A STUDY OF

NEW BIOCHEMICAL MARKERS OF BONE DISEASES

Essay
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The Master Degree
of

Clinical and Chemical Pathology

By

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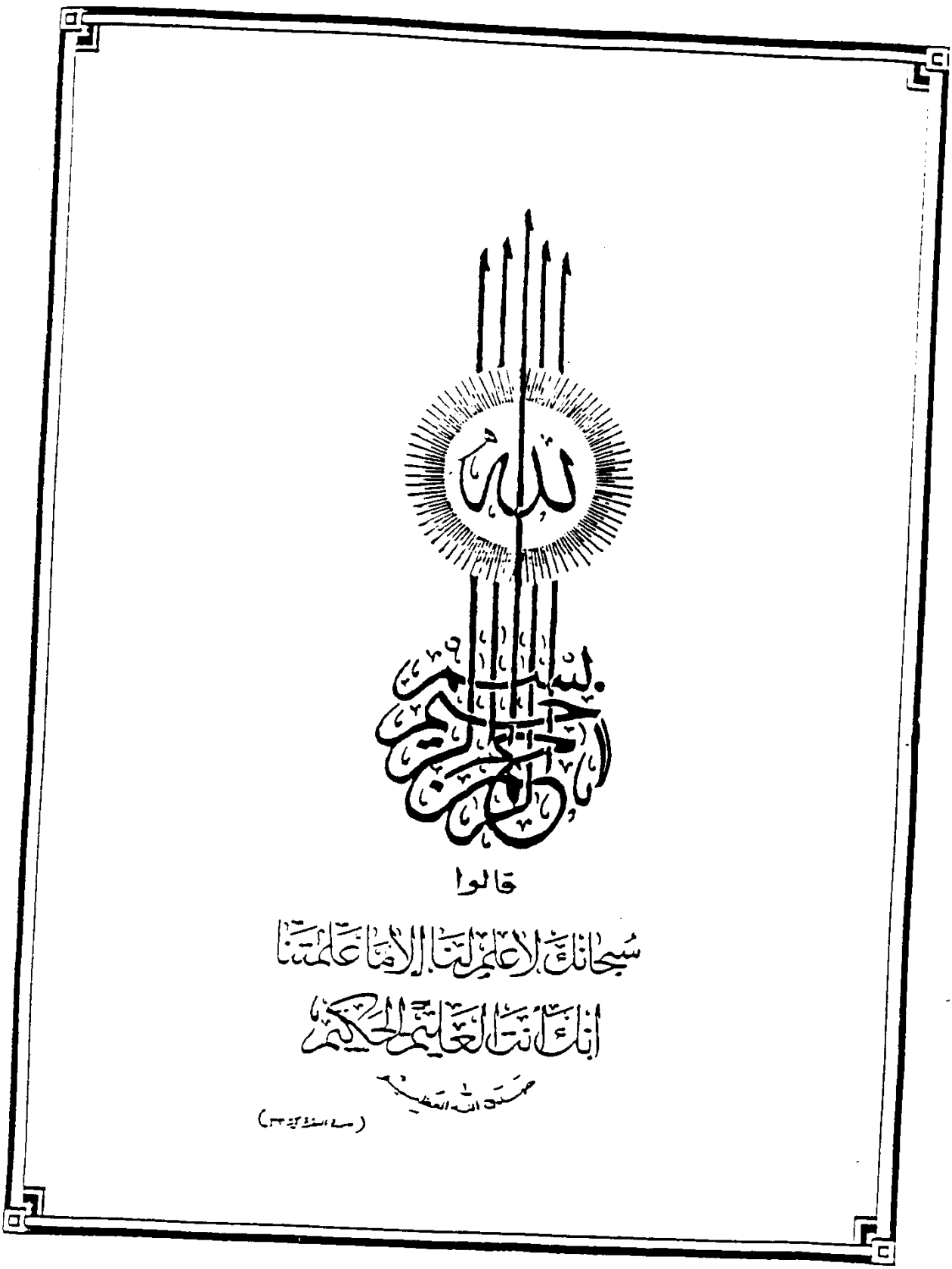

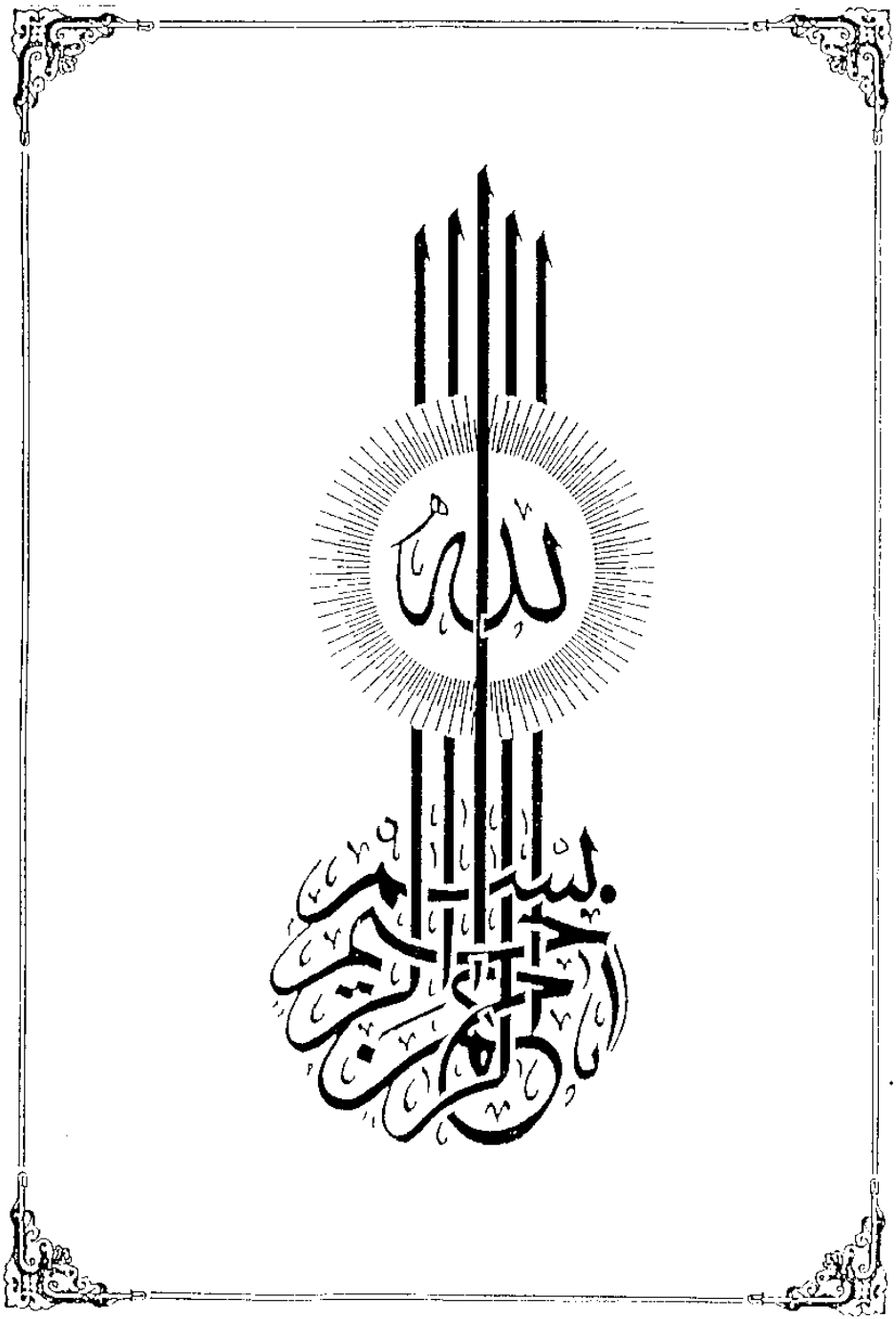

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Abbreviations

ALP	: Alkaline phosphatase
ACP	: Acid phosphatase
BGP	: Bone Gla protein
BSP	: Bone sialoprotein II
CLIA	: Chemiluminoimmunoassay
ICTP	: Carboxy-terminal telopeptide of type I collagen
D-Pyr	: deoxypyridinoline
EIA	: Enzymeimmunoassay
ELISA	: Enzyme-linked immunosorbantassay
GFR	: Glomerular filtration rate
HPLC	: High performance liquid chromatography
MGP	: Matrix Gla protein
INTP	: Amino-terminal telopeptide of type I collagen
OAF	: Osteoclastic activating factor
OC	: Osteocalcin
PHPT	: Primary hyperparathyroidism
PICP	: Carboxy-terminal propeptide of type I collagen
PINP	: Amino-terminal propeptide of type I collagen
PAS	: Prostatic acid phosphatase
PTH	: Parathyroid hormone
Pyr	: Pyridinoline
RIA	: Radioimmunoassay
TRAP	: Tartrate-resistant acid phosphatase

INTRODUCTION

AND

AIM OF THE ESSAY

Introduction and Aim of The Essay

Although the skeleton is generally regarded as a relatively inert organ system, it is infact, actively metabolizing, but at a much slower rate than other organs. Quantitatively, it has been estimated that 10% of the skeleton turns over annually, a proportion that some organ systems turn over each day. The metabolism of the skeleton is signaled by the products of its cellular components. Thus, just as the metabolic activity of the cells of the liver is signaled by the serum concentration of aspartate amino transferase, so is the metabolic activity of the skeleton signaled by the serum concentration of the products of its metabolically active cells, the osteoblast and the osteoclast. Consequently, the products of bone cells can be measured in the serum and used in the clinical assessment of the skeleton ***(Price, 1988).***

In this study we review and update the application of measurements of bone specific proteins and enzymes to clinical assessment of skeletal status in patients with metabolic bone diseases. We will focus on those bone proteins that are

produced exclusively by skeletal cells. These are mainly. Osteocalcin, bone specific alkaline, phosphatase, bone-specific acid phosphatase, and collagen-related proteins and peptides, including amino acid catabolites and procollagen peptides.

In clinical practice, serum measurements, of bone proteins are complemented by a wide variety of additional studies, including biochemical measurements of calcium, phosphorus, and such hormones as the parathyroid hormone, calcitonin and vitamin D metabolites ***(Deftos and Glowaki, 1984).***

The clinical goal of the assay procedures related to the skeleton should be directed to assess separately the processes of bone formation and bone resorption. Bone formation and bone resorption underlie both normal and abnormal skeletal metabolism. These two processes are closely coupled in health and remain coupled in many skeletal diseases. Understanding the separate roles of bone formation and bone resorption will help to answer questions about metabolic abnormalities of the skeleton that intervene in disease states ***(Epstein, 1989).***

For example, in patients with osteoporosis, the question is whether the primary disorder is that of increased bone resorption or decreased bone formation? At least as important, if not more so, will be the elucidation of the effect of therapeutic regimens on bone formation and bone resportion. For example, again in osteoporosis, can sequential therapeutic regimens be devised that stimulate bone formation without stimulating bone resorption, or inhibit bone resportion without inhibiting bone formation? Only serum markers seem applicable to the frequent and quantitative measurements that will be necessary to answer these questions.

The general discussion will focus on the major skeletal diseases, Paget"s disease, osteoporosis, osteomalacia, and the bone disease of hyperparathyroidism. Less common diseases will be considered for specific issues.

BONE CONSTITUENTS

AND

BONE METABOLISM

Bone Constituents and Bone Metabolism

A. Bone constituents

Bone constituents can be classified into cellular and non cellular elements.

I - Cellular constituents of bone :

Five types of cells are present in the skeletal tissue, namely: osteoprogenitor, osteoblasts, osteocytes, osteoclasts, and bone lining cells

1. Osteoprogenitor cells :

These cells can differentiate into osteoblasts or bone-forming cells ***(Owen, 1970)***.

2. Osteoblasts :

Osteoblasts are derived from stromal cells of bone and marrow. As these cells are bone-forming cells, at time when new bone formation is required (as during the healing of fractures), the precursor cells give rise to the generation of osteoblasts ***(Warshwsky, 1982).***

3. Osteocytes :

The osteocytes are coming from the osteoblasts. When the osteoblast is incorporated into the osseous tissue, a new cell is

formed which is the osteocyte. The osteocyte has the ability to synthesize bone matrix, although this ability is less pronounced than that of the osteoblast. It has been proposed that the osteocyte may also be involved in bone resorption, a process called osteocytic osteolysis ***(Warshwsky, 1982).***

4. Osteoclasts :

The osteoclasts have a short life span that is intimately related to the process of bone resorption. The osteoclasts appear to be a product of one of the cell lines of the hematopoietic system, being derived from a haematopoietic stem cell (monocyte-phagocyte line) ***(Hanaoka, 1979).***

Osteoclasts are responsible for bone resorption by two different mechanisms: the secretion of collagenase which digest collagen, mucopolysaccaride and minerals of bone and through the release of bone resorbing factors, such as prostaglandins, interleukin-1 and osteoclast activating factor ***(Jee, 1983).***

5. Bone lining cells :

The precise function of these cells is not known, but may be their ability to differentiate into other types of cells, such as