ALKALINE PHOSPHATASE ISOENZYMES IN CHRONIC RENAL FAILURE UNDER DIALYSIS

Thesis by

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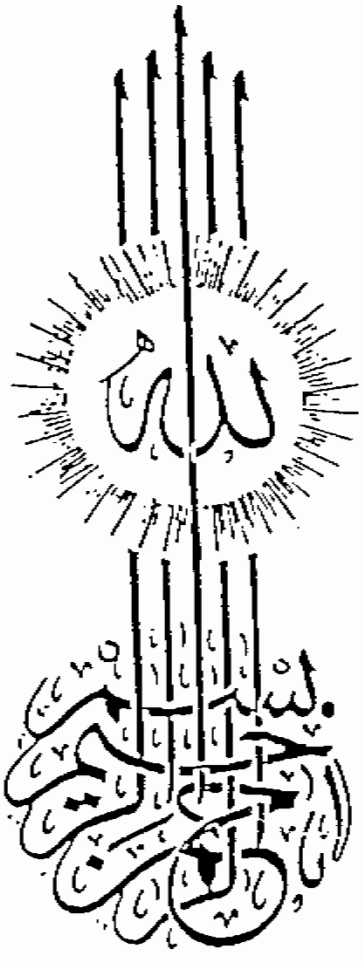

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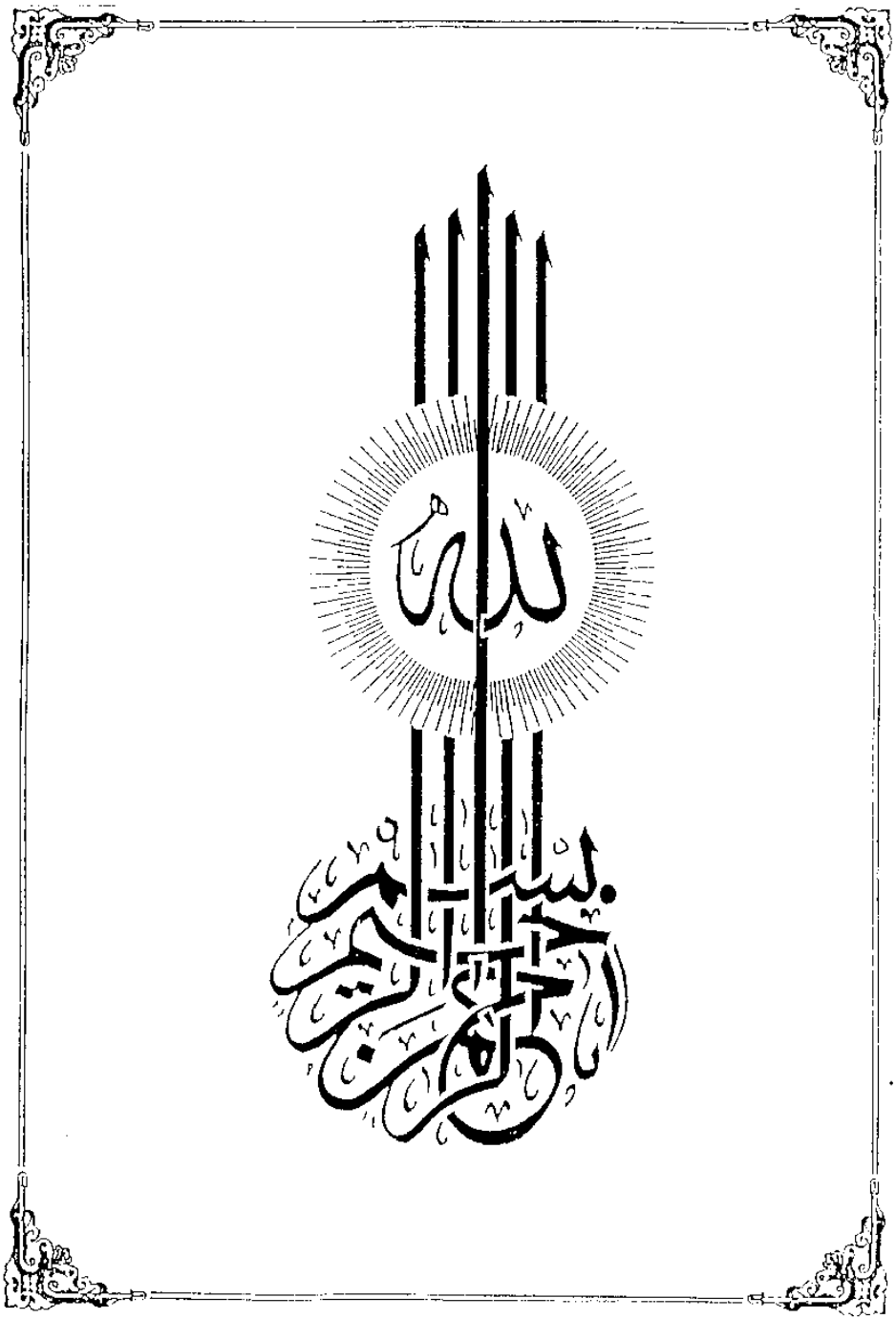

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Aim of the Work

The aim of this work was to study alkaline phosphatase isoenzymes in patients with chronic renal failure under maintenance haemodialysis treatment and to try to find out an easy and reliable method to asses the onset and degree of metabolic bone lesions associated with chronic renal failure and to ensure effective prevention and successful treatment.

INTRODUCTION
AND
REVIEW OF LITERATURE

Metabolic bone disease is a common complication of chronic renal failure and may be progressive in patients on regular dialysis **(Doyle, 1972).**

Barber (1920), reported 10 cases under the name of renal dwarfism, and the aetiology in most cases was interstitial nephritis.

Ginzler and Jaff (1941) stated that in cases of chronic renal failure in adults, skeletal changes consisting of more or less pronounced fibroporotic resorption of bone accompanied by a varying amount of new bone formation regularly occur.

Atallah (1978), in a study about renal osteodystrophy among uraemic patients in Ain Shams University, stated that the incidence of renal osteodystrophy in Egypt is rare.

Pendras and Erichson (1966) draw the attention to the florid form of renal osteodystrophy associated with long term haemodialysis and **Doyle (1972)** described the radiological changes seen in chronic renal failure before and after the start of maintenance haemodialysis therapy.

The nature and type of bone disease which develops in uraemic patient may vary from one patient to another. Multiple reasons may account for these variations as age of the patient, type of underlying renal disease, duration of renal failure, differences in dietary habits, type of therapy employed and treatment with dialysis and its duration. On the other hand secondary hyperparathyroidism and defective

vitamin D activation are considered the major pathogenic mechanisms. **(Madsen., 1979).**

Also, the mode of dialysis and calcium concentration in the fluid are of consequence. **(Asad, et al., 1979).**

By focusing on the confusing pathology of bone, one often loses sight of the fact that the disorder, must emanate from the organ primarily at fault, namely the kidney. The disturbance therefore, must result from impairment of two basic functions of the kidney; namely, excretion of calcium, phosphorous and acid, and as an endocine organ in the regulation of calcium, phosphorous and bone. There is also possibility that accumulated uraemic toxins and/or acid radicals of ill defined nature interfere with bone martix formation and maturation. **(Blak and Jones, 1979)**

Pathogenesis of renal osteodystrophy

Divalent ion metabolism and renal osteodystrophy : -

The disturbances in divalent ion metabolism are common in patients with renal failure. The major features of these abnormalities are hyperphosphataemia, hypocalcaemia , secondary hyperparathyroidism, defective intestinal absorption of calcium, altered vitamin D metabolism and bone disease. The processes causing disordered divalent ion metabolism and osteodystrophy have their onset in the early stages of renal insufficiency, continue throughout the life of the patient, and may be influenced beneficially or adversely by various therapeutic approaches employed. **(Massry, 1982)**.

Secondary hyperparathyroidism in chronic renal failure : -

Patients with chronic renal failure almost always have secondary hyperplasia of the parathyroid gland resulting in elevated blood levels of parathyroid hormon, this abnormality is due to hypocalcaemia which develops during the course of renal insufficiency. At least three hypothesis have been proposed to explain the pathogenesis of the hypocalcaemia. These include : (a) phosphate retention, (b) skeletal resistance to the calcaemic action of parathyroid hormon and (c) altered vitamin D metabolism.

These possibilities are not mutually exclusive, but rather interelated and together form an unified and integrated explanation for the hypocalcaemia of renal failure. **(Massry, 1982).**

(a) Phosphate retention :

Retention of phosphorous in early renal failure would lower ionized serum calcium and thus provoke increased parathyroid hormon secretion in a homeostatic effort to normalize serum phosphorous through the phosphaturic action of parathyroid hormon **(Bricher, 1972).**

It was found that there is a decreased rather than increased fasting plasma phosphorous level in patients with early renal failure. **(Ritz, et al., 1978).**

Tubular phosphorous reabsorption in nephrectomized dogs was investigated both in presence of a normal contralateral kidney and after its removal, i.e, in the presence of azotaemia and hyperphosphataemia. Segmental phosphorous monitoring in the remnant kidney showed noteworthy inhibition of phosphorous reabsorption in the proximal tubule and loop of Henle. It could be shown that this was independent of parathyroid hormon , the state of volume expansion or plasma calcium levels. It was argued that hyperphosphataemia, or the associated phosphorous retention, in azotaemic dogs may have caused the inhibition of phosphorous reabsorption by mechanisms independent of parathyroid hormon. **(Wong et al., 1978).**

(b) Skeletal resistance to calcaemic action of parathyroid hormon :

Hypocalcaemia is frequently encountered in patients with renal failure despite the elevated blood level of parathyroid hormon, suggesting a skeletal resistance to the calcaemic action of the hormon. The calcium response to the infusion of parathyroid hormon or to an acute rise in the blood levels of endogenous parathyroid hormon is markedly blunted in patients with mild to moderate renal failure, indicating that this skeletal resistance occurs early in the course of renal insufficiency. This abnormality has also been documented in patients with advanced renal failure, in those treated with haemodialysis and in many renal transplant recipients **(Massry, 1982).**

Skeletal resistance to calcium-mobilizing action of parathyroid hormon was found to be an abnormality which occurs early in the course of chronic renal failure and is not reversed by a haemodialysis. This derangement is an important factor contributing to the hypocalcaemia in renal failure and hence, plays a role in the pathogenesis of secondary hyperparathyroidism in these patients. **(Ritz et al., 1978).**

(c) Altered vitamin D metabolism and secondary hyperparathyroidism :-

Massry et al., (1977) hypothesized on the basis of data then available that circulating 1,25 dihydroxycholecalciferol levels had to be low in incipient renal failure, and that such deficiency of vitamin D metabolites might be responsible for hyperparathyroidism.

Slatopolski et al., (1978) showed that in patients with early renal failure, 1,25 dihydroxycholecalciferol levels are in the upper normal range. More recently, **Ogura, et al., (1980)** showed normal or only modestly decreased 1,25 dihydroxycholecalciferol levels in patients with renal insufficiency. Consequently the hypothesis of **Massry et al., (1977)** in its original form is no longer tenable. However, although 1,25 dihydroxycholecalciferol levels may be in the upper normal range in incipient renal failure, this does not necessarily imply that such levels are appropriate to the prevailing biochemical milieu.

In early renal failure, hypocalcaemia, hypeparathyroidism, impaired intestinal absorption of calcium and fasting hypophosphataemia are present. All these factors should stimulate 1- Alpha-hydroxylase, therefore it is clearly unwarranted to rule out an early abnormality of vitamin D metabolism only because circulating levels of 1,25 dihydroxycholecalciferol are in the normal range **(Healy et al., 1980).** Preliminary data indicate that in early renal failure, administration of 1,25 dihydroxycholecalciferol causes an increase of initally low