EFFECTS OF RENAL INSUFFICIENCY ON CALCIUM METABOLISM

THESIS

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BY

Nahla Abd El-Salam Attia El-Garf
M.Sc. (DEGREE)

Supervised by

Dr.Ahmed Mohamed Kamel
Head Of Physiology Department
Faculty Of Medicine
Ain-Shams University

Dr.Shoukri Anesti Wakim
Professor Of Physiology
Faculty Of Medicine
Ain-Shams University

Dr.Shadia Ahmed Ezzat
Assist.Professor Of Physiology
Faculty Of Medicine
Ain-Shams University

Dr. Mohamed Nour El-Din
Assist.Professor Of Physiology
Faculty Of Medicine
Ain-Shams University

Physiology Department
Faculty Of Medicine
Ain-Shams University
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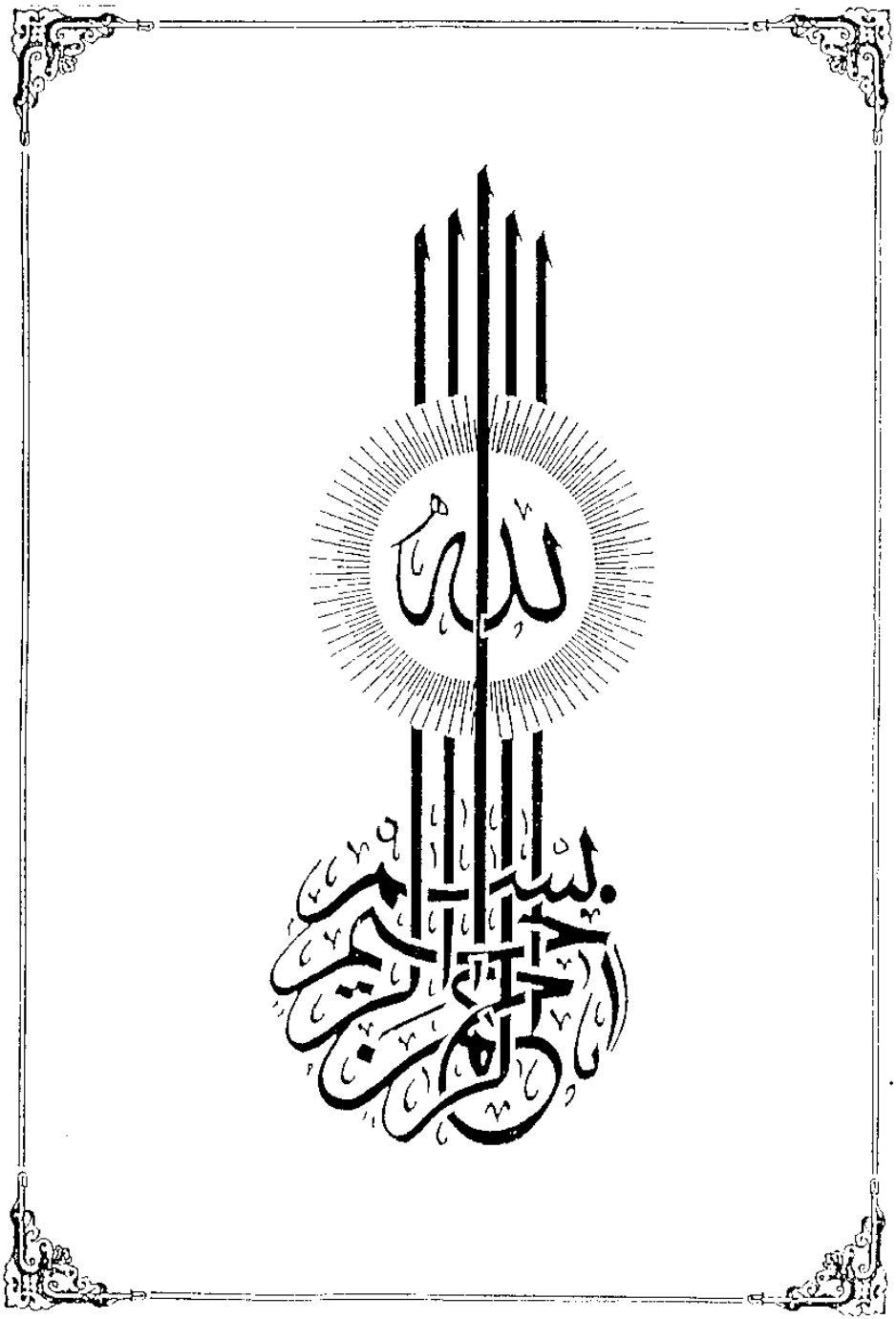
بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما علمتنا إنك إنت العليم الحكيم

صدق الله العظيم

سورة البقرة آيه رقم ٣



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INTRODUCTION

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The metabolic effect of renal insufficiency are complex and involve many systems in the body .

The disturbance in calcium homeostasis is an almost inevitable consequence of renal failure ; it imparts significant morbidity and mortality to patients with renal failure .

As the maintenance of calcium in intra and extracellular fluid is critical to a variety of cellular and organ functions , the disturbance in calcium homeostasis has been implicated in the genesis of abnormalities in cardiovascular and central nervous systems as well as the hematological and bone changes that accompany renal insufficiency .

The pathogenesis of these disturbance is currently under study and the underlying mechanisms are not yet fully clarified .

AIM OF WORK

AIM OF THE WORK

The present work was planned to investigate the effects of renal insufficiency in uremic patients and experimental uremic models (bilateral nephrectomy , bilateral ureteral ligated and five-sixths nephrectomy) on calcium homeostasis .

REVIEW OF LITERATURE

Calcium Homeostasis

Calcium is the most plentiful cation in the body. Over 98 % is in the bones and teeth, the small part of body calcium present in plasma and extracellular fluids. In extracellular fluid calcium exists in three forms, a non diffusable or protein bound fraction, representing approximately 40 % of the total, most of the nondifusable calcium is bound to albumin, with only 10 to 15 % of the protein bound fraction associated with globulin, a diffusable and nonionized fraction in chelates with bicarbonate, phosphate and citrate, about 5 to 15 % of total calcium and the free ionized fraction, the later is the only physiologically active form and is the fraction that is homeostatically regulated. Changes in total serum calcium may not necessarily reflect alterations in ionic calcium concentration, conversely, alterations can be produced in ionic calcium activity without detectable changes in the total serum calcium.

Maintenance of the calcium concentration in intra and extracellular fluids is critical to a variety of cellular and organ functions including neuromuscular activity, hormone release, action of enzymes, regulation with modulation of membrane permeability. cytosolic calcium concentration is maintained at a level approximately 10^{-7} M. by mitochondrial and cell membrane transport. The maintenance of the serum calcium within normal limits is primarily a function of parathyroid hormone (PTH) , vitamin

D, calcitonin and their target organs the gut, the kidney and bone. As there is no net gain or loss from bone in normal adult, calcium homeostasis depends upon a balance between net absorption from the gut and urinary excretion.

Only 30 to 35 % of calcium intake is absorbed in small bowel. Absorption occurs both actively and passively, the passive component is concentration dependent and requires an intake of 3-4 g/day to approach normal rates of absorption, therefore, under normal conditions the active component which is dependent upon vitamin D is the predominant mode of transport. In addition to absorption in the small bowel secretion of calcium occurs throughout the gut in amount approximately 150- 200 mg/day.

About 60 % of plasma calcium is filtered through the glomerular capillaries *(Harris et al., 1974)* and approximately 98 % of the filtered load is reabsorbed under normal conditions.

The bulk of reabsorption takes place in the proximal portions of the nephron. Reabsorption occurs along the convoluted tubules is linked to sodium transport *(Ullrich et al., 1976)*. The tubular epithelium is highly permeable to calcium *(Murayama et al., 1972)*, calcium reabsorption is shown to be active but was not inhibited by *Ouabain (Rouse et al., 1980)*.

Direct studies of the thin limb of Henles have demonstrated low calcium permeability and no active calcium transport *(Rocha et al., 1977)*. The thick ascending limb is clearly a major site of calcium reabsorption . *Suki and associates (1980)* observed that calcium reabsorption in the medullary thick ascending limb is voltage dependent inhibited by furosemide and unaffected by PTH. In the segment of nephron beyond the loop of Henle active calcium transport occurs, in the distal convoluted tubules which is relatively impermeable to calcium. In the distal and granular portion of the cortical nephron approximately 5 to 10 % of the filtered load is reabsorbed and calcium reabsorption is stimulated by PTH and cAMP *(Costanzo , 1978 and Weindhager 1978)* , and by thiazide diuretics *(Costanza and Weindhager, 1980)*.

The important regulators of urinary calcium excretion are the state of the extracellular fluid volume which regulates sodium transport at calcium sodium linked sites and PTH which controls reabsorption of 2 to 4 % of the filtered load in the distal nephron.

Bone is quantitatively the primary calcium reservoir of the body and play an important role in calcium homeostasis. The quiescent surface of bone and bone lining cells sensitive to calcitropic hormones are actively involved in the constant transfer of calcium into and from bone , the simple calcium phosphate compounds

(brushite) represent the primary calcium storage in the superficial layers of bone.

In normal individuals approximately 110 nmol of calcium enter and leave daily *(Parfitt, 1976)* of which quiescent surfaces exchange 100 nmol, ten times the flux exchanged by remodelling surfaces *(Parfitt, 1989)*.

-Hormones That Regulate calcium homeostasis

***Vitamin D :**

Sources : Humans normally acquire vitamin D either from the diet or through ultraviolet irradiation of the provitamin 7-dehydrocholesterol which is abundant in the skin *(Wheatley and Reinertson 1958, Rausch et al, 1969)* and is first converted to previtamin D3 *(Holick and Clark, 1978)* that occurs in dermis and epidermis *(Holick et al, 1980)* and slowly converted to vitamin D3 via temperature dependent reaction. The biosynthesis of previtamin D3 decrease with aging *(Maclaughlin and Holick , 1985)* and also with increase melanin pigment *(Holick et al., 1980)*.The previtamin is localized in the skin as the plasma vit D binding protein has selective affinity for vitamin D3 rather than previtamin D3.

Vitamin D can also be ingested as D3 (cholecalceferol) or D2 (ergocalceferol), vitamin D2 is produced synthetically by ultraviolet irradiation of the plant steroid ergosterol and is added to dairy products and beards sold in the United States.

***Metabolism of vitamin D :**

Vitamin D is absorbed in the proximal small bowel *(Schacter et al., 1965)*, it is incorporated in the chylomicron fraction and absorbed through the lymphatic system. It is carried in plasma bound to a specific vitamin D binding protein, this protein is an alpha-2 globulin with a molecular weight of approximately 59,000 Da *(Imawari et al., 1976)* and transport to the liver as well as other tissues. The liver hydroxylates vitamin D3 to 25 hydroxycholecalceferol *(Ponchon and Deluca , 1969)*, the predominant form of vitamin D3 present in the plasma *(Gray et al., 1971)*. High plasma level of 25 hydroxy cholecalceferol develop in life guards exposed to sunlight *(Haddad and Chyu,1971)*, late in summer there is a seasonal increase in 25-hydroxycholecalceferol *(Stamp and Round, 1974)*.

Mawer and Coworkers (1971) found that a greater fraction of vitamin D3 was converted to 25 (OH) D3 in patients with vitamin D deficiency than in vitamin D replete persons.

In the avian species , tissues other than the liver may be capable of producing 25 (OH) D3 (Tucker et al., 1973) However the liver plays the major role in this conversion in mammals *(Olson et al, 1976)* The formation of 25(OH) D3 is relatively independent of the supply of environmentally derived Vit D3 its concentration in plasma is rising as large doses of dietary vitamin are provided *(Gray et al., 1971)* and it is probably constitutes the circulating reserve of vitamin