

# Serum Anti C1q as a Biomarker of Lupus Nephritis Activity

## Thesis Submitted for partial Fulfillment of Master Degree in Internal Medicine

By

#### Ahmed Hassan Abdo Hassan

MB.B.Ch, Ain Shams University

**Under Supervision of** 

#### Prof Dr. Mohamed Mahmoud Abdel Ghany

Professor of Internal Medicine and Nephrology Faculty of Medicine, Ain Shams University

#### Dr. Dawlat Hussein Sany

Lecturer of Internal Medicine and Nephrology Faculty of Medicine, Ain Shams University

> Faculty of Medicine Ain shams University 2011



## دراسة مستوي الأنتي سي ١ كيو بالمصل كدلالة لنشاط الذئبة الحمراء بالكلي

رسالة توطئة للحصول على درجة الماجيستير في الأمراض الباطنية

مقدمة من

**ط/ أحمد حسن عبده حسن** بكالوريوس الطب و الجراحة – جامعة عين شمس

و تحت إشراف

الأستاذ الدكتور / محمد محمود عبد الغنى أستاذ الأمراض الباطنية و الكلي طب عين شمس

الدكتورة / دولت حسين سائي مدرس الأمراض الباطنية و الكلي طب عين شمس

كلية الطب جامعة عين شمس Kidney disease is one of the most serious manifestations of SLE. Despite the improvement in the medical care of SLE in the past two decades, the prognosis of lupus nephritis remains unsatisfactory

Renal involvement in SLE carries a poor prognosis and significant morbidity and mortality. The 5- and 10-year renal survival rates of lupus nephritis range between 83%–92% and 74–84% respectively, up to 25% of patients still develop end stage renal failure 10 years after onset of renal disease

Early diagnosis and rapid treatment of lupus nephritis are crucial to improving survival in SLE patients. The prognostic significance of lupus nephritis indicates a need for identifying early biomarkers that predict nephritis development

A considerable number of SLE patients present with lupus nephritis, often characterized by flares that can lead to chronic renal failure. Early biological markers may identify patients at high risk of developing such renal flares, which are known to be clinically difficult to predict

For some years, the presence of aAbs against C1q (anti-C1q aAbs) has been described in SLE with renal involvement. Detection of these aAbs has been recommended in the diagnosis and the follow-up of patients with lupus by the European League against Rheumatism (EULAR) since 2007

### **Table of contents**

Section		Title	Page	
	List of abbreviations			
		List of Tables		
List of Figures				
I	Introduc	etion and Aim of the study	1	
	Review of the Literature			
II	Chapter 1	Lupus Nephritis	4	
	Chapter 2	Treatment of Lupus Nephritis	33	
	Chapter 3	Biomarkers for Lupus Nephritis	48	
III	Patients and Methods		69	
IV	Results and statistics		75	
V	Discussion		107	
VI	Summary and Conclusion		115	

Section	Title	Page
VII	Recommendations	118
VIII	References	119
IX	Appendix	143

### **List of Abbreviations:**

No.	Abbreviation	Meaning
1	ACE	Angiotensin-converting enzyme
2	AGT	Angiotensinogen
3	aPL	Antiphospholipid
4	APRIL	A proliferation inducing ligand
5	ARBs	Angiotensin II receptor blockers
6	BAFF	B cell activation factor of the TNF family
7	BANK1	B-cell scaffold protein with ankyrin 1
8	BILAG	British Isles lupus assessment group
9	BLK	B lymphoid tyrosine kinase
10	BLyS	B lymphocyte stimulator
11	BUN	Blood urea nitrogen
12	CH50	Complement hemolytic 50

13	CKD	Chronic kidney disease
14	CLR	Collagen-like region
15	CRP	C – reactive protein
16	CTLA	Cytotoxic T-lymphocyte antigen
17	EPCR	Endothelial protein C receptor
18	ESRD	End stage renal disease
19	EULAR	European League against Rheumatism
20	FDA	Food and drug administration
21	FOXP3	Fork head transcription factor 3
22	GWAS	Genome wide association study
23	HLA	Human leukocyte antigen
24	HUVS	Hypocomplementaemic urticarial vasculitis syndrome
25	ICAM	Intracellular adhesion molecule
26	ICs	Immune complexes
27	IFN	interferon

28	IL	Interleukin 8
29	IRF5	Interferon regulatory factor 5
30	ISN	International society of nephrology
31	ITGAM	Integrin-α <sub>M</sub>
32	LA	Lupus anticoagulant
33	L-FABP	Live-type fatty acid binding protein
34	LN	Lupus nephritis
35	MAGE-B2	Melanoma-associated antigen B2
36	MBL	Mannose-binding lectin
37	mEPCR	Membrane endothelial protein C receptor
38	mTOR	Mammalian target of Rapamycin
39	NGAL	Neutrophil gelatinase-associated Lipocalin
40	NK	Natural killer cells
41	NSAIDs	Nonsteroidal anti-inflammatory drugs

42	OPG	Osteoprotegerin
43	PAI-1	Plasminogen activator inhibitor
44	PAMPs	Pathogen-associated molecular patterns
64	PASW	predictive analytics software
45	PBMCs	Peripheral blood mononuclear cells
46	PCD	Programmed cell death
47	PGA	Physician's global assessment
48	PTPN22	Protein tyrosine phosphatase non-receptor type 22
49	RPS	Renal pathology society
50	SATA4	Signal transducer and activator of transcription 4
51	SLE	Systemic lupus erythematosus
52	SLEDAI	Systemic lupus erythematosus disease activity index
53	TACI	Transmembrane activator & calcium-modulator & cyclophilin ligand interactor

54	TLRs	Toll-like receptors
55	TNF	Tumor necrosis factor
56	TNFRSF6	Tumor necrosis factor receptor super family member 6
57	TREX1	Three prime repair exonuclease
58	ТТР	Thrombotic thrombocytopenic purpura
59	TWEAK	Tumor necrosis factor-like inducer of apoptosis
60	uMCP 1	Urinary Monocyte chemoattractant protein 1
61	VCAM	Vascular cell adhesion molecule
62	VEGF	Vascular endothelial growth factor
63	WHO	World health organization

### **List of Tables:**

Table	Title	Page
1	(ISN/RPS) classification of lupus nephritis	18
2	SLEDAI	25-26
3	Serum biomarkers that correlate with LN activity in cross-sectional studies	65-66
4	Urine biomarkers that correlate with LN activity in cross-sectional studies	66-67
5	Biomarkers that correlate with histological findings in LN	67-68
6	Biomarkers that correlate with prognosis in LN	68
7.1	Sociodemographic data of patients	75
7.2	Sociodemographic data of patients	76

Table	Title	Page
8	Histological grading of LN among activity group	77
9	Difference between studied groups as regard laboratory findings	80
10	Difference between studied groups as regard Anti C1q level	91
11	Difference in all quantitative variables between different grades of LN	92
12	Difference in Anti C1q level between different grades of LN	94
13	Correlations between all studied variables Vs. Anti C1q level	95
14	Correlation between Anti C1q and ESR (multivariate analysis)	105
15	Comparison between studied groups in urine analysis	106

## **List of Figures:**

Figure	Title	Page
1	Box-Plot chart showing difference in Steroids dose between groups	76
2	Pie chart for difference in renal biopsy findings	77
3	Gender difference between groups	78
4	Smoking state between groups	78
5	HCV state between groups	79
6	ALT difference between groups	81
7	Difference in serum Albumin between groups	82

8	Difference in serum total proteins between groups	83
9	Difference in serum creatinine between groups	84
10	Difference in BUN between groups	85
11	Difference in proteinuria between groups	86
12	Difference in Anti DNA titer between groups	87
13	Difference in C3 level between groups	88
14	Difference in C4 level between groups	89
15	Difference in ESR level between groups	90
16	Difference in Anti C1q level between groups	91
17	Difference in proteinuria level between groups	93
18	Difference in Anti C1q level between groups	94

19	Correlation between Anti C1q and Anti DNA	96
20	Correlation between Anti C1q and C3 level	97
21	Correlation between Anti C1q and C4 level	98
22	Correlation between Anti C1q and ESR level	99
23	Correlation between Anti C1q and proteinuria level	100
24	Correlation between Anti C1q and activity index of renal biopsy	101
25	Correlation between Anti C1q and chronicity index of renal biopsy	102
26	Roc curve	104