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**ATINER's Conference Paper Series  
HSC2014-1041**

**Kidney Involvement:  
The Most Important Predictor in  
Lupus Erythematosus**

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Dr. Gregory T. Papanikos  
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This paper should be cited as follows:

**Ktona, E., Barbullushi, M., Backa, T., Idrizi, A., Petrela, E., Sina, E. and Ndreu V., (2014) "Kidney Involvement: The Most Important Predictor in Lupus Erythematosus", Athens: ATINER'S Conference Paper Series, No: HSC2014-1041.**

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URL Conference Papers Series: [www.atiner.gr/papers.htm](http://www.atiner.gr/papers.htm)  
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**ISSN 2241-2891**  
15/07/2014

## **Kidney Involvement: The Most Important Predictor in Lupus Erythematosus**

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### **Abstract**

**Introduction.** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of unusual antibodies in the blood which mistakenly attacks healthy tissue. It can affect the skin, kidneys, joints, brains and other organs. Kidney involvement is an important predictor and contributor of mortality and morbidity at SLE patients. Our study aimed to evaluate the outcome and predictors of renal disease progression in our SLE patients.

**Patients and methods.** A retrospective study of 420 patients diagnosed and treated for SLE was conducted from during the period of 2003 to 2013. All the data were collected from discharged patient charts. Eighty nine per cent of all patients (374) were females and 46 (11%) were males. We measure the glomerular filtration rate, presence of proteinuria ( $>0.5$  g/day) anti-dsDNA, AAN, C3 and C4, hematuria, urinary cellular casts, azotemia and creatinemia, etc.

**Results.** During 10 years of the disease 172 of all patients (41%) develop lupus nephritis. C3, proteinuria and anti-DNA were predictor of kidney damages. Forty one patients developed cardiovascular damages, 32 patients developed pulmonary complication and 12 patients developed nervous system complications.

**Conclusion:** In our study the renal damages are the most important predictors of life quality, morbidity and mortality. Low C3 and C4 levels, proteinuria and positive anti ds-DNA were predictors of an earlier decline in GFR.

**Key words:** Lupus Nephritis, C3, Proteinuria, Anti-ds DNA, Antinuclear antibodies.

## Introduction

Systemic lupus erythematosus (SLE) is the prototypic multisystem autoimmune disorder with an incidence nearly tripled in the last 40 years, range from 2 to 8 per 100.000 per year [1]. Clinical manifestations differ between individuals, with disease severity ranging from very mild to fulminate disease, and many organs may be involved. The organs most frequently affected are joints, skin, kidneys, serous membranes, the haemopoietic system, blood vessels and the central nervous system [2]. Renal disease occurs in 40-70% of adults lupus patients and is a major cause of morbidity and mortality related to the disease. Most patients develop nephritis early in their disease, however nephritis may occur any time during the course of the disease. Renal markers such as low creatinine clearance, C3, proteinuria, and nephritic syndrome are associated with poor prognosis among lupus nephritis (LN) patients.

Our study aimed to evaluate the outcome and predictors of renal disease progression in our SLE patients.

## Patients and Methods

We retrospectively examined 420 patients admitted to University Hospital Centre "Mother Teresa" from July 2003 to December 2013. Cases of SLE were identified from database with the corresponding International Classification of Disease. The criteria of the American College of Rheumatology for classification were obtained from all patients at the time of diagnosis [3]. Age, sex, disease activity, disease duration, autoantibody profile, and organ damage were recorded. In this retrospective study were included patients who were first diagnosed with SLE and other groups were composed from patients with SLE in treatment but without organ damage (lupus nephritis, pulmonary and, nervous system damage). At each patient visit, a complete history, routine laboratory testing, and treatment were performed in a systematic fashion. The renal function was assessed measuring the glomerular filtration rate (GFR) using the Cockcroft-Gault formula [4]. Mild renal disease was defined as a  $GFR \geq 90$  ml/min at renal onset, and the presence of one or more of the following criteria: persistent proteinuria  $> 0.25$ g/day but  $< 3.5$  g/day, or  $\geq 2+$  dipstick, hematuria  $> 5$  RBC/hpf attributed to SLE in two or more occasions and urinary cellular casts. AAN, anti-dsDNA and serum C3, protein in urine, blood test, urea and creatinine levels were measured frequently. AAN were determined by indirect immunofluorescence, whereas anti-dsDNA and cardiolipin by a standard enzyme linked immune sorbent assay (ELISA) [5]. C3 was determined by nephelometry. These indices have been developed in the context of long term observational studies and have been shown to be strong predictors of damage and mortality, and reflect change in disease activity.

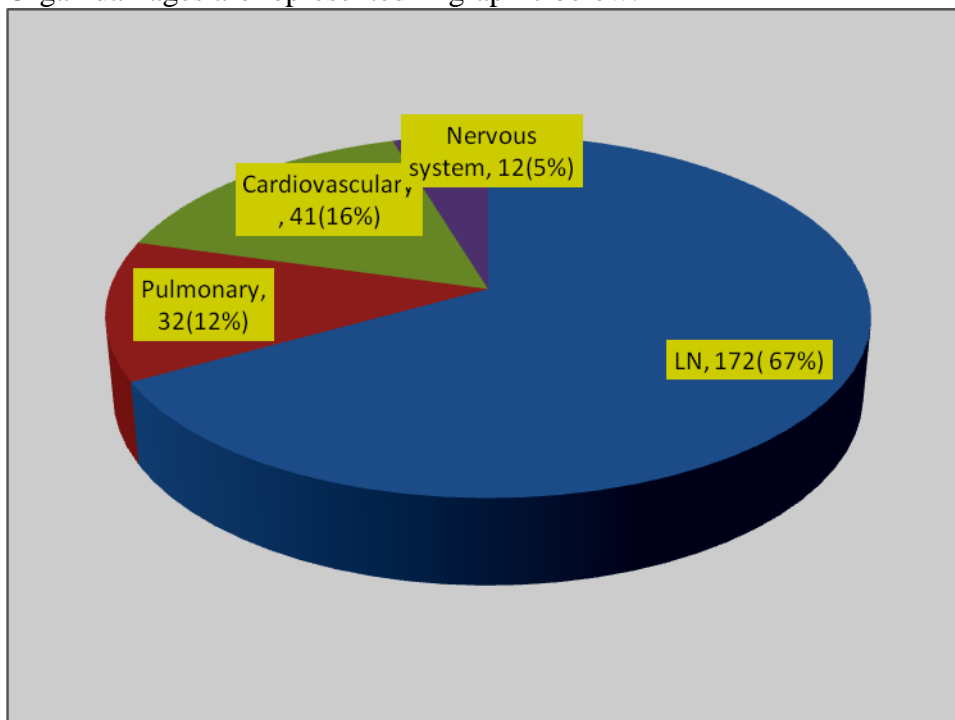
## Statistical Analysis

The statistical analysis was done with SPSS (Statistical Package for Social Sciences) Chicago Illinois version 19.0. The frequencies were done for categorical variables such as organ damage, DNA, C3, etc. Chi square test, OR and confidence interval 95% calculations were performed to see differences between cases and control groups. P value  $\leq 0.05$  was considered as statistical significance.

## Results

420 patients of SLE diagnosis based on the classification criteria of the American College of Rheumatology were included in our study. Out of 420 patients 374 (89%) are females and 46 (11%) were males. 172 of all patients were diagnosed with Lupus Nephritis (LN) and 248 patients had SLE without renal involvement.

Organ damages are represented in graphic below.



**Table 1.** *Organ Damage are Represented in Table 1*

Variable	10 years
Lupus Nephritis (LN)	172 (41%)
Pulmonary System	32 (7.6%)
Cardiovascular System	41(9.7%)
Nervous system	12(2.9%)

Lupus nephritis 172(41%) is the most common complication of patients with SLE. Pulmonary involvement 32(7.6%), cardiovascular damage 41 (9.7%) and nervous system 12 (2.9%) involvement are two other more frequently affected.

We compared 172 patients with lupic nephritis and 248 patients without renal disease. The comparative analysis was done recording their clinical and immunological features (autoantibody profile), and therapy (corticosteroids, immunosuppressive therapy). Extensive data were presented in Table 2.

**Table 2** *Differences in Autoantibodies, Complement Levels and Renal Function Abnormalities in LN and Non Lupus Nephritis*

Variables	LN 172	Non Lupus Nephritis 248	OR	95%CI	X <sup>2</sup>	Pvalue
AAN	151 (87.7%)	159 (64.1%)	4.2	2.33 to 7.16	29.5	0.0001
Anti-ds DNA	127 (73.8%)	125 (50.4%)	2.78	1.79 to 4.34	23.2	0.0001
C3	103(59.8%)	87 (35 %)	2.76	1.81 to 4.21	25.2	0.0001
C4	104(60.4%)	117 (47.1%)	1.71	1.13 to 2.59	7.1	0.007
Proteinuria	85(49.4%)	19 (5.08%)	11.78	6.59 to 21.64	95.4	0.0001
Corticosteroid >0.5mg/kg	118(68.6%)	20(8.06%)	24.9	13.8 to 45.7	168	0.0001
Hydroxychloroquine (Plaquenili)	24(13.9%)	125(50%)	0.16	0.09 to 0.27	58.9	0.0001
Azathioprine	49(28.4%)	16(6.45%)	5.78	3.06 to 11.31	37	0.0001
	61(35.46%)	8(3.22%)	16.49	7.47 to 41.00	76	0.0001

-\*OR=odd ratio,\*\*P value  $\leq 0.05$  as significant level

The analysis of the two groups showed in patients with lupus nephritis a significant statistical higher prevalence of anti-dsDNA antibodies 73,8.% vs 50.4%, p value 0.0001 thus being known their pathogenic role and the correlation with renal disease, as well as a higher prevalence of C3 (59.8% v

s 35 %, p 0.0001), C4 (60.4% v s 47.1%, p 0.007) and proteinuria (49.4% v s 5.08% , p 0.0001). Regarding treatment administration in the studied patients, those with renal disease showed a higher prevalence of treatment with corticosteroids (68.6% vs 8.06%, p 0.0001) and immunosuppressive treatment azathioprine 28.4% vs 6.45%, p 0.0001), cyclophosphamide 35.46% vs 3.22%, p 0.0001).

**Table 3.** Shows the Baseline, Clinical Manifestations, Serologic Markers, Pharmacologic Treatments, of Study Participants by Renal Function Group at Study End. Patients with Proteinuria ( $\geq 0.5$  g/day) and Low C4 Levels at Baseline were more likely to have a decline of GFR ( $p < 0.05$ ).

Variables	GFR $\geq$ 90 mil/min nr=75	GFR $\leq$ 90 mil/min nr=97	P value
Malar Rash	24(32%)	28(28.8%)	0.6
Photosensitivity	23(30.67%)	31(31.9%)	0.8
Oral Ulcers	16(21.33%)	18(18.5%)	0.6
Arthritis	23(30.67%)	26(26.8%)	0.6
Leucopenia	29(38.67%)	28(28.8%)	0.07
Proteinuria $>0.5$ g/day	13(17.33%)	26(26.8%)	0.3
AAN	69(92.00%)	84(86.5%)	0.3
Anti ds-DNA	55(73.33%)	74(76.2%)	0.2
C3	36(48.00%)	51(52.5%)	0.4
C4	31(41.3%)	62(63.9%)	0.1

-\*OR=odd ratio,\*\*P value  $\leq 0.05$  as significant level

No differences were found for clinical manifestations or serologic abnormalities between renal function groups. In addition, no differences were noted for selected comorbidities, pharmacologic treatments. There is no statistical significance between cases with lupus nephritis and GFR $\geq$  90 mil/min nr=75, and patients with lupus nephritis and GFR $\leq$  90 mil/min nr=97.

## Discussion

SLE is characterized by the production of unusual autoantibodies in the blood which mistakenly attacks healthy tissues with a broad spectrum of clinical presentations Lupus nephritis 172 (41%), Pulmonary System 32 (7.6%), Cardiovascular System 41(9.7%), Nervous system 12(2.9%)[6-8] . Females are affected nine times more frequently than males. 374 (89%) of all patients were females and 46 (11%) were males [9]. Sixty-five per cent of patients with SLE have disease onset between the ages of 16 and 55 years, 20% present before age 16, and 15% after the age of 55. In this study fifty-nine per cent of patients with SLE have disease onset between the age of 16-55 years, 15% present before age 16 , and 10% after the age of 55[9-10]. Antibodies against self-antigens are the hallmark for SLE and may be present many years before clinical signs of the disease [11-12]. Autoantibodies called antinuclear



antibodies (ANA) are detectable in >95% of lupus patients. However ANAs are not specific and can be detected in a variety of autoimmune and infectious patients and also in health individuals. Antibodies against double stranded DNA (anti-dsDNA) are the most important antibodies and are involved in the pathogenesis [13-14]. Anti-DNA are highly specific for lupus; present in 50-70% of all patients. In our study AAN is 151 (87.7%) and anti-ds DNA 127 (73.8%) in LN patients[15]. Anti-ds DNA antibodies are probably the most pathogenic type of antibody produced and correlate with the progression of the disease. Studies have shown that anti ds-DNA participate in the pathogenesis of lupus nephritis. 73.8 % of patients with lupus nephritis are positive for anti ds-DNA [16]. Positivity of AAN and anti -DNA accompanied with low titer of complement C3 are indicators of lupus nephritis. Other antibodies are associated to specific disease manifestation: anti-dsDNA, AAN, anti-Sm and anti-C1q antibodies to nephritis, anti-Ro to skin disease etc [17]. Clinical manifestations differ between individuals, with disease severity ranging from very mild to fulminate disease, and many organs may be involved. Renal markers such as low creatinine clearance, C3, proteinuria, and nephritic syndrome are associated with poor prognosis among LN patients [18]. C4 activation is associated with the pre-flare period of renal disease in lupus patients. C4 deficiency in SLE may be the result of an inherited deficiency and/or complement consumption due to active disease. Inheritance of one or more null alleles for C4 predisposes to the development of SLE. Proteinuria appears to be both a marker of glomerular dysfunction and a direct mediator of renal disease progression. Proteinuria is a prognostic factor of renal disease progression in SLE patients [19-20]. Thus, lupus patients with mild renal involvement should be routinely monitored with urine protein quantification and must be closely evaluated and treated for factors that are associated with worsening of proteinuria and its related decline in renal function [21]. Finally, we recognize that the evaluation of adjusted mean serum C4 and urine protein levels as numeric variables is a better method to evaluate outcome.

Our study has some limitations. The definition renal disease was based on laboratory parameters of renal disease and not on kidney biopsy findings. However, we performed an analysis to evaluate if patients with biopsy proven LN differed from those with LN based on abnormal laboratory parameters and found that both groups were similar with regards to clinical signs of renal disease and other parameters related to disease activity.

## **Conclusion**

Although the reasons why some patients with lupus develop clinical nephritis remain elusive, those who developed nephritis were likely to have a high morbidity and mortality. Low C3 and C4 levels, proteinuria and positive anti ds-DNA were predictors of an earlier decline in GFR. The awareness of these factors may contribute to early identification of individuals at risk of

renal deterioration. Lupus nephritis leads to the development of end-stage renal disease, decreased survival, and higher health care costs.

Conflict of interest: None Declared

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