A STUDY OF RENAL OSTEODYSTROPHY IN AIN SHAMS UNIVERSITY DIALYSIS CENTRE

THESIS

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By

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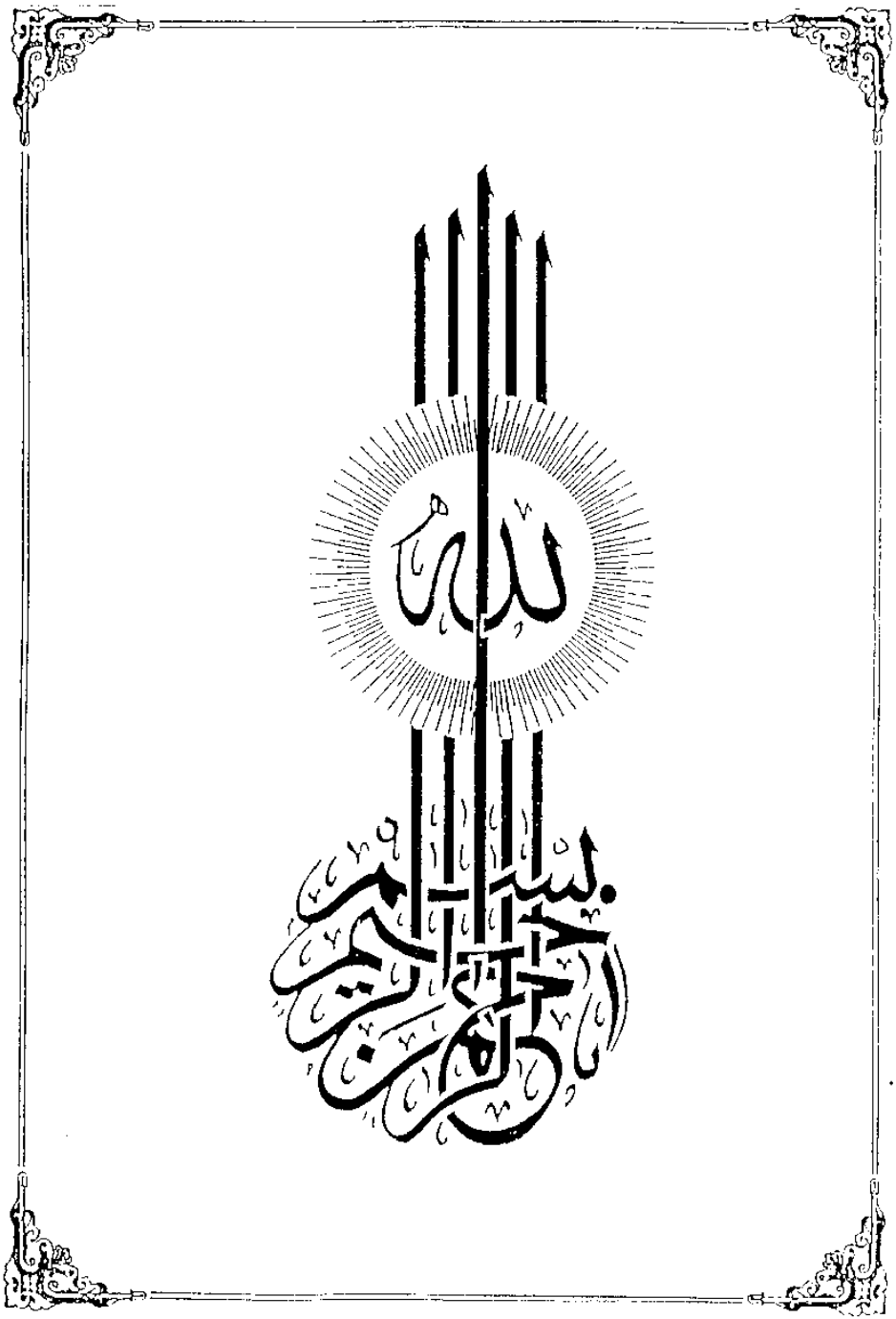

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Renal osteodystrophy is one of the major complications in patients on long-term haemodialysis (Boner et al., 1983).

Siddigai and Kerr (1971) reported that bone disease is the single most important unsolved problem in long-term haemodialysis.

Kanis (1978) stated that despite the scientific progress in recent years, the pathogenesis of bone disease in renal failure remains poorly understood.

Roux and Duriez (1981) examined 103 patients on haemodialysis and found histological evidence of bone involvement in 101.

In Israel, Boner et al., (1983) reported that radiological signs of osteal involvement were found in 67% of dialysed patients.

In Egypt, Rihan et al., (1976) showed that radiological evidence of renal osteodystrophy was found in 32% of the studied cases.

From all the previous studies, it was suggested to find out the prevalence of renal osteodystrophy on biochemical and radiological ground in the Dialysis Centre of Ain Shams University Hospitals and also to study different factors affecting this prevalence.

The study included 20 patients with end-stage renal failure under maintenance haemodialysis. Clinical manifestations, biochemical parameters and radiological examination were carefully assessed to find out a relation between the different parameters and the prevelance of renal osteodystrophy.

AIM OF WORK

The aim of this work was to study the prevalence of renal osteodystrophy in patients with end-stage renal failure under maintenance haemodialysis treatment in the Dialysis Centre of Ain Shams University Hospitals and to find out a relation between this prevelance and different possible aetiologic factors.

These factors include age, sex duration of haemodialysis, aetiology of CRF, water treatment, biochemical parameters, heparin, diet and different therapeutic agents as phosphate binders, calcium supplements and vitamin D analogues.

This work also suggested possible prophylactic and therapeutic measures of renal osteodystrophy.

REVIEW OF LITERATURE

PHYSIOLOGY AND MINERALIZATION OF BONE

Before discussing the effect of uraemia on skeletal system, it is important to delineate certain well established points about normal bone formation and composition.

The inorganic constituents of bone by dry weight comprise about 65 to 70% and the organic constituents comprise about 30 to 35%, of which about 90 to 95% is the extra cellular matrix consisting of fibrous protein collagen. Other organic constituents include small amounts of proteinpolysaccharides (PPS) and lipids, particularly phospholipids (Turek, 1977).

Collagen :

Gallop (1972) stated that collagen forms a highly ordered system of collagen fibres with a unique protein composition of about one-third glycine residues, one-fifth imino-acid residues, a large number of alanine residues and completely lacking cysteine.

A single collagen fibril is a three stranded coil composed of three adjacent left handed helices (designated collagen polymers α , α_1, α_2). These are bounded together

by intermolecular and intramolecular cross linkages and twisted about a common axis.

Proteinpolysaccharides :

These substances comprise 4 to 5% of the organic constituents of bone. They are compounds consisting of polypeptide chains to which side chains of highly sulfated polysaccharides are covalently bound. The principal polysaccharide of bone is chondroitin-4-sulfate (chondroitin sulfate A). Its role is not clear, but it appears to inhibit mineralization of bone by strongly complexing with Ca++ ions.

Lipids :

Robbins & Cotran (1979) stated that less than 0.1% of the organic constituents of bone is comprised of triglycerides, free fatty acids, phospholipids and cholesterol. Under electron microscopy, it can be observed that phospholipids disappear just before mineralization takes place. This suggests that lipids participate in some unknown manner in the process of mineralization.

Inorganic Constituents :

Clark (1975) stated that the dry weight of bone is composed of 65 to 70% inorganic material, 95% of which is a calcium and phosphate solid. The main Ca-P solid

is a poorly crystalline hydroxyapatite having the unit cell formula $Ca_{10}(PO_4)_6(H_2O)_2$.

Inorganic constituents include small but significant amount of carbonate (4 to 6% by dry weight) and smaller amounts (1%) of other ions such as Na+, K+, Mg++ and Cl^-. In addition to the crystalline hydroxyapatite, bone mineral also contains calcium phosphate salts in non crystalline amorphus pattern.

The Cellular Phase :

The cells of bone include osteoblasts, osteocytes and osteoclasts. They are of mesenchymal origin . The function of osteoblast is the formation of collagenous matrix in bone. This matrix is deposited on a bone forming surface, then mineralization follows. The alkaline phosphatase enzyme which is derived from osteoblasts prepares the organic matrix for calcification by catalyzing the hydrolysis of pyrophosphate which inhibits biological calcification (Russel, 1965).

During the course of calcification, the osteoblasts become osteocytes which transport minerals between the skeleton and the surrounding extracellular fluids.

The last type of bone cell is the osteoclast which is a multinucleated cell lying in grooves in relationship

with areas of resorption. Resorption of bone is an equally complex and poorly understood process. Resorption involves osteoclasts and perhaps osteocytes. Osteoclasts contain acid phosphatase, but the function of this enzyme in mobilizing bone minerals is not known. A number of humoral factors accelerate bone resorption including parathyroid hormone, prostaglandins and heparin (Robbins & Cotran 1979).

Hormonal regulation of Bone Metabolism :

The hormones concerned with control of skeletal metabolism and calcium homeostasis in general include parathyroid hormone, calcitonin and vit.D.

Parathyroid Hormone (PTH) :

It is now recognised that the principal form of PTH stored & released from the parathyroid glands is an 84-amino acid, single chain polypeptide synthesized through precursor forms (Habener, 1978).

Secretion of Parathyroid Hormone :

Habener et al., (1971) stated that the concentration of calcium in the circulation is an important controlling factor for PTH secretion. In vitro studies showed that a number of factors e.g., catecholamines, prostaglandins, steroids & many drugs are capable of influencing PTH secretion .

cAMP represents a major cellular regulator of PTH secretion. Activators of adenylate cyclase (as B-adrenergic catecholamines, dopamine & prostaglandin E_1) increase concentrations of cAMP in parathyroid cells. cAMP produced in response to these agonists or in response to cyclic nucleotide phosphodiesterase inhibitors, stimulates release of PTH. Conversely certain agents that inhibit PTH release or secretion for example, calcium, α-adrenergic catecholamines, and prostaglandin $F_{2\alpha}$, inhibit cAMP accumulation in parathyroid cells (Habener & Potts 1976) .

Effect of Ions on Secretion :

Calcium is the classically recognized regulator of PTH secretion. Its inhibitory effect on secretion has been extensively documented with in vivo as well as in vitro experiments. Nevertheless, the precise mechanism whereby calcium regulates secretion has not been established (Williams, 1981).

He mentioned also that in some tissues there is calcium-binding protein (calmodulin) that regulates either the adenylate cyclase enzyme or cyclic nucleotide phosphodiesterase (or both). (Kemper et al., 1974).

Indeed it has been shown that calcium can inhibit adenylate cyclase activity in parathyroid tissue. The effect of calcium on inhibiting cAMP accumulation is less marked than the effect of calcium on inhibiting PTH release.

Magnesium also can affect PTH secretion. High concentrations of magnesium inhibit PTH secretion in a manner similar to calcium. Meanwhile profound hypo magnesemia interferes with PTH secretion (Williams, 1981).

Effect of Vitamin D :

Canterbury (1978) stated that high affinity binding sites have been found in parathyroid glands for 1,25-dihydroxycholecalciferol [1,25-$(oH)_2$ -D] and high concentrations of this vitamin D metabolite modulate parathyroid release in vivo. 25-hydroxycholecalciferol as well as 24, 25-$(oH)_2$ -D and 25, 26-$(oH)_2$ -D cause acute inhibition of PTH release in dogs.

Effect of Aluminium :

A number of studies have been carried out on the toxic effect of aluminium on bone mineralization, and its relation with calcium and parathyroid hormone metabolism (Cumming et al., 1982).