CALCIUM HOMEOSTASIS IN THYROTOXICOSIS

Thesis Submitted

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Submitted by

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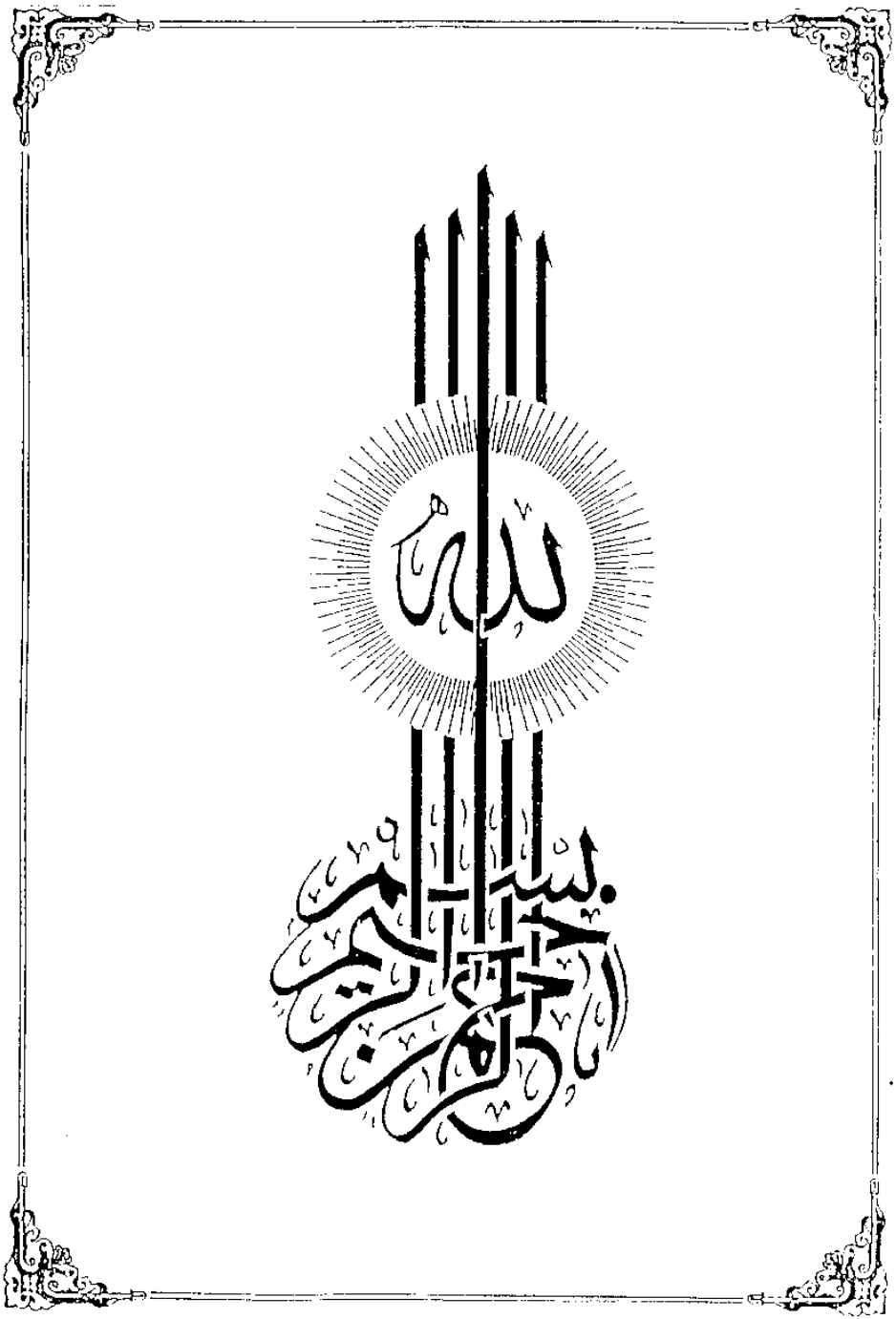

AIM OF THE WORK

Since Von Recklinghausen's original report 1891 of thyrotoxicosis associated with bone changes; various studies reported the occassional occurence of osteoporosis and various changes in calcium metabolism in thyrotoxicosis. There is a tendency towards hypercalcaemia, hypercalciuria and a negative calcium balance in association with thyrotoxicosis. Moreover, hypocalcaemia has been reported following thyroidectomies for patients with thyrotoxicosis.

The aim of this work is to review the changes in bone and calcium metabolism in thyrotoxicosis, their pathogenesis, and their prevention and treatment.

C O N T E N T S

CHAPTER (I)

HISTORICAL INTRODUCTION.

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Although the thyroid gland has been first described by Galen in his "De Voce" and more fully later by Versalius 1543, (Rolleston, 1936), however, it was not until the year 1656 where the gland was given it's name "Thyroid" or oblong shield by Wharton (Rolleston, 1936). Since then, the role of the gland was the subject of interest and speculations. Wharton (Rolleston, 1936) suggested that the gland was there to round and beautify the neck by filling the empty spaces around the larynx, especially in females, to whom, for this reason, a larger gland has been described. Cowper W. (Cowper W., 1668) held that the thyroid like the thymus was a lymphatic gland for the upper body. Whereas Varcellone (1711), argued that the thyroid is a bag of worms whose eggs, and occasionally themselves crossed for digestive purposes into the oesophagus. Even as late as 1825 (Parry, 1825) and up to 1884 (Magnus, L., 1859) the gland was proposed as a "vascular shunt", cushioning the brain against sudden increases in blood flow (Harington, 1933).

The relationship between the thyroid and the various body functions was studied by experimental thyroidectomy as early as 1827 (Cooper, A.P., 1827), and the concept of an internal secretory function was formulated by King 9 years later (King T.W., 1836).

Since then, parathyroids were not recognized until Gley, (1891) redescribed them, death generally followed thyroidectomies performed in those days. Then Reverdin, J. (1883) and Kocher, T., (1883), became aware of the similarity between myxoedema and the clinical picture which developed after successful removal of the thyroid. However Semon, F. (Rolleston, 1936) and Horsley,(1885), were responsible for the recognition of the fact that loss of the thyroid caused both the spontaneous and operative disorders; until then, the prevailing idea had been that asphyxia or injury to the nervous system (Hadden, W.B., 1881), was the cause. It was not until 1896 that Vassale and Generali separated the entity of myxoedema following thyroidectomy from tetany (Welch, D.A., 1898). The final unquestionable identification of the functional roles of the parathyroids came in 1898, with the removal of the parathyroids alone

and the production of tetany, and in 1909 with the demonstration of hypocalcaemia following parathyroidcetomy. (Mc Callum, et al., 1909).

In the year 1891 Von Recklinghausen was the first to describe a 23 year old woman with five years history of thyrotoxicosis who complained of back and arm pains and who had scoliosis. At necropsy, all the bones were very soft and the pelvis was severely deformed. Von Recklinghausen pointed out that this condition did not seem to be late rickets and although the patient had never been pregnant, it had the characteristics of osteomalacia. Since then, a number of hypothesis have been made to explain the mechanisms responsible for the changes found in bone and mineral metabolism in hyperthyroidism. Aub et al.,(1929), suggested that the thyroid hormone acted directly on bone to promote bone resorption, an effect which was thought later to be independent of PTH. Aub et al.,(1932), concluded that the thyroid hormone had a direct effect on the kidney and caused a negative calcium balance by increasing the renal excretion of calcium. Hansman and Wilson (1934)

presented evidence which led them to suggest that the thyroid hormone had no effect per se on calcium and that changes found in some patients with hyperthyroidism were the result of parathyroid overactivity. This view is supported by the observation that a parathyroid adenoma is found frequently in hyperthyroid patients with hypercalcaemia (Jackson, et al., 1961); but is in conflict with other workers who concluded that there is diminished parathyroid activity in hyperthyroidism (Harden, et al., 1964; Adams, et al., 1967). A new link between the thyroid and calcium metabolism was introduced with the discovery of calcitonin (1962) by Copp and his Co-workers. This calcium lowering principle was soon linked in most species with the parafollicular cells of the thyroid proper and renamed " Thyrocalcitonin ".

Some confusion also existed concerning the precise nature of the bone lesion in patients with hyperthyroidism. It has been described as osteomalacia, as osteoporosis, and as osteitis fibrosa cystica. In two patients, there was evidence of excessive destruction, with eroded areas filled with connective tissue and osteoclasts (Hunter, D., 1930). In 1933, typical changes of osteitis fibrosa were described,

which included increased osteoclastic activity, increased vascularity and connective tissue proliferation (Askanazy, 1933). Subsequently, the vertebral bodies of 20 patients with active hyperthyroidism who came at autopsy were examined (Follis, R.H., 1953). Evidence of excessive destruction of bone " osteitis fibrosa" of varying degree was found in 6 patients, and osteoporosis, (i.e. bone containing a decreased number of trabeculae which in turn are thinner than normal). Thus, the common histological feature present in all reports has been excessive bone destruction, with other abnormalities superimposed. These findings are not compatible with the hypothesis that bone formation is decreased and bone resorption normal in the bone of patients with thyrotoxicosis. Kinetic studies using radio-active calcium (^{45}Ca) in 4 thyrotoxic patients, (Krane et al., 1956) revealed that the size of the various calcium compartments was strikingly increased. The rates of calcium deposition and resorption in bone increased several folds in these subjects and returned towards normal when the hyperthyroidism was treated.

More recently, the microscopic morphology has been

described in a series of hyperthyroid subjects, in whom the clinical state of the patients was well documented. Adams, Jowsey and Kelly (. 1967), using micrographical techniques on bone specimens obtained by biopsy after the patients ingested flourescene labelled tetracycline as a marker for new bone formation, revealed increased bone resorption in all subjects, as well as increased bone formation in some. There was no increase in the width of osteoid seams in the biopsies from their patients and therefore no osteomalacia.

In a later study by (Adams & Jowsey, 1967) using quantitative microradiography, similar increases in bone resorption were observed accompanied by less striking increases in bone formation in both intact and parathyroidectomized dogs fed thyroxine for 9-11 weeks.

CHAPTER (II)
PHYSIOLOGY OF BONE AND CALCIUM METABOLISM

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CALCIUM.

There is about 1-2 Kg of calcium in the average adult human body, of which 98% is found in the skeleton. (Krane et al., 1977). The calcium of the mineral phase at the surface of bone crystals is in equilbrium with ions of the extracellular fluid, but only a minor proportion of the total calcium (about 0.5%) is exchangeable as determined by isotope dilution techniques (Krane et al., 1977). In plasma, in normal adults, the range of concentration is 8.8 to 10.4 mg/100 ml (2.2 - 2.6 m M) (Krane et al., 1977). It is present in three forms, free ions, bound to plasma proteins mainly albumin, to a lesser extent globulin, and to a small extent as diffusible complexes (Krane et al., 1977). It is the concentration of free Ca^{++} ions that is of critical importance in regulating the level of neuromuscular irritability as well as a variety of other cellular functions and that is subject to exoquisite hormonal control especially through parathyroid hormone & calcitonin, (Krane et al., 1977) The rather wide range of serum calcium is largely due to the wide variations in serum protein concentrations, especially

of serum albumin. The serum albumin and hence the total calcium, but not the ionized calcium, falls in hypoproteinaemic states, with age, in liver diseases and often in the presence of systemic diseases, whereas, it increases with venous stasis.

The concentration of calcium ions in the extracellular fluid is kept constant by the interaction of a number of processes which are constantly feeding calcium into and withdrawing calcium from the extracellular fluid. Decrease in the concentration of free Ca ions in plasma results in increased neuromuscular irritability, and the syndrome of tetany (Krane et al., 1977). The level of calcium ions that determines which features of tetany will be manifested is highly variable in different individuals. An increase in bicarbonate (as in non-respiratory alkalosis); phosphate; citrate (as in massive blood transfusion) or other organic ions will result in an increase in complexed Ca and a reduction in ionized calcium levels, thus producing tetany in the presence of normal total calcium concentration. Respiratory alkalosis produces tetany by reducing the proportion of ionized calcium; acidosis, non-respiratory or respiratory