanation for the link of complement deficiency with SLE (16).

**Anti-C1q Antibody and lupus Nephritis**

Anti-C1q antibody is present in approximately one third of patients with SLE, especially in those with high disease activity and renal involvement. Anti-C1q antibody can predict renal flare. Hence, anti-C1q antibody can be used as a biomarker for monitoring patients with LN (17).

There are several autoantibodies that required attention in LN, including their use in diagnosis and monitoring, and their role in the pathogenesis. Anti-nucleosome and anti-C1q antibodies demonstrated an association with the development of glomerulonephritis in SLE. It has been suggested that autoantibodies to C1q were found to be elevated in the sera of SLE patients and are closely associated with renal involvement (18).

Some Studies have found that monitoring anti-C1q might be valuable for the clinical SLE patients management as a non-invasive biological marker of renal disease. A Brazilian study on SLE patients confirmed the association of anti-C1q antibodies with nephritis and disease activity (19).

Anti-C1q levels were found to better correlate with renal flares in patients with proliferative lupus nephritis than the other markers, but not all patients with renal flares had increased levels of anti-C1q (13). In another study, patients with SLE and changes in renal disease activity showing an association between anti-C1q and changes in urine protein concentrations and a renal activity score as well as a modified SLEDAI. In addition, it was reported that levels of anti-C1q antibodies decreased after successful treatment of lupus nephritis (20).

**Pathogenic Role of Anti-C1q in lupus nephritis**

Anti-C1q may either contribute to the formation of circulating immune complexes that are deposited in the kidneys or contribute to local formation of immune complexes on the glomerular basement membrane. By interfering with activation of the complement system through the classical pathway, anti-C1q may hamper immune complex solubilization, further contributing to immune complex deposition in the kidney. In addition, anti-C1q may be pathogenic by disturbing the clearance of apoptotic cells, resulting in induction of autoimmunity or aggravating the autoimmune inflammatory state. On a pathophysiological level, it has been speculated that anti-C1q are necessary, but not sufficient, for producing the immune damage in the glomeruli because many individuals with SLE or (HUVS) have high titers of anti-C1q but no renal involvement on a clinical basis (21).

In experimental models, the single injection of either anti-glomerular basement membrane (GMB) or anti-C1q antibodies did not result in overt renal disease, the presence of both a prerequisite for inducing full-blown renal disease. Interestingly, lupus nephritis is characterized by the deposition of C1q along glomerular and tubular basement membranes, and another study showed that anti-C1q are found in the same deposits. C1q and the anti-C1q antibodies are one of the central elements in severe lupus nephritis (22).

**C1q antibody as biomarker of LN**

The traditional clinical biomarkers for SLE, (C3, C4) and anti- double-stranded DNA antibodies (ADNA) have low sensitivity (49 – 79%) and specificity (51 – 74%) for concurrent renal flare and do not reliably predict impending flare when measured serially, with sensitivities and specificities around 50 and 70%, respectively. Studies reported the presence of anti-C1q antibody in seven of 12 (58%) lupus nephritis patients. Six of these seven patients were in renal flare and thereby have a role as a predictive marker in LN (23).

The association of anti-C1q antibodies with lupus nephritis has been demonstrated by the
discovery of anti-C1q antibodies in lupus nephritis kidneys. The clinical relevance of anti-C1q antibodies in adult patients with active SLE nephritis was raised in several clinical studies (24).

Abdel Kader et al., (23) study was designed to evaluate the diagnostic performance of anti-C1q antibodies in a cohort of pediatric and adolescent SLE patients with and without LN, and to correlate findings with other disease variables, and standard laboratory investigations used to assess renal function, SLE nephritis and activity indices and the results revealed that anti-C1q antibodies were found to be significantly higher in patients with active lupus nephritis than those without active nephritis than control individual.

Noteworthy, in the non-proliferative forms only anti-C1q was able to differentiate between renal flares and quiescent renal disease. However, only 54% of flares that developed in the non-proliferative forms were associated with high titers of anti-C1q in comparison with 80% of those that occurred in patients with the proliferative forms. In patients with antiphospholipid antibodies, anti-C1q seem to be less reliable in predicting renal flares as a high number of flares in these patients occurred with normal values of anti-C1q (25).

In Xiao et al., (26) study, they showed that the prevalence of anti-C1q antibodies was 54.4%, and the presence of anti-C1q antibodies was closely correlated with acute injury indices of renal histopathology, with a better correlation compared with anti-dsDNA antibodies, such as endocapillary hypercellularity, karyorrhexis/fibrinoid necrosis, subendothelial hyaline deposits and leukocyte infiltration. However, similar to anti-dsDNA antibodies, the presence of the autoantibodies was not a risk factor of the renal survival. anti-C1q antibodies are more closely correlated with renal disease activity than other autoantibodies

References


C1q Autoantibodies in Lupus Nephritis. 1173(1), 47-51.


26. Xiao-wei Yang, Ying Tan, Feng Yu, Ming-hui Zhao, (2012): Combination of anti-C1q and anti-dsDNA antibodies is associated with higher renal disease activity and predicts renal prognosis of patients with lupus nephritis, Nephrology Dialysis Transplantation, Volume 27, Issue 9, Pages 3552–3559.