

**ROLE OF VITAMIN D IN THE
PATHOGENESIS OF MULTIPLE SCLEROSIS
AND ITS EFFECT ON BONE AND COGNITION**

THESIS

**Submitted for partial fulfillment of M.Sc. Degree in
Neuropsychiatry**

By

Mohamed Ibrahim Mohamed Hegazy

M.B.B.Ch. – Cairo University

Supervised by

Prof. Dr. Ahmed Talaat El Ghoneimy

Professor of Neurology Cairo University
Head of Neurology Department Cairo University

Prof. Dr. Adel Hassanein Gad

Professor of Neurology – Cairo University

Dr. Hatem Samir Mohamed

Ass. Professor of Neurology – Cairo University

Department of Neurology
Faculty of medicine
Cairo University

2008

بسم الله الرحمن الرحيم

"ويسئلك عن الروح قل الروح من أمر ربي
وما أوتيتم من العلم إلا قليلا"

صدق الله العظيم
(الآية: ٨٥، سورة الإسراء)

ACKNOWLEDGEMENT

I would like to express my deepest gratitude and sincere thanks to Prof. Dr. **Ahmed Talaat El Ghoneimy**, Professor and head of Neurology Department, Cairo University, the unique as a God Father, for his continuous guidance. I appreciate his hard support and powerful push.

I am extremely grateful to Prof. Dr. **Adel Hasanein Gad**, Professor of Neurology, Cairo University, for his great care, continuous guidance and valuable suggestion, saving no effort or time during the whole work.

I wish to express my deepest thanks and gratitude to Dr. **Hatem Samir Mohamed**, Assistant Professor of Neurology, Cairo University, for his kind support, constructive criticism and valuable assistance without which, this work could not have been accomplished.

I would like to extend my appreciation and deep thanks to Dr. **Neveen Mohie**, Lecturer of Neurology, Cairo University, for her kind help and guidance throughout this work.

I would like to thank Dr. **Gehan Ramzy**, Lecturer of Neurology, Cairo University for her assistance and guidance in the clinical part of this work.

I would also like to thank Dr. **Marwa Farghaly**, Assistant Lecturer of Neurology, Cairo University, for her continuous support and advice, and Dr. **Amr Hassan**, Assistant Lecturer of Neurology, Cairo University, for helping me in the editing of this work.

I wish to thank Dr. **Susan Brown**, the director of the Osteoporosis Education Project (OEP) for giving us permission to use the “adult osteoporosis risk assessment questionnaire”.

I also wish to thank members of Neurology Department, Cairo University, for their support and encouragement throughout the work.

Finally, I am really grateful to all patients who participated in this work.

Mohamed Hegazy

2008

TO MY FAMILY

CONTENTS

| | Page |
|---|------|
| Abstract | |
| Acknowledgement | |
| List of Abbreviations | |
| List of Tables | |
| List of Figures | |
| Introduction | 1 |
| Aim of the Work | 3 |
| Review of Literature: | |
| . Pathogenesis of multiple sclerosis | 4 |
| . Vitamin D physiology and its effect on bone | 23 |
| . Vitamin D and multiple sclerosis | 35 |
| . Vitamin D and cognition | 47 |
| . Multiple sclerosis and bone | 51 |
| . Multiple sclerosis and cognition | 61 |
| Subjects and Methods | 81 |
| Results | 96 |
| Summary of Results | 135 |
| Discussion | 137 |
| Summary and Conclusions | 149 |
| Recommendations | 154 |
| References | 155 |
| Appendices | 226 |
| Arabic Summary | |

LIST OF ABBREVIATIONS

| | |
|--------------|--|
| ADAM | A Disintegrin And Metalloproteinase Domain |
| aBMD | Areal Bone Mineral Density |
| AMP | Adenosine Monophosphate |
| ANOVA | Analysis of Variance |
| APCs | Antigen Presenting Cells |
| ATP | Adenosine Triphosphate |
| AZA | Azathioprine |
| BBB | Blood-Brain Barrier |
| BM | Bone Marrow |
| BMC | Bone Mineral Content |
| BMD | Bone Mineral Density |
| BMD H | Bone Mineral Density at Hip joint |
| BMD L | Bone Mineral Density at Lumbar spine |
| BMD W | Bone Mineral Density at Wrist joint |
| BMI | Body Mass Index |
| BRB | Brief Repeatable Battery |
| Ca i | Ionized Calcium |
| Ca T | Total Calcium |
| CBC | Complete blood count |
| CCL | Chemokine C-Motif Ligand |
| CD | Clusters Of Differentiation |
| CDR | Clinical Dementia Rating |
| CDT | Clock Drawing Test |
| CLIA | Chemiluminiscent Enzyme Immunoassay |
| CMV | Cytomegalovirus. |
| CNS | Central Nervous System |
| CPM | Cyclophosphamide |
| CSF | Cerebrospinal Fluid |
| CXCL | Chemokine (C-X-C Motif) Ligand |
| DC | Dendritic Cells |
| DSST | Digit Symbol Substitution Test |
| DXA | Dual Energy X-Ray Absorptiometry |

| | |
|-------------------|---|
| EAE | Experimental Allergic Encephalomyelitis |
| EBV | Epstein-Barr Virus |
| EDSS | Expanded Disability Status Scale |
| FBS | Fasting Blood Sugar |
| FLAIR | Fluid Attenuated Inversion Recovery |
| FNB | Food and Nutrition Board |
| FSS | Fatigue Severity Scale |
| FST | Faces Symbol Test |
| FST 90 | Face Symbol Test 90 seconds |
| FST T | Face Symbol Test Total |
| GH | Growth Hormone |
| GIO | Glucocorticoids Induced Osteoporosis |
| HHV | Human Herpes Virus |
| HLA | Human Leukocyte Antigen |
| HPT | Hyperparathyroidism |
| IFN | Interferon |
| IGF | Insulin-Like Growth Factor |
| Igs | Immunoglobulins |
| IL | Interleukin |
| IM | Immunomodulatory |
| iNOS | Inducible Nitric Oxide Synthase |
| ISCD | International Society for Clinical Densitometry |
| IU | International Units |
| JNK | c-Jun N-terminal Kinase |
| LFA-1 | Leukocyte Functional Antigen. |
| M | Mean |
| MAP kinase | Mitogen-Activated Protein Kinase |
| MBP | Myelin Basic Protein |
| MCP | Monocyte Chemotactic Protein |
| MHC | Major Histocompatibility Complex |
| MMF | Mycophenolate Mofetil |
| MMPs | Matrix Metalloproteinases |
| MMSE | Mini-Mental State Examination |
| MP | Methyl Prednisolone |

| | |
|--------------------------------|--|
| MRI | Magnetic Resonance Imaging |
| MRS | Magnetic Resonance Spectroscopy |
| MS | Multiple Sclerosis |
| MSNQ | MS Neuropsychological Screening Questionnaire |
| NG2 | Neural Glia Antigen 2 |
| NKT | Natural Killer T Cell |
| NO | Nitric Oxide |
| NP | Neuropsychological |
| OEP | Osteoporosis Education Project |
| OPG | Osteoprotegerin |
| PASAT | Paced Auditory Serial Addition Task |
| PET | Positron Emission Tomography |
| PMN | Polymorphnuclear Neutrophils |
| PPBS | Post Prandial Blood Sugar |
| PPMS | Primary Progressive Multiple Sclerosis |
| PTH | Parathyroid hormone |
| PTHrP | PTH Related Peptide |
| RANK | Receptor Activator Nuclear Factor-Kb |
| RANKL | Receptor Activator Nuclear Factor-Kb Ligand |
| RANTES | Regulated Upon Activation, Normal T-Cell Expressed, and Secreted |
| ROI | Regions of Interest |
| RRMS | Relapsing-Remitting Multiple Sclerosis |
| SBT | Short Blessed Test |
| SD | Standard Deviation |
| SDMT | Symbol Digit Modalities Test |
| SHPT | Secondary Hyperparathyroidism |
| SPMS | Secondary-Progressive Multiple Sclerosis |
| TGF-β | Transforming Growth Factor Beta |
| Th1 | T Helper 1 |
| Th2 | T Helper 2 |
| TLR | Toll-Like Receptors |
| TNF-α | Tumor Necrosis Factor-A |
| TRAF-6 | TNF Receptor Associated Factor-6 |
| TRAIL | Tumor Necrosis Factor Related Apoptosis-Including Ligand |
| Treg | Regulatory T Cell (Suppressor T Cell) |

| | |
|---------------|---------------------------------|
| UV | Ultraviolet |
| VCAM-1 | Vascular Cell Adhesion Molecule |
| VDR | Vitamin D Receptors |
| VEP | Visual Evoked Potential |
| VLA-4 | Very Late Antigen-4 |
| WHO | World Health Organization |

LIST OF TABLES

| Table | Title | Page |
|-------|--|------|
| 1 | Glucocorticoids equivalent dose | 83 |
| 2 | Normative data for PASAT Gronwall 3 seconds version ... | 89 |
| 3 | Normative data for the FST | 90 |
| 4 | World Health Organization classification of Bone Mineral Density | 93 |
| 5 | Age distribution in study groups | 97 |
| 6 | School attendance in study groups | 98 |
| 7 | Type of Multiple Sclerosis in study groups | 98 |
| 8 | Duration of illness in study groups | 99 |
| 9 | Severity of multiple sclerosis as assessed by EDSS and FSS | 100 |
| 10 | VEP affection in study groups | 100 |
| 11 | Correlation between duration of illness and EDSS | 100 |
| 12 | Mean level of vitamin D in study groups | 101 |
| 13 | Vitamin D status in study groups | 101 |
| 14 | Vitamin D status in MS types | 102 |
| 15 | Vitamin D level in females and males | 103 |
| 16 | Correlation between vitamin D level and age | 103 |
| 17 | Correlation between vitamin D level and markers of calcium metabolism | 104 |
| 18 | Correlation between vitamin D level and disease severity as assessed by EDSS | 104 |
| 19 | Correlation between vitamin D level and duration of illness | 105 |
| 20 | Correlation between vitamin D level and cumulative dose of multiple sclerosis treatment..... | 105 |
| 21 | Correlation between vitamin D level and bone indices..... | 106 |
| 22 | Markers of calcium metabolism in study groups..... | 107 |
| 23 | Markers of calcium metabolism in MS types..... | 108 |

| Table | Title | Page |
|--------------|--|-------------|
| 24 | Markers of calcium metabolism in females and males..... | 109 |
| 25 | Correlation between markers of calcium metabolism and age | 109 |
| 26 | Correlation between markers of calcium metabolism and duration of illness in months..... | 110 |
| 27 | Correlation between markers of calcium metabolism and disease severity as assessed by EDSS and FSS..... | 110 |
| 28 | Correlation between markers of calcium metabolism and cumulative dose of multiple sclerosis treatment..... | 111 |
| 29 | Calcium Supplementation status in study groups..... | 112 |
| 30 | Correlation between cumulative dose of calcium supplementation and markers of calcium metabolism..... | 113 |
| 31 | Correlation between cumulative dose of calcium supplementation and disease severity as assessed by EDSS and FSS..... | 113 |
| 32 | Bone indices in study groups..... | 114 |
| 33 | Bone indices in MS types..... | 115 |
| 34 | Bone indices in females and males..... | 116 |
| 35 | Bone status in study groups..... | 118 |
| 36 | Bone status in MS types..... | 118 |
| 37 | Bone status in females and males..... | 119 |
| 38 | Correlation between bone indices and age..... | 119 |
| 39 | Correlation between risk of developing osteoporosis as assessed by osteoporosis questionnaire and BMD..... | 120 |
| 40 | Correlation between bone indices and duration of illness in months..... | 120 |
| 41 | Correlation between bone indices and disease severity as assessed by EDSS and FSS..... | 121 |

| Table | Title | Page |
|--------------|---|-------------|
| 42 | Correlation between bone indices and cumulative dose of multiple sclerosis treatment..... | 122 |
| 43 | Cognitive tests scores in study groups..... | 123 |
| 44 | Cognitive function tests in study groups..... | 124 |
| 45 | The scores of cognitive function tests in MS types..... | 126 |
| 46 | Correlation between cognitive function tests and age..... | 126 |
| 47 | Correlation between cognitive function tests and total years of school attendance..... | 127 |
| 48 | Correlation between cognitive function tests and vitamin D level..... | 128 |
| 49 | Correlation between cognitive function tests and markers of calcium metabolism..... | 129 |
| 50 | Correlation between cognitive function tests and cumulative dose of calcium supplementation..... | 131 |
| 51 | Correlation between cognitive function tests and duration of illness in months..... | 132 |
| 52 | Correlation between cognitive function tests and FSS..... | 133 |
| 53 | Correlation between cognitive function tests and cumulative dose of multiple sclerosis treatment..... | 134 |

LIST OF FIGURES

| Fig. | Title | Page |
|-------------|---|-------------|
| 1 | Leukocytes in MS from activation to demyelination | 7 |
| 2 | Various factors influencing the onset of MS | 13 |
| 3 | Cellular contributions to MS | 18 |
| 4 | Acquisition of vitamin D in humans..... | 25 |
| 5 | Effect of vitamin D on immune cells | 38 |
| 6 | A proposed model of MS pathogenesis | 46 |
| 7 | Direct and indirect effects of glucocorticoids on bone | 54 |
| 8 | DXA General Electric Lunar [®] scanner | 92 |
| 9 | Gender distribution in study groups | 97 |
| 10 | Duration of Illness in study groups | 99 |
| 11 | Vitamin D level in MS types | 102 |
| 12 | Alkaline Phosphatase in study groups | 107 |
| 13 | Alkaline phosphatase in all MS types | 108 |
| 14 | Calcium Supplementation status in study groups | 112 |
| 15 | BMD H in study groups | 114 |
| 16 | BMD H in MS Types | 115 |
| 17 | Osteoporosis questionnaire mean score in females and males | 116 |
| 18 | BMD W in females and males. | 117 |
| 19 | Bone status in study groups | 117 |
| 20 | Correlation between risk of developing osteoporosis as assessed by osteoporosis questionnaire and duration of illness | 121 |
| 21 | Correlation between BMD H and EDSS | 122 |

| Fig. | Title | Page |
|-------------|---|-------------|
| 22 | Correlation between risk of developing osteoporosis as assessed by osteoporosis questionnaire and cumulative dose of steroids | 123 |
| 23 | PASAT in study groups | 124 |
| 24 | FST 90 in study groups | 125 |
| 25 | FST T in study groups | 125 |
| 26 | Correlation between PASAT score and total years of school attendance | 127 |
| 27 | Correlation between FST 90 and parathyroid hormone in group 1..... | 130 |
| 28 | Correlation between 90 and FSS in whole study population | 133 |