BONE METABOLISM AND RELATED HORMONES IN INSULIN-DEPENDNT DIABETES MELLITUS

Thesis

Submitted for partial Fullfilment of the master degree

IN

(Internal Medicine).

By

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(M.B., B. ch.)

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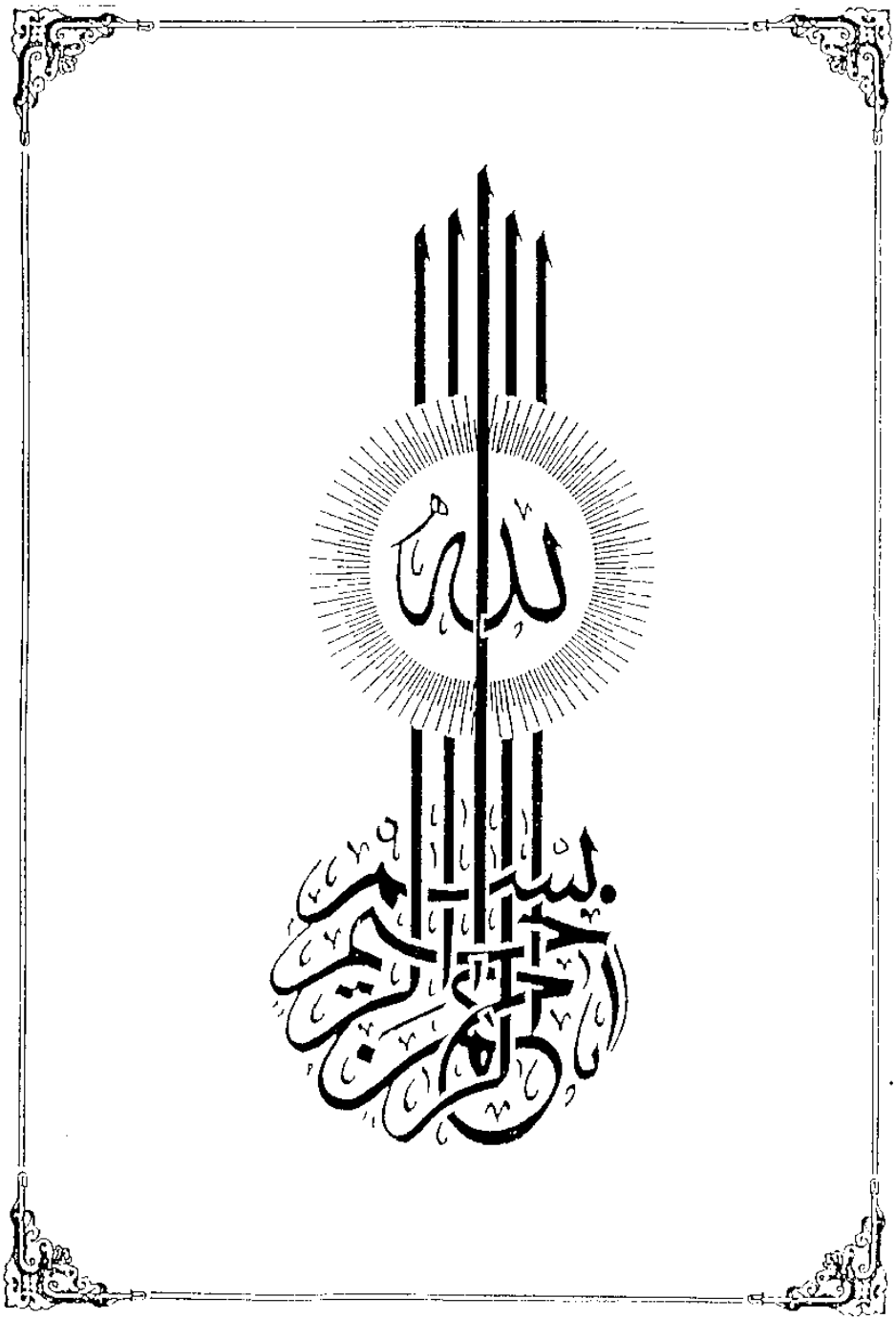

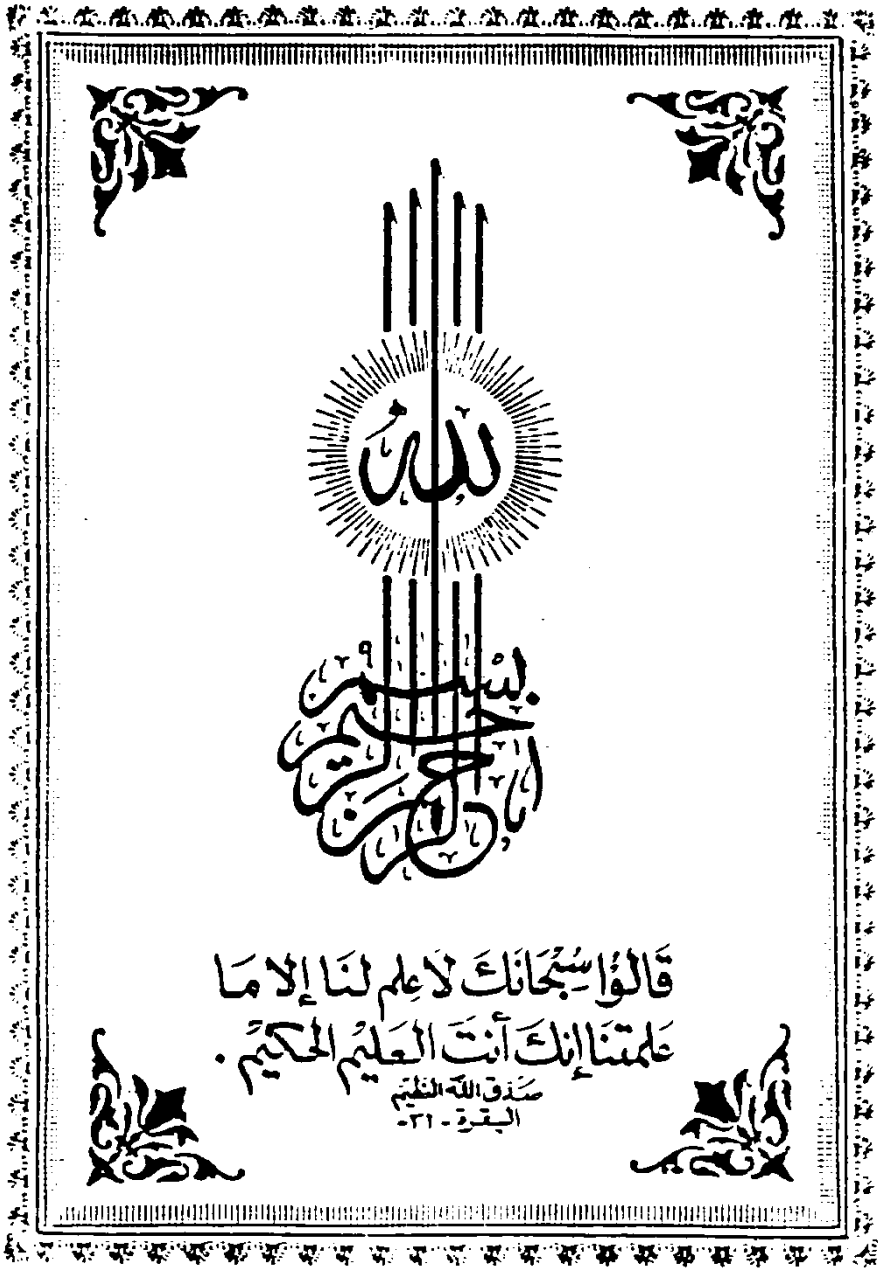

Above all and first of all thanks to **GOD .**

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DETECATED TO

THE MEMORY OF MY BROTHER

HOSAM MAHMOUD AHMED

LIST OF ABBREVIATIONS

Alb.	albumin
alk.p.ase	alkaline phosphatase
B / B0 %.	percent binding
bili.	bilirubin
bio.	bioavailable
Ca	calcium
Ca++	calcium ion
creat.	creatinine
CT	Calcitonin
DM	diabetes mellitus
E_2	estradiol
F	Female
F.amine	Fructosamine
F.B.G	Fasting blood glucose.
glob.	globulin
GM–CSF	granulocyte macrophage–colony stimulating factor
H.S	highly significant
Ht.	Height
IDD	insulin–dependent diabetic
IDDM	insulin–dependent diabetes mellitus
M	Male
N	number
n	total number
NIDD	non insulin–dependent diabetic
N.S	non significant
PGs.	prostaglandins
Ph.	phosphorus.
Pt.	patient
QCT	Quantitative computerized tomography
RIA	radioimmunoassay
S.	serum
S.D	standard deviation
STZ	streptozotocin
T	total
Te	tesosterone
U	unit
Vit.	vitamin
V.H.S	very highly significant.
Wt.	weight
$\bar{X}$	mean value
$1,25(OH)_2-D_3$	1,25 dihydroxycholecalciferol
2 hr. PP.BG	2 hours postprandial blood glucose level

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Bone is a specialized connective tissue formed of inorganic and organic bone matrices (Junqueira et al, 1992). It is metabolically active and can be affected by many metabolic disorders (Nuki et al, 1993). The musculo skeletal system can be affected by many forms of disorders in diabetes mellitus including osteopenia (Podolsky and marble 1985). Such diabetic osteopenia has been recognized as one of the chronic complications of insulin–dependent diabetes mellitus and non insulin–dependent diabetes mellitus (Takeshitz et al, 1993). However some epidemiological studies showed bone mass to be unchanged and in others – even more positive trends were reported (Ziegler, 1989).

Many studies have been conducted to find out the relationship between diabetes mellitus and both calcium and phosphorus metabolism which could affect the process of bone mineralization, Also many investigations were done to find out the relationship between diabetes mellitus and parathyroid hormone and calcitonin which affect calcium and phosphorus metabolism and the bone remodelling process.

Such studies have given conflicting results (Schwarz et al, 1992 ; Mc Nair et al, 1979 ; Amado et al, 1987 ; Fogh–Andersen et al, 1988 ; Nyomba et al, 1986).

Organic bone matrix metabolism is under the effect of many hormones and factors including the anabolic sex hormones, which are strongly known to affect bone metabolism (Martin et al, 1988). Hypogonadism in both males and females can predispose to bone fracture (Swartz and Young, 1988).

Sex hormone bioavailability is not only determined by its free part but also by the albumin bound part which is also bioavailable (Raynaud 1983). All plasma protein including albumin can be glycated (Bent–Hansen et al, 1993). Glycated materials may interfere with its normal function or breakdown (Walkins et al, 1990).

Little is known about the anabolic sex hormones and its bioavailable part in diabetes mellitus.

AIM OF THE WORK

The aim of our work is to clarify the pattern of disturbance of

calcium, phosphorus, parathyriod hormone and calcitonin in insulin–dependent diabetic patients ; And to study the total serum level and its bioavailable portion of the anabolic sex hormones in such patients. Osteopenia will be asceratined in some cases by quantitative computerized tomography technique.

REVIEW OF LITERATURE

CHAPTER I

HISTOLOGY OF THE BONE

HISTOLOGY OF THE BONE

Bone is one of the hardest tissue in the body, second only to cartilage in its ability to withstand stress. It is a specialized connective tissue composed of **bone matrix** and **bone cells : Osteocytes** whic are found in lacunae; **osteoblasts,** and **osteoclasts** . Bone matrix has a **canalicular system** which permits the nutrition of osteocytes; the filopodial processes of osteocytes to communicate with their neighbours and the internal and external surfaces of the bone; and the blood vessels to traverse the matrix. All bone surfaces have a layer of connective tissue containing osteogenic cells **—endosteum** on the inner surface and **periosteum** on the outer (Junqueira et al, 1992).

BONE CELLS

A. OSTEOBLASTS

By definition, osteoblasts are cells which synthesize bone matrix, but it is recognized that the **osteoblast family** includes related osteocytes and bone lining cells and may also contain as yet unrecognized functional types (Martin et al, 1988) .

In vitro studies, proberties of osteoblast phenotypes are : first, it can produce, type–I collagen, alkaline phosphatase, osteocalcin, osteonectin, osteopontin, prostanoids, growth factors, and osteoclast stimulating factor; second it has receptors and / or responses to , PTH, PGs, $1,25–(OH)_2–D_3$. epidermal growth factors, interleukin–1, tumor necrosis factor and retenoids (Matrin et al, 1988).

While osteoblast has the above properties, possession of all of these is by no means necessary in all cells of the lineage. There is a concept developed about heterogenecity among osteoblast lineage. At different stages of differentiation and at different sites of the bone, carrying out a speceific function, certain of these proberties. will be expressed (Martin et al 1988).

THE MAIN TYPES OF MATURE OSTEOBLASTS ARE :

1- OSTEOBLASTS :

These are columnar cells lying on the matrix they have produced (Martin et al, 1988), and exclusively located at the surfaces side by

side in a way that resembles surface epithelium (Junqueira et al, 1992).

The cells are connected with each other by gap junction, which may also connect them with adjacent lining cells (Martin et al, 1988). Osteoblasts have eccentric nuclei, prominent Golgi complex and abundant rough endoplasmic reticulum reflecting their capacity of protein synthesis (Junqueira et al, 1992). They are rich in alkaline phosphatase, synthesize type I collagen and osteocalcin and have receptors for PTH. When its activity declines, osteoblasts flatten, become less basophilic, and alkaline phosphatase declins (Martin et al, 1988).

2- *BONE LINING CELLS*
(*INACTIVE OSTEOBLASTS, ENDOSTEAL LINING CELLS*)

They are yet another representative of the osteoblast familly, in which synthetic capability has been lost, they come to lie as flattened cells with cylinderical nuclei and little cytoplasm and endoplasmic reticulum. It has gap junction (Martin et al 1988).

It covers trabecular and endosteal surfaces of bone forming a functional "membrane" separating bone fluid from interstitial fluid. It also separates bone surface from the action of osteoclasts. It has also other possible functions as their possible role in mediating the action of bone resorbing hormones (Martin et al 1988) and important role in bone remodelling (Reeve and Zanelli, 1992).

3- *OSTEOCYTES*

Osteocytes are osteoblasts surrounded by the newly synthesized matrix (discussed latter). Lacunae and canaliculi appear because of the deposition of bone matrix around the cell and its processes (Martin et al 1988).

FUNCTIONS OF OSTEOBLASTS :

Osteoblasts, not only lay down organic component of the matrix, but also essential for deposition of the inorganic component of the matrix (Mattheus et al, 1973) . Active osteoblasts secret the organic matrix component at the surface of older bone in contact with them producing a layer of the osteoid between it and the bone (bone apposition) which