

Fracture Risk Assessment In Female Patients with Systemic Lupus Erythematosus

Thesis

*Submitted for the partial fulfillment of M.D. Degree
in Internal Medicine*

By

Dina Mostafa Abd EL-Khalik

(M.B.B.CH. M.Sc. Internal Medicine)

Under supervision of

Prof. Dr. Eman Ahmed Hafez

Professor of Geriatric Medicine

Faculty of Medicine - Ain Shams University

Prof. Dr. Sarah Ahmed Hamza

Professor of Geriatric Medicine

Faculty of Medicine, Ain Shams University

Prof. Dr. Samah Abdel Rahman EL Bakry

Professor of Internal Medicine and Rheumatology

Faculty of Medicine, Ain Shams University

Dr. Shafica Ibrahim Ibrahim

Lecturer of Internal Medicine and Rheumatology

Faculty of Medicine, Ain Shams University

Dr. Caroline Samy Morad

Lecturer of Internal Medicine and Rheumatology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2016

تقييم احتمالية التعرض للكسور لدى الإناث المصابات بالذئبة الحمراء

رسالة توطئة للحصول على درجة الدكتوراة في الباطنة العامة
مقدمة من

الطبيبة/ دينا مصطفى عبد الخالق

بكالوريوس الطب والجراحة - ماجستير أمراض الباطنة

تحت إشراف

أ.د / إيمان أحمد حافظ

أستاذ أمراض الباطنة العامة والروماتيزم

كلية الطب - جامعة عين شمس

أ.د/ سارة احمد حمزة

أستاذ طب و صحة المسنين

كلية الطب - جامعة عين شمس

أ.د/ سماح عبد الرحمن البكرى

أستاذ أمراض الباطنة العامة والروماتيزم

كلية الطب - جامعة عين شمس

د / شفيقة إبراهيم إبراهيم

مدرس أمراض الباطنة العامة والروماتيزم

كلية الطب - جامعة عين شمس

د / كارولين سامى مراد

مدرس أمراض الباطنة العامة والروماتيزم

كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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

صَدَقَ اللَّهُ الْعَظِيمُ



سورة البقرة آية (٣٢)



ACKNOWLEDGEMENT

*First, I thank **God** for granting me the power to proceed and to accomplish this work.*

*I would like to express my deepest gratitude and ultimate thanks to **Prof. Dr. Eman Ahmed Hafez**, Professor of Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University, for accepting to supervise this work and for her constant help, valuable supervision, guiding comments and a wealth of references throughout the work. She generously devoted much of her precious time and provided unlimited support, effort and in depth guidance together with her enthusiastic interest, I sincerely appreciate all the encouragement and support given by her.*

*I am deeply grateful to **Prof. Dr. Sarah Ahmed Hamza**, Professor of Geriatric Medicine, Faculty of medicine, Ain Shams University, I am grateful for her helpful notes and valuable recommendations throughout this work.*

*I am eternally grateful to **Prof. Dr. Samah Abdel Rahman EL Bakry**, Professor of Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University for her great help and kind advice, careful supervision. She gave me much of her time, effort and her great experience and knowledge.*

*My sincere thanks and deep appreciation goes to **Dr. Shafica Ibrahim Ibrahim**, Lecturer of Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University, for her faithful guidance, valuable comments and constructive criticism, meticulous revision of the thesis helping me to accomplish this work, the best it could be.*

*I assert my thanks to **Dr. Caroline Samy Morad**, Lecturer of Internal Medicine and Rheumatology, Ain Shams University, for her close and kind supervision, her constant support and scientific guidance, for her trust in my performance and my work..*

Finally, I would like to express my love and respect to my family for their valuable emotional support and continuous encouragement which brought the best out of me. I owe you every achievement throughout my life.



Dina Mostafa Abd EL-Khalik

List of Contents

Title	Page
• List of Abbreviations	I
• List of Tables.....	V
• List of Figures	X
• Introduction.....	1
• Aim of the Work	3
• Review of Literature.....	
• Chapter 1: Systemic Lupus Erythematosus	4
• Chapter 2: osteoporosis and fractures in SLE	50
• Patients and Methods	90
• Results.....	99
• Discussion	144
• Summary and Conclusion	165
• Recommendations	167
• References.....	169
• Arabic Summary	-
-	

List of Abbreviations

Abbreviation	Full term
1,25[OH]2D	1,25-dihydroxyvitamin D
5-HTT	5- hydroxy tryptamine
AACE	American Association of Clinical Endocrinologists
Ab	Antibody
ACD	Anemia of chronic disease
ACEI	Angiotensin converting enzyme inhibitor
ACL	anticardiolipin antibodies
aCL	Anti-cardiolipin antibody
ACLE	Acute Cutaneous Lupus Erythematosus
ACR	American College of Rheumatology
AIHA	Autoimmune hemolytic anemia
ALKP	Alkaline phosphatase
ALT	Alanine Amino Transferase
AMPs	Antimicrobial peptides
ANA	Antinuclear antibody
ANCA	Antineutrophil cytoplasmic antibody
Anti-DNA	Anti Deoxyribonucleic acid
Anti-ds DNA	Anti double stranded Deoxyribonucleic acid
Anti-RNP	Antiribonuclear protein antibody
Anti-Sm	Anti-Smith antibody
APCs	Antigen-presenting cells
aPL	Anti-phospholipid antibody
APLS	Antiphospholipid Syndrome
AST	Aspartate amino transferase
AUC	Area under curve
BAFF	B cell activating factor
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BP	Bisphosphonates
BSAP	Serum bone specific alkaline phosphatase
BTMs	Bone turnover markers

** List of Abbreviations**

BUN	Blood Urea Nitrogen
Ca	Calcium
CAD	Coronary artery disease
CAPS	Catastrophic APS
CBC	Complete blood count
CI	Chronicity index
CLD	Chronic liver disease
CMR	Cardiovascular magnetic resonance
CMV	Cytomegalovirus
CRP	C-reactive protein
CS	Corticosteroids
CsA	Cyclosporin A
CSF	Cerebrospinal fluid
CTX	Serum C-telopeptide
DCs	dendritic cells
DEXA	Dual energy X-ray absorptiometry
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
Ds	Doublestranded
DVT	Deep venous thrombosis
EBNA-1	EBV nuclear antigen 1
EBV	Epstein–Barr virus
ECLAM	European community Lupus Activity Measure
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disease
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FRAX®	The WHO Fracture Risk Assessment Tool
FN	Femoral neck
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
GIOP	Glucocorticoid-induced osteoporosis
GIT	Gastrointestinal tract
Hb	Hemoglobin
HCQ	Hydroxychloroquine
Hcy	Homocysteine
HLA	Human leukocyte antigens
HRCT	High resolution computed tomography

List of Abbreviations

HRT	Hormonal replacement therapy
HS	Highly significant
ICs	Immune complexes
IDA	Iron deficiency anemia
Ig	Immunoglobulin
IL	Interleukin
ILD	Interstitial lung disease
INF-α	Interferon- α
ISN	International Society of Nephrology
IQR	Interquartile range
IUGR	Intrauterine growth restriction
LAC	lupus anticoagulant antibodies
LBMD	Low bone mineral density
LDL	Low density lipo protiens
LN	Lupus nephritis
LS	Lumbar spine
MRA	Magnetic resonance angiography
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
NOF	National Osteoporosis Foundation
NOGG	National Osteoporosis Guideline Group
NPSLE	Neuropsychiatric systemic lupus erythematosus
NS	Non significant
NSAIDs	Nonsteroidal anti-inflammatory drugs
NTX	Urinary N-telopeptide
OC	Osteocalcin
OP	Osteoporosis
PAH	Pulmonary arterial hypertension
PE	Pulmonary embolism
PINP	aminoterminal propeptide of type I procollagen
PO4	phosphorus
PPI	Proton pump inhibitors
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
RA	Rheumatoid arthritis
RANKL	Nuclear factor κ B ligand

*** List of Abbreviations***

RANTES	Regulated on Activation Normal T Cell Expressed and Secreted
RBP s	RNA binding proteins
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
S	Significant
SD	Standard deviations
SE	Standard error
SELENA	Safety of Estrogen in lupus Erythematosus National Assessment
SERMs	Selective oestrogen receptor modulators
SLAM	Systemic Lupus Activity Measure
SLE	Systemic lupus erythematosus
SLEDAI	SLE disease activity index
SLICC	Systemic lupus international collaborating clinics
SPF	Skin protection factor
SPSS 20	Statistical package for Social Science
SSRI	Selective serotonin reuptake inhibitors
TGF β	Transforming growth factor β (TGF β):
TIA	Transient ischemic stroke
TLC	Total leucocytic count
TLRs	Toll like receptors
TNF	Tumor necrosis factor
Treg	Regulatory T cells
US	Ultrasound
UV	Ultraviolet
VDR	Vitamin D receptor
WHO	World Health Organization

List of Tables

Table No.	Title	Page
Table (1)	: Nineteen case definitions for NPSLE based on the 1999 ACR recommendations in neuropsychiatric lupus syndrome	26
Table (2)	: The 1997 ACR Classification Criteria of SLE	32
Table (3)	: Recent SLICC Classification Criteria of SLE	33
Table (4)	: 2015 ACR/SLICC revised criteria for diagnosis of SLE	34
Table (5)	: Auto antibodies of SLE	36
Table (6)	: SLE disease activity index	39
Table (7)	: (SLICC/ACR) Damage Index.	41
Table (8)	: WHO diagnostic criteria for osteoporosis	52
Table (9)	: FDA-approved medications for osteoporosis	79
Table (10)	: Pharmacological therapies for osteoporosis	87
Table (11)	: ACR recommendations for postmenopausal women and men ≥ 50 years using GC therapy ≥ 3 months	89
Table (12)	: ACR recommendations for premenopausal women and men < 50 years with a history of fracture.	89
Table (13)	: FRAX clinical risk factors for the assessment of fracture probability	96
Table (14)	: Demographic data among 70 SLE female patients	99
Table (15)	: Clinical data among 70 SLE female patients	99
Table (16)	: Treatments prescribed to the 70 SLE female patients during the course of disease	100
Table (17)	: laboratory data among 70 SLE female patients	101
Table (18)	: autoantibody profile and urine analysis among 70 female patients with SLE	101
Table (19)	: Doses of drugs prescribed to the 70 SLE female patients	102
Table (20)	: BMD variables for the 70 SLE female patients	102

List of Tables

Table No.	Title	Page
Table (21)	: frequency of osteoporosis and osteopenia in the 70 SLE female patients	102
Table (22)	: FRAX scores among the 70 SLE female patients	103
Table (23)	: Comparison between patients with NBMD and LBMD at LS and FN as regard some demographic and clinical data using Student's t-test	104
Table (24)	: Comparison between patients with NBMD and LBMD at LS and FN as regard the presence of previous fractures using Chi square t-test	105
Table (25)	: Comparison between patients with NBMD and LBMD at LS and FN as regard the menstrual status using chi square	106
Table (26)	: Comparative study between patients with NBMD and LBMD at LS and FN as regard BMD variables using Student's t-test	107
Table (27)	: Comparison between patients with NBMD and LBMD at LS and FN as regard FRAX-MAJOR and FRAX-HIP using Mann Whitney's test	107
Table (28)	: Comparison between patients with NBMD and LBMD at LS and FN as regard FRAX-Major $\geq$ 20% and FRAX-HIP $\geq$ 3% using chi-square	109
Table (29)	: Comparison between patients with NBMD and LBMD at LS and FN as regard some laboratory investigations using Student's t-test	110
Table (30)	: Comparison between patients with NBMD and LBMD at LS and FN as regard medications received by patients using chi-square	111
Table (31)	: Comparison between patients with NBMD and LBMD at LS and FN as regard the cumulative and current dose of corticosteroids using Student's t-test	113

List of Tables

Table No.	Title	Page
Table (32)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard some demographic and clinical data using Student's t-test	113
Table (33)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard menstrual status using Fisher exact test	114
Table (34)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard the presence of previous fractures using Chi square t-test	115
Table (35)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard BMD variables using Student's t-test	116
Table (36)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard FRAX-MAJOR and FRAX-HIP using Mann Whitney's test	117
Table (37)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard FRAX-Major $\geq$ 20% and FRAX-HIP $\geq$ 3% using chi-square	118
Table (38)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard some laboratory investigations using Student's t-test	120
Table (39)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard medications received by patients using chi-square	121
Table (40)	: Comparison between patients with osteopenia and osteoporosis at LS and FN as regard the cumulative dose of corticosteroids using Student's t-test	123
Table (41)	: Correlation between BMD at LS and FN and some demographic and clinical data among 70 SLE patients using Pearson correlation test	123

Table No.	Title	Page
Table (42)	: Correlation between BMD at LS and FN and some laboratory investigations among 70 SLE patients using Pearson correlation test	125
Table (43)	: Correlation between BMD at LS and FN and some medications used among 70 SLE patients using Pearson and spearman correlation test	126
Table (44)	: Correlation between serum Osteocalcin and some demographic and clinical data among 70 SLE patients using Pearson correlation test	128
Table (45)	: Correlation between serum osteocalcin and some laboratory investigations among 70 SLE patients using Pearson correlation test	129
Table (46)	: Correlation between serum osteocalcin and some medications used among 70 SLE patients using Pearson and spearman correlation test	130
Table (47)	: Correlation between FRAX-MAJOR, FRAX-hip and some demographic and clinical data among 70 SLE patients using Pearson correlation test	132
Table (48)	: Correlation between FRAX-MAJOR, FRAX-HIP and some laboratory investigations among 70 SLE patients using Pearson correlation test	134
Table (49)	: Correlation between FRAX-MAJOR, FRAX-hip and some medications used among 70 SLE patients using Pearson and spearman correlation test	135
Table (50)	: Correlation between FRAX-MAJOR, FRAX-HIP, serum osteocalcin, BMD LS, BMD FN, T-score, Z-score and each other among 70 SLE patients	138
Table (51)	: An agreement between FRAX MAJOR $\geq$ 20 and FRAX HIP $\geq$ 3	139
Table (52)	: Roc curve of serum osteocalcin level to discriminate normal BMD from low BMD	140

*** List of Tables***

Table No.	Title	Page
Table (53)	: Roc curve of serum osteocalcin to discriminate osteopenia from osteoporosis	140
Table (54)	: Linear Regression model for the Factors affecting BMD LS	141
Table (55)	: Linear Regression model for the Factors affecting BMD FN	142
Table (56)	: Linear Regression model for the Factors affecting FRAX MAJOR	142
Table (57)	: Linear Regression model for the Factors affecting FRAX HIP	143