



THE ROLE OF SERUM RESISTIN IN PRIMARY KNEE OSTEOARTHRITIS

Thesis

Submitted for Partial Fulfillment of Master Degree
In Physical Medicine, Rheumatology and Rehabilitation

By

Salwa Mohamed Ahmed Ibrahim

(M.B;B.Ch.)

Faculty of Medicine - Ain Shams University

Supervised by

Dr. Mona Abdullah El-sebaie

Professor of Physical Medicine, Rheumatology
and Rehabilitation

Dr. Mohamed Ali Elwy

Professor of Physical Medicine, Rheumatology
and Rehabilitation

Dr. Mahmoud Mohamed Fathalla

Professor of Physical Medicine, Rheumatology
and Rehabilitation

Faculty of Medicine
Ain Shams University
2016

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْحَكِيمُ

صَدَقَ اللَّهُ الْعَظِيمُ



سورة البقرة آية (٣٢)

Acknowledgement

*I would like to start by thanking **ALLAH**, the most beneficent and the most merciful for his many blessings throughout my life and through whom everything is possible.*

*It is with sincere gratitude that I thank my supervisor, **Prof. Dr. Mona Abdullah El-Sebaie**, Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for her guidance and encouragement throughout my work. Her creative comments made completion of this work possible.*

*Thanks are extended to **Prof. Dr. Mohamed Ali Elwy**, Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for his great effort, continuous help and guidance.*

*I am greatly indebted to **Prof. Dr. Mahmoud Mohamed Fathalla**, Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for being such an outstanding teacher who devoted much of his time, effort and experience in supervising this work.*

*Last but not least, I would like to thank **my family** for their help and support.*

Safwa Mohamed

List of Contents

Title	Page
▪ List of Abbreviations	II
▪ List of Tables	VIII
▪ List of Figures	XI
▪ Introduction	1
▪ Aim of the Work	5
▪ Review of Literature	0
- Chapter one: Aetiology of Osteoarthritis	6
- Chapter two: Pathogenesis of Osteoarthritis.....	17
- Chapter three: Resistin	41
- Chapter four: Osteoarthritis and Resistin.....	61
▪ Patients and Methods	65
▪ Results	80
▪ Discussion	99
▪ Summary and Conclusion	107
▪ Recommendations	111
▪ References	112
▪ Arabic Summary	-

List of Abbreviations

μL	Microliter
ACL	Anterior cruciate ligament
ACLL	Anterior cruciate ligament laxity
ACR	American College of Rheumatology
Acrp-30	Adipocyte complement related protein - 30
ADL	Activity of Daily Living
ADMATSA	disintegrin and metalloproteinase with thrombospondin motifs
ADSF	Adipocyte specific secretory factor
AGEs	Advanced glycation end products
Akt	A serine/threonine kinase
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate kinase
ANA	Antinuclear antibody
AP	Alkaline phosphatase
apM1	Adipose most abundant gene transcript
ASAA	Acute phase serum amyloid A
AST	Aspartate aminotransferase
BMI	Body mass index
BMLOL	Bone marrow like oedema lesions
BMP	Bone morphogenic protein

List of Abbreviations

C/EBPα	CCAAT/enhancer binding protein α
C3	Complement component 3
CBC	Complete blood count
CCL	Chemokine C-C motif ligand
CCR 5	C-C chemokine receptor type 5
CD	Cluster of differentiation
CKD	Chronic kidney disease
CMKLR-1	Chemokine like receptor -1
COX - 2	Cyclooxygenase -2
CRP	C-Reactive Protein
CVDs	Cardiovascular diseases
CXCL	Chemokine C-X-C motif ligand
Cys	Cysteine
DM	Diabetes mellitus
ECM	Extracellular matrix
ELISA	Enzyme Linked Immune Sorbent Assay
Erk	Extracellular signal regulated kinase
ESR	Erythrocyte sedimentation rate
ET-1	Endothelin- 1
FIZZ	Found in inflammatory zone
FN	False negative
FP	False positive

List of Abbreviations

GBP-28	Gelatin Binding Protein - 28
GFR	Glomerular filtration rate
GLUT	Glucose transporter
GSK- 3	Glycogen synthase kinase-3
HDL	High density lipoprotein
HGF	Hepatocyte growth factor
HMM	High Molecular Mass
HS	Highly significant
ICAM-1	Intercellular adhesion molecule - 1
ICE	IL-1 β converting enzyme
IGF-1	Insulinlike growth factor -1
IL	Interleukin
IL -1R	Interleukin -1 receptor
IL-1RA	Interleukin -1 receptor antagonist
iNOS	Inducible nitric oxide synthase
IP-3	Inositol triphosphate
IP-3R	Inositol triphosphate receptor
IPFP	Infrapatellar fat pad
IRS-1	Insulin receptor substrate -1
IκB	Inhibitor of kappaB
KDa	Kilo Dalton
kg/m²	Kilogram per meter square
K-L	Kellgren and Lawrence

List of Abbreviations

LCLL	Lateral collateral ligament laxity
LCN2	Lipocalin 2
LMM	Low Molecular Mass
LMW	Low molecular weight
LN	Lupus nephritis
LPS	Lipopolysaccharide
LTB 4	Leukotriene B4
LTC 4	Leukotriene C4
mRNA	messenger Ribonucleic acid
MAPKS	Mitogen activated protein kinases
MCLL	Medial collateral ligament laxity
MCP-1	Monocytechemoattractant protein-1
mm/hr	Millimeter per hour
MMP	Matrix metalloproteinase
MRI	Magnetic Resonance Imaging
NAFLD	Non alcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis.
ng/ml	Nanogram per milliter
NK κB	Nuclear factor kappa B
NOS	Nitric oxide synthase
NS	Non significant
NSAIDS	Non steroidal antiinflammatory drugs
OA	Osteoarthritis

List of Abbreviations

P	Level of significance
PAI-1	Plasminogen activator inhibitor- 1
PBEF	Pre B cell colony enhancing factor
PBMCs	Peripheral blood mononuclear cells
PCLL	Posterior cruciate ligament laxity
PFF	Patellofemoral friction
PGE2	Prostaglandin E2
PGs	Prostaglandins
PI3K	Phosphoinositol 3 Kinase
PLA2	Phospholipase A2
PLC	Phospholipase C
PPAR-γ	Peroxisome proliferator activated receptor-γ
PTH	Parathyroid hormone
r	Spearman rank coefficient or Pearson correlation
RA	Rheumatoidarthritis
RANTES	Regulated on Activation Normal T Cell Expressed and Secreted
RARRES-2	Retinoic acid receptor responder- 2
RELMS	Resistin like molecules
RETN	Resistin gene
RF	Rheumatoid factor
RNA	Ribonucleic acid

List of Abbreviations

RNS	Reactive nitrogen species
ROC	Receiver Operating Characteristics
ROM	Range of motion
ROS	Reactive oxygen species
S	Significant
SAA 3	Serum Amyloid A3
SD	Standard deviation
SF	Synovial fluid
SFOA	Synovial fluid signs of osteoarthritis
SLE	Systemic lupus erythematosus
SOCS-3	Suppressor of cytokine signaling -3
SPSS	Statistical package for Social Science
T2DM	Type 2 diabetes mellitus
TACE	TNF- α converting enzyme
TGF-β	Transforming growth factor - β
TIMP	Tissue inhibitor of metalloproteinases
TKR	Total knee replacement
TLR- 4	Toll like receptor
TN	True negative
TNF- α	Tumor necrosis factor -alpha
TNFR	Tumor necrosis factorreceptor
TP	True positive
TZDs	Thiazolidinediones

List of Abbreviations

UPA	Urokinase plasminogen activator
VAS	Visual analog scale
VCAM-1	vascular cell adhesion molecule- 1
VEGFR	Vascular endothelial growth factor receptor
VLDL	Very low density lipoprotein
vs	Versus
VSMC	Vascular smooth muscle cell
WAT	White adipose tissue
WOMAC	Western Ontario and McMaster Universities

List of Tables

Table No.	Title	Page
Table (1):	Enzymes associated with ECM degradation	34
Table (2):	ACR Classification Criteria for knee OA	66
Table (3):	Age and anthropometric data	80
Table (4):	Sex distribution among controls	80
Table (5):	Description of serum resistin level among controls	81
Table (6):	Age and anthropometric data	81
Table (7):	Sex distribution among patients	81
Table (8):	Description of special habits, menstrual history, drug history and family history of OA among patients	82
Table (9):	Description of disease duration	82
Table (10):	Description of laterality and most affected side	83
Table (11):	Description of clinical data	84
Table (12):	Description of functional status assessment using WOMAC score	85
Table (13):	Radiological classification of patients according to K-L grading	86
Table (14):	Description of laboratory data among study patients	86

List of Tables (Cont.)

Table No.	Title	Page
Table (15):	Correlation between serum resistin level and some parameters among study patients	87
Table (16):	Correlation between Disease duration and K-L grading	89
Table (17):	Correlation between serum resistin level and the following: WOMAC and K-L grading among study patients	89
Table (18):	Comparison between mean values of serum resistin in patient groups classified according to sex, taking of the following drugs: NSAIDs & Glucosamine	92
Table (19):	Comparison between serum resistin level and clinical data in patients group...	93
Table (20):	Comparison between mean values of serum resistin in patient groups classified according to K-L grading	94
Table (21):	Comparison between patients and controls as regards age and anthropometric data.....	96
Table (22):	Comparison between patients and controls as regards sex.....	96
Table (23):	Comparison between patients and controls as regards serum resistin level	97

List of Tables (Cont.)

Table No.	Title	Page
Table (24):	ROC (receiver operating characteristic) Curve for diagnosis of cases from controls using serum resistin level.....	98

List of Figures

Figure No.	Title	Page
Fig. (1):	Schematic representation of key catabolic events of cartilage matrix in OA.....	18
Fig. (2):	Interaction between synovium and cartilage in OA	24
Fig. (3):	Ribbon diagram of resistin and RELM- β	45
Fig. (4):	Structure of human RETN, the gene coding for resistin	46
Fig. (5):	Resistin induced intracellular signaling pathways.....	51
Fig. (6):	Correlation between serum resistin level and age in patients group	87
Fig. (7):	Correlation between serum resistin level and disease duration in patients group.....	88
Fig. (8):	Correlation between serum resistin level and total WOMAC (likert) in patients group.....	90
Fig. (9):	Correlation between serum resistin level and total WOMAC (VAS) in patients group.....	90
Fig. (10):	Correlation between serum resistin level and K-L grading in patients group	91