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RESEARCH ARTICLE

Complements as a Predictive Biomarker of Lupus Nephritis in Female Patients with Systemic Lupus Erythematosus

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ABSTRACT

Background: Lupus nephritis (LN) has been demonstrated in about 40–50 percent of all systemic lupus erythematosus (SLE) patients. Patients having renal flares are at risk from suffering serious kidney damage, and usually have a poor prognosis. Unfortunately, renal flare pathogenesis in LN patients remains unclear, and no known predictions of an impending renal flare exist. **Aim**: The present study aims to measure circulating levels of anti-C1q antibodies, C3, C4, TNF-α and soluble TNF-α receptor, serum creatinine and blood urea nitrogen (BUN) as biomarkers for active LN. **Materials and Methods**: The study included 180 SLE female patients meeting the revised classification requirements of the modified American College of Rheumatology (ACR); 90 female patients with active proliferative LN (biopsy-proven) and other 90 patients with inactive LN. Patients were receiving mycophenolate mofetil; the study was conducted between 2018 and 2019. Results: We found that low levels of complement C3 and C4 in combination with high levels of BUN, creatinine, anti-C1q antibodies and positive anti-dsDNA antibodies were more likely to be associated with lupus nephritis development in SLE patients. Also, high levels of TNF-α and its soluble receptor can be used as an indication of active disease activity and flare development. **Conclusion**: Monitoring of Anti-C1q antibodies, C3, C4, serum creatinine, and BUN levels in SLE patients can improve LN prognosis. TNF-α can also be used as an indicator for active LN and concomitant flare. This early diagnosis combined with prompt care would help decrease morbidity and mortality in LN patients.

Keywords: ANA, C3, C4, Lupus nephritis, TNF-α

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INTRODUCTION

SLE is a chronic autoimmune inflammatory condition affecting every organ but most commonly destroying the kidney. This is more prevalent among women than men in all age groups with the highest female / male ratio at reproductive age, ranging from 8:1 to 15:1, and the lowest in children at about 4:3 (Danchenko *et al.,* 2006; Mina and Brunner, 2010; Schwartzman-Morris and Putterman, 2012; Elamir *et al.,* 2019; Farid *et al.,* 2019). The prevalence of SLE and the chances of developing lupus nephritis (LN) vary considerably according to different parts of the world, different races and ethnicities (Danchenko *et al.,* 2006; Osio-Salido and Manapat-Reyes, 2010; Pons-Estel *et al.,* 2015).

At least 50 per cent of SLE patients show symptoms of nephritis during their disease at any point (Ruiz-Irastorza *et al.,* 2001). LN was identified as one of the most important factors influencing the SLE route, but it is sadly unrecognized before full-blown nephritis and/or renal failure nephrotic syndrome emerges. In SLE patients LN accounts substantially for morbidity and mortality (Vu and Escalante, 1999). Nevertheless, early detection and prompt, successful care will typically improve the prognosis. The complement system is usually triggered in LN and can directly cause kidney damage or indirectly increase kidney inflammation through the infiltration of leukocytes into the kidney (Almaani *et al.,* 2017).

Autoantibodies to complement components found in SLE patients can play a significant role in the development of LN in this respect. In several studies antibodies to anti-C1q have been associated with SLE and lupus nephritis (Trouw and Daha, 2005; Trendelenburg *et al.,* 2006). Also, changes in plasma levels of complement C3 and C4 can serve as biomarkers of SLE flare (Walport, 2002).

Cytokines are a group of polypeptides that the host produces in response to various injuries. It is implicated in immunity and response to inflammation. There are many cytokines that have been implicated in autoimmune disorders, like interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ, (IFN- γ) and tumor necrosis factor-α (TNF-α). At the other hand, it fails to completely discover the biological function of soluble cytokine receptors. It can modify cytokine concentrations by acting as a stabilizing binding protein or by regulating the number of membrane receptors or by specifically inhibiting the association of ligand-receptors in extracellular space (Metsariune *et al.,* 1992). Cytokines play the most important role in the pathogenesis of many inflammatory and autoimmune diseases (Linker-Israeli, 1992; Gordon and Emery, 1993; Handwerger *et al.,* 1994). TNF-α is a pro-inflammatory cytokine which has several effects on B and T lymphocytes and also on the process of apoptosis which describes its role in SLE (Rieckmann *et al.,* 2016). TNF-α can induce the secretion of membrane receptors (Aderka *et al.,* 1993) that become soluble and bind to TNF-α, avoiding other inhibitory cytokines from inactivating it (Aderka *et al .,* 1992). Several studies suggest that TNF-α and its receptors could be elevated in the serum of SLE patients (Gabay *et al.,* 1997; Davas *et al.,* 1999). TNF-α and its receptors have been associated with higher disease activity and kidney involvement (Zhu *et al.,* 2009). TNF-α has been found in glomeruli in many LN cases. Aringer et al. (2002) reported that renal inflammation correlates with TNF-α secretion. This interdependence may suggest TNF-α ‘s role as a destructive inflammatory cytokine in LN. Many studies have investigated the level of TNF-α in patients with SLE.

Thus, the aim of this study was to explore the relationship between circulating levels of anti-C1q antibodies, C3, C4, TNF-α, soluble TNF-α receptor, serum creatinine, and blood urea nitrogen (BUN) levels in patients with proliferative LN.

PATIENTS AND METHODS

Patients

The study recruited 180 female SLE patients who met the updated American College of Rheumatology (ACR) revised SLE classification criteria (Hochberg, 1997). The disease activity assessment was performed using the SLE disease activity index (SLEDAI) (Bombardier et al., 1992). The control group consisted of twenty healthy individuals matched by age and sex to the SLE group. The patients were chosen from the Department of Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, Cairo, Egypt, outpatient clinic and inpatient section. Informed consent of all study participants has been obtained. The study excluded patients with any of the following: diabetes and uncontrolled hypertension for more than one year. Patients were receiving mycophenolate mofetil; the study was conducted between 2018 and 2019. All patients included in this research were subjected to a clinical review of cardiopulmonary, gastrointestinal, neurological, and musculoskeletal systems; and regular kidney function (creatinine, and BUN) laboratory measurements. The blood samples were obtained from both patients and controls; the sera were isolated and preserved at 4°C.

Immunological measurements

Serum levels of TNF-α and soluble TNF-α receptor were determined by human TNF alpha ELISA kit (ab181421) and Human Soluble TNF Receptor I ELISA Kit (ab100642), respectively. Human anti-double-stranded DNA antibody (Anti-dsDNA) ELISA Kit (MBS269122), complement c1q ELISA kit (ab170246) and anti-nuclear antibody (ANA) ELISA Kit (MBS702970) were used for measuring of ANA, anti-C1q and anti-dsDNA antibodies, respectively. Serum complement levels were measured by Complement C3 ELISA Kit (ab108823) and Complement C4 ELISA Kit (ab108824).

Statistical analysis

Data were described as means, or frequencies (number of cases) and percentages when appropriate. All statistical analysis was performed using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. Comparison between quantitative measurements was done by t-test.

RESULTS

This study included 90 female patients with active proliferative LN and other 90 female patients with inactive LN. Their age ranged from 20 to 41 years, with a mean age of 25.8 ± 2.35 years. Their age of onset of SLE ranged from 12 to 35 years, with mean age of onset 22.7 ± 7.01 years. The disease duration ranged from 3 months to 10 years, with a mean duration 43.71 ± 21.51 months. The SLEDAI score ranged from 4 to 29 with a mean of 21.2 ± 3.25. The clinical characteristics of the SLE patients are presented in Table 1 and laboratory features in Table 2.

Table 1. Clinical characteristics of SLE patients Clinical manifestations

Clinical manifestations	Patients with inactive LN (n=90)		Patients with active LN (n=90)	
	No.	%	No.	%
Fever	80	88.8	83	92.2
Weight loss	50	55.5	65	72.2
Fatigue	82	91.1	86	95.5
Lupus headache	20	22.2	35	38.8
Photosensitivity	75	83.3	81	90
Malar rush	87	96.6	88	97.7
Oral ulcers	81	90	85	94.4
Arthritis	66	73.3	75	83.3
nephritis	90	100	90	100

ANA concentration in both inactive (152.35 ± 89.57) and active (320.69 ± 89.54) LN patients was significantly higher than that of the healthy control group (2.01±1.5). The same behavior was observed with anti-ds DNA level; where its level in active LN cases (250.91 ± 87.01) was nearly double that of inactive cases (108.81 ± 52.91). Also, the level of anti-c1q antibodies in inactive LN patients was less than that of patients with active LN, 14.42 ± 20.59 and 52.58 ± 34.1 respectively.

Complement proteins C3 and C4 recorded a low level in active LN patients, 85±83.01 and 15±63.02 respectively, in comparison to patients with the inactive disease or healthy controls. Serum creatinine and BUN levels in control and inactive LN patients groups were nearly the same, but its level in active cases was highly elevated (1.2±37.5 and 37±56.81 for creatinine and BUN respectively). Level of TNF-α and its soluble receptor was significantly elevated in patients with active LN (757.94±41.96, 1459.59±51.68, respectively) in comparison to the control group and patients with inactive LN (Table 2).

DISCUSSION

Involvement of kidney damage is noticed in most patients leading to LN during the SLE disease history. This greatly leads to morbidity and mortality in patients with LN (Abeeda *et al.,* 2016). Asymptomatic hematuria/proteinuria, nephrotic syndrome, or nephritic syndrome may be classified as LN.

Table 2. laboratory characteristics and immune profile of SLE patients.

Data	Healthy controls (Mean±SD)	SLE patients with inactive LN (Mean±SD)	SLE patients with active LN (Mean±SD)
ANA (U/ml)	2.01±1.5	152.35 ± 89.57*	320.69 ± 89.54*
Anti-ds DNA (U/ml)	5.6±5.2	108.81 ± 52.91*	250.91 ± 87.01*
Anti-C1q antibodies (U/ml)	1.2±2.6	14.42 ± 20.59*	52.58 ± 34.1*
C3 (mg/dl)	120±26.35	97±58.35	85±83.01
C4 (mg/dl)	30±48.23	19±73.12	15±63.02
Serum creatinine (mg/dl)	0.5±65.2	0.5±50.1	1.2±37.5
BUN (mg/dl)	12.5±72.52	13±37.2	37±56.81*
TNF-α (pg/ml)	167.13±10.6	257.25±54.32*	757.94±41.96*
Soluble TNF-α receptor	747.83±14.38	957.21±52.21	1459.59±51.68*

ANA: Anti-Nuclear Antibody, Anti-dsDNA: double-strand (ds) DNA, C3 and C4: complement proteins, BUN: blood urea nitrogen, TNF-α: tumor necrosis factor- alpha. *: represent a significant difference in comparison to that of the control group (P<0.05).

This is accompanied by hypertension and renal dysfunction of various degrees (D'Agati, 1998). The complement system plays an important role in SLE pathogenesis, in particular by activating the classical pathway (Walport, 2002).

The classical pathway launched with immune complexes interaction with the C1q protein, the first component of the classical pathway (Herrmann *et al.,* 2000). C1q binds portions of immune complexes (Fc) and participates in self-antigen removal produced during programmed cell death (Walport *et al.,* 1998; Walport, 2001). Trouw and Daha (2005) reported the prevalence of anti-C1q antibodies in fifty per cent of patients with SLE, particularly those with LN. In addition, Fremeaux-Bacchi *et al*. (2004) and Trendelenburg *et al.* (2006) added the LN development in patients with a high level of anti-C1q antibodies. According to our results, the level of these antibodies in patients with active LN (52.58 ± 34.1) was higher than that of the other group with inactive LN (14.42 ± 20.59). Also, ANA and anti-ds DNA level were higher in patients with active LN, 320.69 ± 89.54 and 250.91 ± 87.01 respectively, than that of the other group. Jaekell *et al.* (2006) stated that anti-C1q antibodies are as reliable as anti-ds DNA antibodies and is able to close a diagnosis hole in some cases. However, the levels of anti-C1q antibodies appear to decrease during SLE therapy with rituximab (Vallerskog *et al.,* 2007).

Based on clinical and laboratory results, Horvath *et al.* (2001) found a strong positive association between high-titer anti-C1q antibodies and lupus disease. Almost half (29/70) of active-stage SLE patients but only 10/66 of inactive-stage patients had elevated levels of anti-C1q.

Abeeda et al. (2016) documented a link between anti-C1q and renal failure and raised the possibility of using anti-C1q antibodies as a predictor for activity in LN disease, especially in the renal flare. Anti-C1q antibodies are higher in renal flares than in nonrenal flares in a follow-up study performed weekly in Adult patients, and their level matches disease severity more closely in renal lupus than in non-renal lupus (Coremans et al., 1995). Mosca et al. (2006) reported that anti-C1q antibodies are a better method than anti-dsDNA antibodies to indicate the presence of renal flares in SLE. Heinln *et al.* (2007) described how anti-C1q antibodies play a role in LN development. They documented the presence of anti-C1q antibodies on the basement membrane of the glomerulus that leads to the development of deposited immune complexes in the kidney. Clearly, the complement system plays a crucial role in the pathophysiology of lupus, particularly LN, but the complexity of that function is complex and confusing. This confusion may indeed be due to various pathways of activation, numerous regulators and regulatory points in the activation pathways and genetic variations. Complement has obvious opposing roles in LN, where it appears to defend against the initiation of lupus and disease activity (through the classical pathway), but also participates in LN-related tissue damages. (Birmingham *et al.,* 2017). Low concentrations of C3 and C4 demonstrate the stimulation of the complement; it has long been used as a measure of increased activity in the LN disease. Low levels of C3 and C4 have recently been added to revised lupus diagnosis criteria (Petri *et al.,* 2012). Birmingham et al. (2010) assessed bimonthly levels of C3 and C4 in 71 LN patients who were accompanied with 70 renal flares for 35 months. They showed the reduced levels of C3 and C4 at flare but not two months before flare.

These results were in agreement with our results, where C3 and C4 circulating levels (85±83.01 and 15±63.02, respectively) in SLE patients with active LN were lower than that of other patients with inactive LN (97±58.35 and 19±73.12 for C3 and C4 respectively). However, our findings reveal some interesting relationships between low levels of C3 and C4 in the renal flare. Furthermore, they can be used as biomarkers for renal flare.

In our results, serum creatinine in patients with active LN (1.2±37.5) is higher than that (0.5±50.1) of patients with inactive LN. The same thing was noticed with BUN, its level (37 ± 56.81) is much higher in active LN patients. Petri (2000) reported that patients with the low level of C3 complement, high levels of BUN, creatinine, and positive anti-dsDNA were much more likely to experience lupus nephritis than patients without these routine laboratory abnormalities. Satirapoj *et al.* (2007) also

reported that laboratory abnormalities associated with lupus nephritis development were BUN > 12 mg/dl, serum creatinine > 1.3 mg/dl, low levels of C3 and positive anti-dsDNA antibodies. According to our results, TNF-α level in SLE patients with active LN (757.94±41.96) was significantly elevated than that 257.25±54.32 in inactive LN patients.

In contrast with our studies, there was no correlation between TNF-α concentration and SLE behavior observed by Gordon and Emery (1993). Metsariune *et al.* (1992) reported that the above differences could be due to the different sensitivity and specificity of cytokine measurement methods (ELISA and bioassay), and the number of patients included in the study. Robak *et al.* (1996) reported that TNF-α plays an important part in SLE pathogenesis. In vitro studies indicate a disrupted TNF-α development in SLE. Malave *et al.* (1989) demonstrated a reduction in the expression of TNF-α by lectin-stimulated mononuclear cells in SLE patients, given the fact that the mRNA for TNF-α is higher in these cells than in healthy people. In addition, monocytes in SLE patients will spontaneously secrete TNF-α in the in vitro culture, with these cells being a good stimulator of their development by immunologic complexes (Maini *et al.,* 1994). In SLE a higher concentration of TNF-α was also observed in infected tissues relative to healthy tissues. It should be added also that excessive development of TNF-α may be genetically conditioned. It may be correlated with the existence of the TNF-α gene, and this existence may result in autoimmune disease development, like SLE, being affected (Robak *et al.,* 1996). In addition, we found an important association between the amount of soluble TNF-α receptors and LN activity. A similar relation between TNF-α receptor level and SLE activity has been identified in several studies (Aderka *et al.,* 1993), renal (Zhu *et al.,* 2009) and cutaneous involvement (Zampieri *et al.,* 2006). Mahmoud *et al.* (2005) documented, in 44 patients, extreme LN was related to high levels of TNF-α and its soluble receptor.

In conclusion, LN prognosis can be improved by monitoring levels of anti-C1q antibodies, C3, C4, serum creatinine and BUN in SLE patients. Furthermore, TNF-α can be used as an indication for active LN and concurrent flare. This early diagnosis in combination with timely effective treatment will aid in decreasing morbidity and mortality in LN patients.

Conflicts of interest

All authors have approved this article and declare no conflicts of interest.

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Egyptian Association for Cancer Research (EACR)
http://eacr.tanta.edu.eg/

EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (http://acdd.tanta.edu.eg). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: https://jcbr.journals.ekb.eg) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

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