POSTMENOPAUSAL OSTEOPOROSIS IN RELATION TO SEX HORMONES AND DIFFERENT LINES OF TREATMENT

THESIS

Submitted in Partial Fulfillment of the Requirements for The M.D. Degree in Physical Medicine

By

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الكليـــة:

صفحـــة العنـــــوان

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الدرجـة العلميـــة : ...ماجستير...العلوم...المصرية...في التربية عمل
القسم التابع لـــــه : ...مناهج...وطرق...تدريس...في التربية عمل
أســـم الكليـــــة : ...التربية.....
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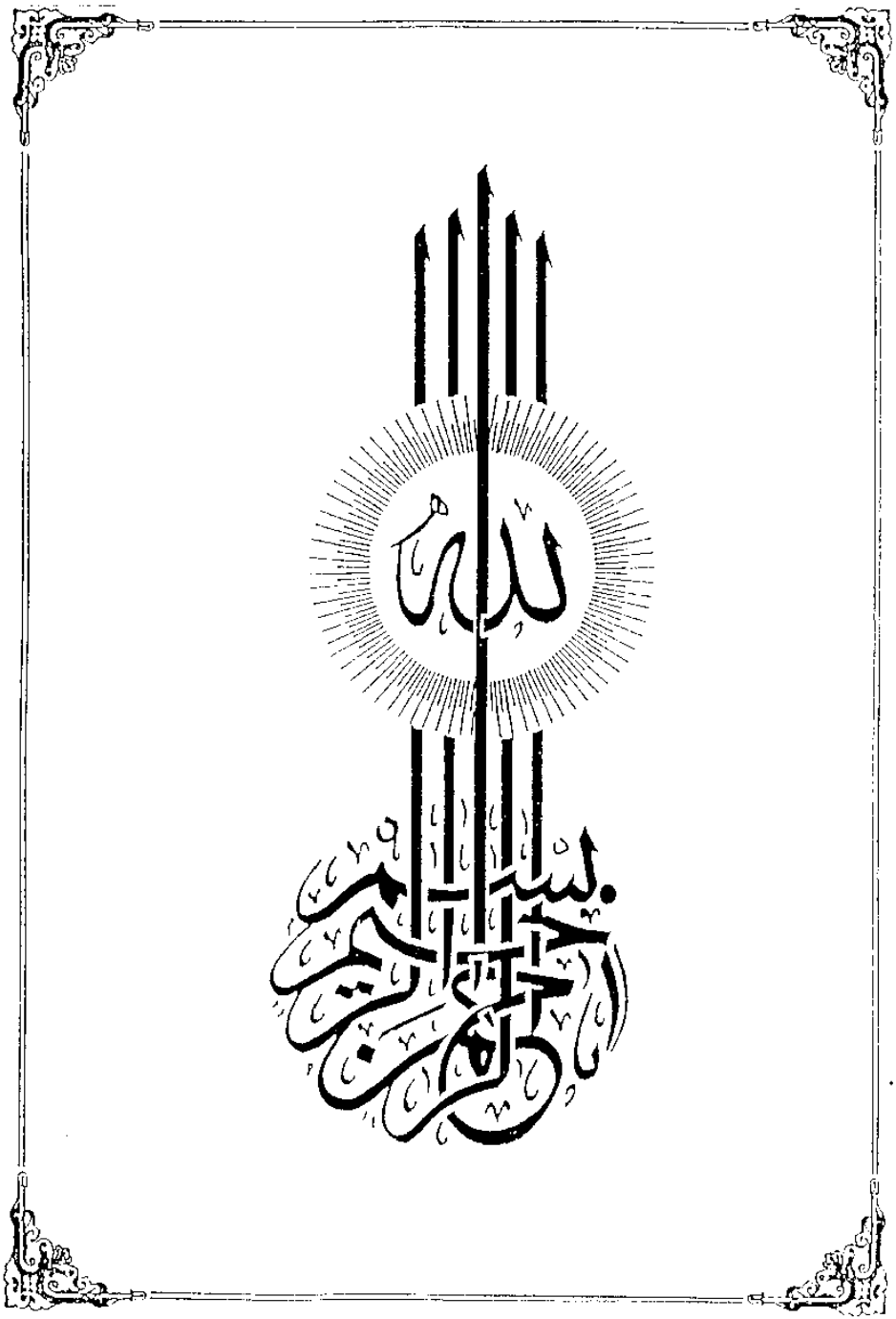

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رسالـــة ماجســـتير / دكتـــوراه

أسم الطـــالب: ...

عنوان الرسالة: ...

أســم الدرجـــة : إماجستـــير / دكتـــوراه

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موافقة مجلس الجامعة
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شكـــــر

الشكـــر للســـادة الأســـاتذة الـــذين قامـوا بالإشـــراف

وهـــم :

1) أ.د. محمد عبد السلام [illegible]

2) أ.د. [illegible]

3) د. [illegible]

4) د. [illegible]

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ثم الأشخـــاص الذيـــن تعـــاونوا معـــي فـي البحـــث

وهـــم :

1) [illegible]

2) ....

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وكـــذلك الهيئـات الآتيـــة :

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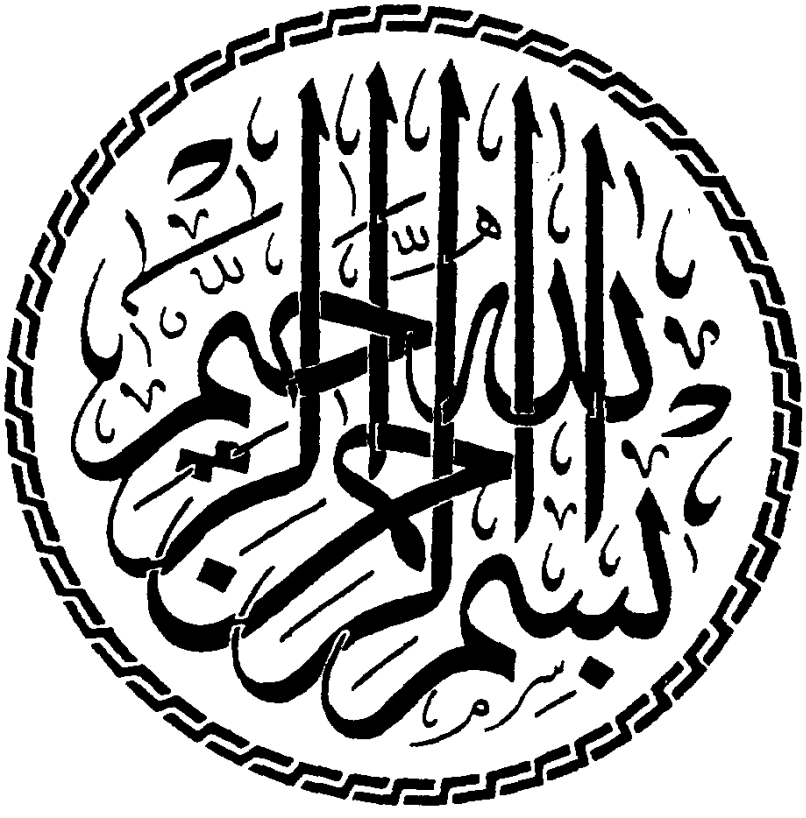

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CONTENTS

LIST OF ABBREVIATIONS

(ADFR)	:	Activate depress free regimen
(A)	:	Amino-acids
(BGP)	:	Osteocalcin
(BMC)	:	Bone mineral content
(BMD)	:	Bone mineral density
(BMI)	:	Body mass index
(CA)	:	Cortical area
(CAMP)	:	Cyclic AMP
(1,25-$(OH)_2$-D)	:	1, 25 dihydroxy vitamin D
(DEXA)	:	Dual energy x-ray absorptiometry
(DPA)	:	Dual photon absorptiometry
(ECF)	:	Extra cellular fluid
(QCT index)	:	Fracture index
(GFR)	:	Glomerular filtration rate
(GSD)	:	General standard deviation
(HRT)	:	Hormone replacement therapy
(HDL)	:	High density lipoprotein
(HA)	:	Hydroxy apatite
(OHpr)	:	Hydroxy proline
(IGF-1)	:	Insulin like growth factor
(IL 1)	:	Interleukin I
(I U)	:	International unit
(KVP)	:	Kilo volt power
($L_{1,2,3}$)	:	Lumbar vertebrae 1, 2, 3
(TM PO_4)	:	Maximum tubular resorption of phosphate
(MW)	:	Medullary width
(Ng/mL)	:	Nanogram/mL
(OAF)	:	Osteoclast-activating factor
(PTH)	:	Parathyroid hormone
(Pg/mL)	:	Picogram/mL
(PHP)	:	Primary hyperparathyroidism
(PGE_2)	:	Prostaglandin E_2
(QCT)	:	Quantitative computed tomography
(ROI)	:	Region of interest
(SPO)	:	Single photon absorptiometry
(S.D)	:	Standard deviation
(TA)	:	Total area
(TOF-ß)	:	Transforming growth factor-ß
(TNF)	:	Tumor necrosis factor
(UTV)	:	Ultra sound transmission velocity

INTRODUCTION

INTRODUCTION

Osteoporosis has emerged as a major health problem requiring intervention at both the individual and community levels. It is characterized by low bone mass and increased susceptibility to fractures primarily in the spine, wrist and hip resulting in a great morbidity and mortality. Women are the targets for postmenopausal osteoporosis induced by the estrogenic deficit at menopause ***(Wark et al., 1993)***.

Interest in postmenopausal osteoporosis among the developed countries has been promoted, especially with the dramatic increase in the life expectancy owing to the more attention to health issues relevant to women and the recent advances in diagnostic technology. Concern about osteoporosis in Egypt still gains little attention.

The pathogenesis of osteoporosis is heterogenous and multifactorial. Bone mass increases rapidly in childhood and the adolescent years, reaching a peak in the third decade of life ***(Riggs et al., 1981)***. Low peak bone mass achieved and or increase rate of bone loss than formation critically occurring at menopause and being more apparent in trabecular bone finally result in osteopenia.

The most important risk factors for primary osteoporosis are race, gender, body habits, nutritional habits with low intake of milk and dairy products, coffee and alcohol intake and lastly the degree of physical activity. Premature menopause in women is also a major cause of accelerated bone loss leading to osteoporosis ***(Riggs and Melton, 1986)***.

The treatment of osteoporosis is currently far from satisfactory. Much of the problem lies in the fact that the majority of patients are in old age groups and consequently have reduced bone turn over rats therefore, any manipulations that

reduce bone resorption or increase bone formation require an extended period of time before improvement is manifested clinically. The arrival of new techniques of bone mineral density measurement such as dual photon absorptiometry (DPA), dual energy x-ray absorptiometry (DEXA) and quantitative computed tomography (QCT) allowed precise and accurate evaluation of various lines of management of this problem ***(Lindsay, 1988)***.

Several lines for prevention and treatment of osteoporosis have been investigated in the last decades. These lines of treatment either inhibit bone resorption or increase bone formation. Calcitonin is one of the main antiosteoclastic drugs used in treatment of osteoporosis. It reduces the number and shorten the life span of osteoclasts resulting is a smaller resorption cavities ***(Burchardt, 1985)***. Several forms of calcitonin have been introduced for prevention of osteoporosis and are thought to be promising i.e. intranasal and suppositories, but these forms have not been investigated thoroughly in cases of established osteoporosis. Also there is controversial data about exercising programs as a supportive line for medical treatment.

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AIM OF WORK

BONE HISTOLOGY AND PHYSIOLOGY

Histology:

Bone is composed primarily of three elements; a protein matrix a mineral phase, and bone cell ***(Raisz, 1977)***. The matrix occupies about 50 percent of the total bone volume. About 95 percent of bone matrix is composed of the fibrous protein collagen, and the remainder is primarily a mucopolysaccharide ground substance ***(Raiz and Kream, 1983)***.

Collagen forms a highly ordered system of collagen fibers with the typical axial periodicity of 640 A to 700 A and a unique protein composition of about one third glycine residues, one fifth amino acid residues, a large number of alanine residues, and very few aromatic amino acids; cysteine is completely lacking ***(Martin and Suda, 1989)***. More than 15 different kinds of collagens have now been identified in different tissues and vertebrates ***(Vander et al., 1991)***.

A single collagen fibril is a three-stranded coil composed of three adjacent left-handed helices (designated collagen polymers α1, α1, α2) bound together by intermolecular and intramolecular cross linkages and twisted about a common axis (Fig.1). When newly synthesized (young) collagen is denatured, it separates into two α1 chains and one α2 chain, each with a molecular weight of about 100,000. Older collagen gives rise to two double and one triple chain (ß11, ß12, and τ 112) whose molecular weights are 200,000 and 300,000, respectively ***(Charlene et al., 1993)***.

Although the composition is similar to other types of collagen, bone collagen (Type I) differs from most of the soft tissue collagens in certain respects. Bone collagen is insoluble in solvents used to extract collagens from other tissue (neutral salt

solutions and weak organic acids). This characteristic is thought to be due to the presence of strong intermolecular bonds between and along the length of adjacent macromolecules ***(Theodore, 1989)***.

A large number of mutations in the type 1 pro-collagen genes have been reported and this is may be responsible for osteogenesis imperfecta. Recently, similar reports indicates that such mutation may be responsible for postmenopausal osteoporosis ***(Spotilai et al., 1991)***.

Other bone-specific proteins have been described. Osteonectin, a 32,000 molecular weight protein found only in mineralized bone and dentin, has sites that bind selectively to bone hydroxyapatite crystals and bone collagen ***(Termine et al, 1981)***. This protein appears to link bone mineral and collagen and may therefore play a role in initiating the mineralization of bone matrix. Osteocalcin (also called bone Gla protein) is a 5800 molecular weight protein that constitutes about 25 percent of the noncollagenous protein of mammalian bone. Osteocalcin contains three residues of the vitamin K-dependent amino acid gamma (τ) carboxyglutamic acid and binds strongly to hydroxyapatite crystals in an association that requires the τ-carboxyglutamic side chains. The role of osteocalcin in bone metabolism is undefined, as vitamin K-deficient animals with low osteocalcin levels have no detectable abnormalities in bone structure or mineralization. However, because osteocalcin is elaborated exclusively by osteoblasts, the circulating levels of this bone-specific protein reflect the level of osteoblastic activity ***(Watrous and Andrews, 1989)***.

Protein polysaccharide comprise 4% to 5% of the organic constituents of bone. They are compounds consisting of a poly peptide chain to which side chains of highly sulfated polysaccharides are covalently bound. The principal polysaccharide of bone