الجسيم المناعى م البولى كعلامة حيوية جديدة للكشف عن مدى نشاط الالتهاب الكلوى المصاحب لمرض الذئبة الحمراء

رسالة مقدمه من الطبيب/ صلاح سعيد محمد الطبيب/ صلاح سعيد محمد ما جستير الباطنة العامه عين شمس كلية الطب - جامعة توطئة للحصول على درجة الدكتوراه في أمراض الباطنة العامة حت إشراف

ا.د/ احمد عزيز عبدالنبي

أستاذ الباطنة العامة و الكلى عين شمس كلية الطب - جامعة

ا.د/ دالیا فایز محمد

أستاذ الباطنة العامة و الروماتيزم عين شمس كلية الطب - جامعة

۱.د.م/ هیام محمد عارف

أستاذ مساعد الباطنة العامة و الكلى عين شمس كلية الطب – جامعة

ا.د.م/ رانيا حمدي الكباريتي

أستاذ مساعد الباثولوجيا الاكلينيكية عين شمس كلية الطب - جامعة

د/هيثم عزات عبد العزيز

مدرس الباطنة العامة و الكلى عين شمس كلية الطب - جامعة كليسة الطبب جامعة عين شمس جامعة عين شمس ٢٠١٥

Urinary immunoglobulin M as a novel biomarker for disease activity of lupus nephritis

Thesis

Submitted For Partial Fulfillment Of Doctorate Degree (M.D) In Internal Medicine

Bv

SALAH SAID MOHAMED

M.Sc

Faculty of medicine Ain Shams university

Supervised by

PROF. DR. AHMED AZIZ ABD EL NABI

Professor Of Internal Medicine &Nephrology Faculty of medicine Ain Shams university

PROF. DR. DALIA FAYEZ MOHAMED

Professor Of Internal Medicine & Rheumatology
Faculty of medicine
Ain Shams university

DR. HAYAM MOHAMED AREF

Ass. Professor Of Internal Medicine &Nephrology
Faculty of medicine
Ain Shams university

DR. RANIA HAMDY EL-KABARITY

Ass. Professor Of Clinical pathology Faculty of medicine Ain Shams university

DR. HAITHAM EZZAT ABD-EL AZIZ

Lecturer Of Internal Medicine &Nephrology Faculty of medicine Ain Shams university

> Faculty of medicine Ain Shams university 2015

بسر الدارين الركيد

وعَلَمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وكَانَ فَعَلَمُ وكَانَ فَعَلَمُ وكَانَ فَعَلَمُ وكَانَ فَعَلَمُ وكانَ فَضَلَ اللهِ عَلَيْكَ عَظِيماً

صدق الله العظيم

النساء: من الآية ١١٣

ACKNOWLEDGEMENT

First of all, I would like to express my prayerful thanks to ALLAH for every thing in my life.

I would like to express my profound gratitude and deep appreciation to PROF. DR.AHMED AZIZ ABD EL NABI, Professor of INTERNAL MEDEDINE NEPHROLOGY, Faculty of Medicine AIN SHAMS University, for giving me the privilege to work under her supervision, her continuous encouragement, guidance and teaching extended beyond scientific scope, to moral and ethical arts of life.

I would like to express my sincere thanks, respect and appreciation to PROF.DR.DALIA FAYEZ MOHAMED, Professor of Rheumatology and Rehabilitation, Faculty of Medicine AIN SHAMS University, for continuous guidance, valuable advice and generous thought in my work.

I would like to express my profound gratitude to PROF.HAYAM MOHAMED AREF, ass. Professor of INTERNAL MEDEDING NEPHROLOGY, Faculty of Medicine AIN SHAMS University, for her generous support and kind cooperation.

I would like to express my thanks to PROF RANIA HAMDY. Assistant Professor of Clinical Pathology, Faculty of Medicine AIN SHAMS university, for help to complete this work.

I would like also to express my thanks to DR HAITHAM EZZAT ABD-EL AZIZ Lecturer Of Internal Medicine & Nephrology Faculty of Medicine AIN SHAMS University, for his support and sympathy during accomplishment of my work.

Finally all my love and thanks to my family for help and support.

CONTENTS

List of contents	Page
• LIST OF TABLES	I
LIST OF FIGURES	IV
• LIST OF ABBREVIATIONS	VI
• INTRODUCTION	1
AIM OF THE WORK	4
• REVIEW OF LITERATURE	5
CHAPTER 1:SYSTEMIC LUPUS ERYTHEMATOSUS	5
• CHAPTER 2:LUPUS NEPHRITIS	32
CHAPTER 3:NATURAL IMMUNOGLOBULIN M	83
PATIENTS AND METHODS	93
• RESULTS	101
• DISCUSION	137
SUMMARY AND CONCLUSION	158
• REFERENCES	165
• ARABIC SUMMARY	

LIST OF ABBREVIATIONS

Ab	:Monoclonal antibody.
ACE	: Angiotensin Converting Enzyme.
ACR	:American College of Rheumatology.
AGP	: α1-acid-glycoprotein
ALMS	: the Aspreva Lupus Management Study
ANAs	:Anti-Nuclear Antibodies.
ANCA	: Antineutrophil cytoplasmic-antigen autoantibodies.
Anti-dsDNA	:Anti-Double stranded Deoxy Ribonucleic Acid.
Anti La/SS-B	: Extractable nuclear antigens
AP-l	:Activator protein-1.
APRIL	:A Proliferation-Inducing Ligand.
ARBs	:Angiotensin II Receptor Blockers.
ASCT	:Autologous stem cell transplantation.
AZA	:Azathioprine.
β2-GPI	: IgM antiphospholipid antibodies that bind to beta-2-glycoprotein I
B2 cells	: follicular B cells
BCR	: B cell receptors
BILAG	:British Isles Lupus Assessment Group.
BLyS	:B-lymphocyte Stimulator.
BUN	:Blood Urea Nitrogen.
BXSB	: In-bred strains of mice
BWF:	1hybrid between NZ andWNZ
C1INH	:Complement 1 Inhibitor.
C1q	:Complement 1q.
C2	:Complement 2.
C3	:Complement 3.
C4	:Complement 4.
CAMs	: Cell adhesion molecules

cAMP	:Cyclic adenosine monophosphate.
CCR5	: C-C chemokine receptor type 5
cGN	:Crescent glomerulonephritis.
CH 50	: Total hemolytic complement.
CNS	:Central Nervous System.
CNV	: the gene copy number variation
СР	: ceruloplasmin
CRP	:Reactive Protein.
CTLA4	: Cytotoxic T-Lymphocyte Antigen 4
CXCR	:Human CXC chemokine receptors.
CXCL10	: chemokine (C-X-C motif) ligand 10
CYC	:Cyclophosphamide.
DARC	:Duffy antigen receptor for chemokines.
DCs	: Dendritic Cells
DLE	: Discoid lupus erythematosus.
DNA	: Double stranded DNA.
DN T cells	: Double negative T cells
DN T cells DPLN	: Double negative T cells : diffuse proliferative lupus nephritis
DPLN	: diffuse proliferative lupus nephritis
DPLN DSG	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin
DPLN DSG EBV	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus.
DPLN DSG EBV ECLAM	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus. :European Consensus Lupus Activity Measurment.
DPLN DSG EBV ECLAM ELNT	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus. :European Consensus Lupus Activity Measurment. : The Euro-Lupus Nephritis Trial
DPLN DSG EBV ECLAM ELNT ENA-78	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus. :European Consensus Lupus Activity Measurment. : The Euro-Lupus Nephritis Trial :Epithelial neutrophil activating protein-78.
DPLN DSG EBV ECLAM ELNT ENA-78	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus. :European Consensus Lupus Activity Measurment. : The Euro-Lupus Nephritis Trial :Epithelial neutrophil activating protein-78. : Extractable nuclear antigen antibodies
DPLN DSG EBV ECLAM ELNT ENA-78 ENAS ESR	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus. :European Consensus Lupus Activity Measurment. : The Euro-Lupus Nephritis Trial :Epithelial neutrophil activating protein-78. : Extractable nuclear antigen antibodies :Erythrocyte Sedimentation Rate.
DPLN DSG EBV ECLAM ELNT ENA-78 ENAS ESR	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus. :European Consensus Lupus Activity Measurment. : The Euro-Lupus Nephritis Trial :Epithelial neutrophil activating protein-78. : Extractable nuclear antigen antibodies :Erythrocyte Sedimentation Rate. :End stage renal disease.
DPLN DSG EBV ECLAM ELNT ENA-78 ENAS ESR ESRD EXPLORER	: diffuse proliferative lupus nephritis : novel immunosuppressant 15-deoxyspergualin :Epstein Barr Virus. :European Consensus Lupus Activity Measurment. : The Euro-Lupus Nephritis Trial :Epithelial neutrophil activating protein-78. : Extractable nuclear antigen antibodies :Erythrocyte Sedimentation Rate. :End stage renal disease. : Rituximab in patients with Severe Systemic Lupus Erythematosus

FhT cells	: Follicular helper T cells
GBM	: Glomerular basement membrane .
GC	:Glucocortecoid.
GM-CSF	: Granulocyte macrophage colony stimulating factor
GWAS	: Genome-wide association study
HA-IgG	: Heat-aggregated IgG
HLA	:Human Leukocyte Antigens.
HMGB1	: High mobility group box 1 protein
ICAM-1	: Intracellular adhesion molecule-1.
ICOS	: Inducing costimulator
IFN	:Interferon.
IgA	: Immunoglobulin A.
IgG	: Immunoglobulin G.
IgG2	: Immunoglobulin G subclass 2
IL	:Interleukin.
IP-10	: IFN-gamma-induced protein 10
ISN/RPS	:International Society of Pathology/Renal Pathology Society.
ITGAM	:Integrin-α-M
IVP	: Intravenous pyelogram.
κβNF KIM-1	: kappa beta nuclear factor : kidney injury molecule-1
LAI	:Lupus Activity Index.
LDL	:Low density lipoproteins.
LN	:Lupus Nephritis.
LNDAI	: LN disease activity index
LUNAR	: The LUpus Nephritis Assessment with Rituximab
LPGDS	: lipocalin-type prostaglandin D-synthetase
mABs	: Monoclonal antibodies
MAC	: Complement membrane attack complex
MALDI-TOF MS	: Matrix Assisted Laser Desorption/Ionization Time Of Flight Mass Spectrometry

MASP	:Mannan-binding lectin-Associated Serine Protease.
MBL	:Mannan-Binding Lectin pathway.
MCP-1	:Monocyte chemoattractant proteins-1.
MCP-4	:Monocyte chemoattractant proteins-4.
MESNA	:Mercaptoethylamine sulfonate sodium.
MIP-1	:macrophage inflammatory proteins 1.
MLN	: membranous lupus nephritis
MMF	:Mycophenolate mofetil.
MPC-1	: Monocyte chemoattractant protein-1
MRL-Faslpr	: Mice homozygous for the apoptosis-defective Faslpr mutation
mRNA	: Messenger ribonucleic acid.
NFAT	: Nuclear factor of activated T cells
NGAL	: Neutrophil Gelatinase-Associated Lipocalin
NIH	:National Institutes of Health.
NSAIDs	:Non Steroidal Anti-Inflammatory Drugs.
NZB	: New Zealand Black mice
NZWF1	: New ZealandWhite F1 mice
PCR	: Polymerase chain reaction.
(PD-1)	: Programmed death 1 costimulatory receptor
PDGF	: Platelet-derived growth factor
PTEC	: Proximal tubular epithelial cells
PTPN22	the protein tyrosine phosphatase Lyp
PTT	: Partial thromboplastin time.
RANTES	:Regulated upon activated normal T cell expressed and secreted
RTX	:Rituximab.
SB2M/SCysC	: Serum Beta 2-Microglobulin/ Cystatin C Index
SCLE	: Subacute cutaneous lupus erythematosus.
SHP-2	: Nonreceptor protein tyrosine phosphatase
SLAM	:Systemic Lupus Activity Measure.

SLE	:Systemic Lupus Erythematosus.
SLEDI	:Systemic Lupus Erythematosus Disease Activity Index.
SELDI-TOF MS	: Surface Enhanced Laser Desorption Ionization Time Of Flight Mass Spectrometry
SLICC	:Systemic Lupus International Collaborating Clinics.
SMIP	:Small Modular ImmunoPharmaceutical.
SNPs	: Single nucleotide polymorphisms
TCR	: T cell receptor
TdT	: terminal deoxynucleotidyl transferase
TF	: transferrin
TGF	: Transforming growth factor
TLR4	: Toll-like receptor 4
TNF-alpha	:Tumor Necrosis Factor alpha.
TRAIL	: TNF related apoptosis-inducing ligand
Tregs	: T regulatory cells
TWEAK	: TNF-related weak inducer of apoptosis
UV	: Ultraviolet.
Th2, th1	: Lymphocyte T helper 2, T helper1
Th17	: T helper 17
TLR	: Toll-like receptors
TOSO/FAIM3	: a distinct Fc receptor for IgM expressed on B cells
WHO	:World Health Organization classification.

List of Tables

Item	Page
Table A:	24
Table B: The Systemic Lupus Erythematosus Disease	25
Activity Index (SLEDAI) 2000.	
Table C Systemic Lupus International Collaborating	29
Clincs/American College of Rheumatology	
(SLICC/ACR) Damage Index.	
Table (1): Comparison between the studied groups as	95
regards general data	
Table (2) Comparison between the studied groups as	95
regards quantitative lab data by using one	
way ANOVA test	
Table (3): Table (3) Comparison between the studied	95
groups as regards qualitative lab data by	
using chi-square test.	
Table (4) Comparison between the studied groups as	98
regards SLEDI, SDI and MDRD using one	
way ANOVA test.	
•	
Table (5) Comparison between the studied groups as	98
regards urinary IgM difference by using one	
way ANOVA test .	
	0.0
	98

Table6 . Frequency distribution of renal biopsy results	
among LN group:	
Table 7. Comparison between different grades in renal	99
biopsy regarding renal parameters in LN	
patients group:	
Table 8. Comparison between different grades in renal	100
biopsy regarding disease activity scoring	
systems in LN group patients:	
Table 9 . Comparison between different grades in renal	100
biopsy regarding urinary IGM in LN group	
patients	
Table (10) Correlation between urinary IgM versus	101
different variables among control group	
Table (11) Correlation between urinary IgM versus	101
different variables among LN group by using	
Spearman correlation.	
Table (12) Correlation between urinary IgM versus	102
different variables among SLE group by	102
using Spearman correlation.	
	4.0.5
Table (13) Correlation between urinary IgM versus	102

different variables among LN group by linear regression analysis	
inical regression analysis	
Table (14) Correlation between nephropathy versus	102
different predictors by binary logistic regression analysis	
Table 15: Multi-Regression Analysis for predictors of LN	`103
activity in SLE group versus LN group:	
Table 16 ROC curve analysis showing the diagnostic	104
performance of u-IgM and creatinine, BUN and protienuria for	
discriminating patient with LN from those	
SLE without nephritis	
Table 17 ROC curve analysis showing the diagnostic	108
performance of GFR, SDI-global, pyuria	
and heamaturia for discriminating patients	
with LN from those SLE without nephritis.	
Table 18 ROC curve analysis showing the diagnostic performance of	111
u-IgM and SLEDAI and their combination for	
discriminating patient with LN from those	
SLE without nephritis	
Table 19 ROC curve analysis showing the diagnostic	114

performance of	
u-IgM and combination of Anti ds-DNA with u-IgM	
fordiscriminating patients with LN from	
SLE without nephritis	
Table 20 DOC surve analysis showing the diagnostic	101
Table 20 ROC curve analysis showing the diagnostic	121
performance of	
u-IgM and combination of u-IgM with Anti ds-DNA	
and Proteinuria for discriminating those	
with SLE from healthy controls.	
Table 21 ROC curve analysis showing the diagnostic	125
performance of	
combination of u-IgM with Anti ds-DNA and	
Proteinuria for discriminating patients with	
SLE from healthy controls.	
DEE HOM Meaning Controls.	

List of Figures

Item	Page
Figure (1): ROC curve analysis showing the diagnostic	105
performance of Proteinuria, BUN, creatinine	
and u-IgM for discriminating patients with LN	
from those SLE	
Figure (2): ROC curve analysis showing the diagnostic	18
performance of GFR , SDI-global , pyuria and	
heamaturia for discriminating patients with LN	
from those SLE	
Figure (3): ROC curve analysis showing the diagnostic	111
performance of u-IgM and SLEDAI and their	
combination for discriminating patients with	
LN from those SLE without nephritis.	
Figure (4): ROC curve analysis showing the diagnostic	114
performance of u-IgM and Anti ds-DNA and	
their combination for discriminating patients	
with LN from SLE	
Figure (5): Comparison between SLE patients group and LN	115
patients group regarding SLEDAI-2K (global:	
0-105).	
Figure (6): Comparison between SLE patients group and LN	115
patients group regarding renal domain	
SLEDAI-2K (0-16),	
Figure (7): Comparison between SLE patients group and LN	116
patients group regarding SDI global damage	
score(0-47)	
Figure (8): Comparison between SLE patients group and LN	116