SEX DIFFERENCES AND ABO TYPING IN VITAMIN D DEFICIENCY RICKETS IN EGYPT

Thesis

Submitted For The Partial Fulfilment
Of The Master Degree

Of

(PAEDIATRICS)

By

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1987

بسم الله الرحمن الرحيم

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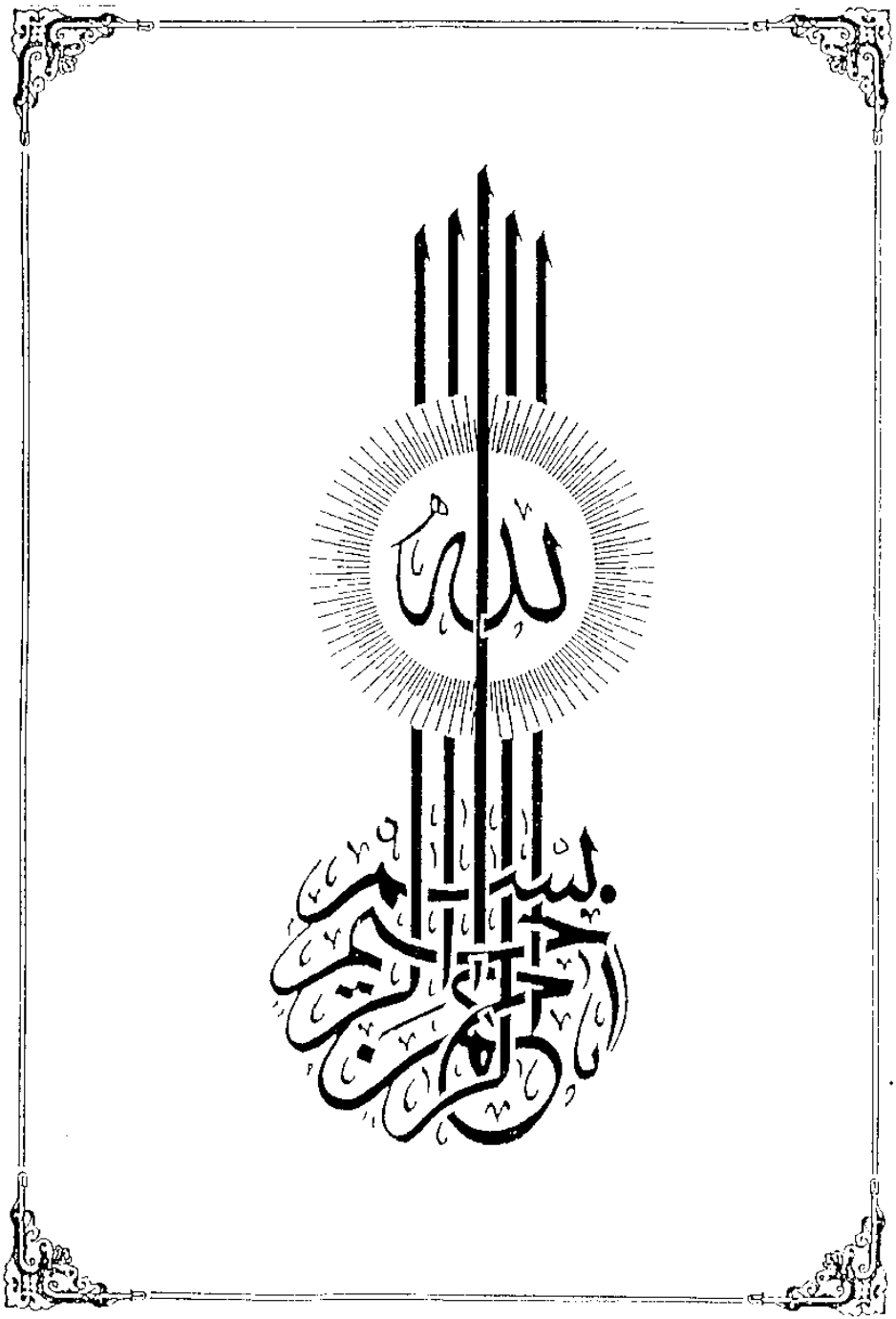

ACKNOWLEDGEMENT

All words fail to express my deep gratitude for the endless advices and efforts granted by Professor Dr. FARDIA FARID, Ass. Professor of Pediatrics, Faculty of Medicine, Ain Shams University, and the senior supervisor of this thesis. Her great interest in the topic and sharp observations have greatly helped this work to be successfully accomplished. My deep gratitude is due to her courtesy and the generous way in which she has given her advices, guides and supervision.

I am also grateful to Dr. MOHAMMAD S. EL-KHOLEY, Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University who has provided the greatest help in writing and completing this thesis. I am thankful for his kindness and help.

Finally, I am very thankful for those who helped and guided me in this work.

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C O N T E N T S

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INTRODUCTION AND AIM OF THE WORK

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During the last 10-20 years rickets due to vitamin D deficiency has almost disappeared from the United States and from many countries of Western Europe. However, rickets continues to occur in warm countries like Egypt (Lapatsanis et al., 1968).

Jonxis et al. (1952), studied the aminoaciduria of vitamin D deficiency rickets and found that some members of the families of rachitic infants were also excreting abnormally large amounts of aminoacids. They have suggested that there might be a hereditary factor in the pathogenesis of the disease. The possibility received additional support when sex differences in infants with nutritional rickets were found by Childs et al. (1962).

With this idea in mind, our work has been conducted in order to study sex differences together with the ABO typing in vitamin D deficiency rickets in Egyptian infants and children inorder to reveal if any association exists between rickets and ABO groups and/or sex.

REVIEW OF LITERATURE

PHYSIOLOGY OF BONE FORMATION

Chemistry and biochemistry of bone:

The average adult human skeleton contains about 1200 gm of calcium and 1500 gm of phosphate plus a mixture of other minerals such as magnesium, sodium, fluoride and other trace minerals as well as carbonate and citrate compounds. These minerals are present in the form of millions of tiny crystals located in and around the collagen fibers.

The chemical nature of bone on a weight basis is 60% inorganic material, 25% collagen traces of muco-polysaccharides and other proteins and 15% water (in the free form not attached to colloids as bound water is). About 5% of the total volume of bone consists of cells (Ganong, 1983).

Since the great majority of the cyrstals are extracellular they are in contact with body fluids and thereby a dynamic equilibrium between the calcium and phosphorus in the blood and bone - is possible. PTH and vitamin D regulate this equilibrium. In general however, most of the bone crystals in the mass of the skeleton are reasonably stable (Guyton, 1986).

Mechanism of bone mineralization:

Essentially there are two phases in the growth of bone. First there is the formation of calcifiable matrix or collagen which is produced by oesteoblasts. Second there is the calcification phase, which begins as a precipitate of calcium phosphate from supersaturated serum. The initial precipitate appears to be octacalcium phosphate, which has an amorphous appearance. Then there is a laying down of amorphous calcium phosphate within spaces or compartments in the collagen fibrils known as seeding or nucleation. The amorphous mass is converted into hydroxyapatite by free lysyl and hydroxylysyl amino acid groups and a fat soluble inductor substance. The apatite grows in ribbons within the fibril to form crystallites. The crystallites grow and coalesce to form crystals. As the bone matures the crystals grow to such a size that they displace the water between them. The mineralization of cementum is probably similar to that of bone because of its histological resemblance (Sobel, 1960).

CALCIUM BALANCE

In spite of a varying diet, the amount of calcium absorbed from the intestine, the amount excreted in the urine, and the amount deposited or withdrawn from bone are so regulated that the level of plasma ionised calcium remains constant. Three hormones are primarily concerned with the regulation of calcium metabolism and balance and effect a constant product of Ca x P levels in the blood. 1,25 dihydroxycholecalciferol is a steroid hormone formed from vitamin D by successive hydroxylations in the liver and kidney. It increases calcium absorption from intestine and bone. Parathyroid hormone, which is secreted by the parathyroid glands, mobilizes calcium from bone and increases urinary phosphate excretion. Calcitonin, a calcium lowering hormone that is secreted by the parafollicular (C-cells) in the thyroid gland, inhibits bone resorption. All three hormones operate in concert to maintain the constancy of the calcium level in the body fluids (Walter and Israel, 1979).

P T H

The net effect of parathormone is raising serum calcium and lowering serum phosphorus. This action is carried out through its effect on the kidney, bone and gastrointestinal tract (Ganong, 1983).

PTH decreases tubular reabsorption of phosphate leading to phosphaturia and increases tubular reabsorption of calcium from the distal tubules. It has a direct action of bone leading to increased bone resorption. Vitamin D is necessary for the action of PTH on bone PTH increases calcium absorption from the intestine. PTH may act on the intestine through regulating the formation of 1,25 OH_2D_3. In addition effects of PTH on the kidney lead to increased excretion of potassium bicarbonate, aminoacids and under some circumstances sodium while decreasing the excretion of magnesium, ammonia.

The action of PTH on the kidney and bone has been demonstrated to be mediated through the adenyl cyclase system, PTH stimulates adenyl cyclase activity and raises cyclic 3,5 AMP level in bone and kidney (Kaplan,1979). PTH secretion is stimulated by even the slight decrease in calcium ion concentration in the plasma and on the other hand any condition which increases plasma calcium ion concentration causes decreased activity of the para-

THE VITAMINS D

The healing of rachitic lesions and the normalization of bone by vitamin D were the basis for the discovery of vitamin D.

The vitamins D are actually a group of compounds. All are sterols which occur in nature, chiefly in the animal organism. Certain of these sterols (known as provitamins D), when subjected to long-wave ultraviolet light, acquire the physiologic property of curing or preventing rickets (Harper et al., 1977).

History

In 1807 Bardsley wrote about the use of cod liver oil in treating osteomalcia, while the first trials to use it in treating rickets was made in 1824.

In 1890 Palm spoke about an antirachitic effect present in the sunlight.

In 1919, Mellanby was able to produce "rickets" in puppies (by keeping them out of sunlight) and further he could cure their disease by the use of cod liver oil.

In 1922, McCollum et al. found that the anti-rachitic factor in cod liver oil was stable and named it vitamin D.

In 1923, Goldblatt and Soames succeeded in curing rachitic rats by feeding them extracts of livers from rats already subjected to ultraviolet light. One year afterwards, Steenbock and Black (1924) demonstrated that the antirachitic activity could be produced in various foods (milk, wheat,...etc) and animals by ultra-violet irradiation.

In 1931, after the investigation of plant derived material, Askew and coworkers, and later in 1932 Windaus, succeeded in isolating and identifying vitamin D_2.

In 1936 . Windaus achieved the isolation and identification of vitamin D_3 from irradiated cholesterol.

In 1966, a new era was opened with the discovery that vitamin D is converted into more active forms in the body before exerting its biological effects.

In 1968, Deluca et al. found out that vitamin D is hydroxylated in the liver to 25 hydroxyvitamin D.

In 1970, Fraser and Kodicek discovered that the kidney produces the biologically most active from of vitamin D virtually identified as 1,25-dihydroxy-vitamin D (1,25-$[OH]_2$-D_3).

By considering the facts that vitamin D is not required in the diet under conditions of adequate ultraviolet irradiation of the skin and that it is the precursor of at least one hormone which functions in calcium and phosphate metabolism, it is likely that the vitamin is not truely a vitamin but must be regarded as a prohormone (Kodicek, 1974).

In 1972, synthesis of $1,25(OH)_2D_3$ was described (Semunter et al., 1972). Also synthesis of 1α OH D_3 was described (Holick et al., 1973).

Chemistry of the vitamins D:

Vitamin-D_2 (activated ergosterol, ergocalciferol or viosterol):

This is the plant type vitamin D_2, manufactured by the action of ultraviolet light on ergosterol, a sterol found in the plant kingdom (e.g., in ergot and in yeast). It occurs very rarely in nature.