EFFECT OF CALCIUM SUPPLEMENTATION DURING PREGNANCY ON BLOOD PRESSURE

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"To my wife Amani

&

my daughter Amira"

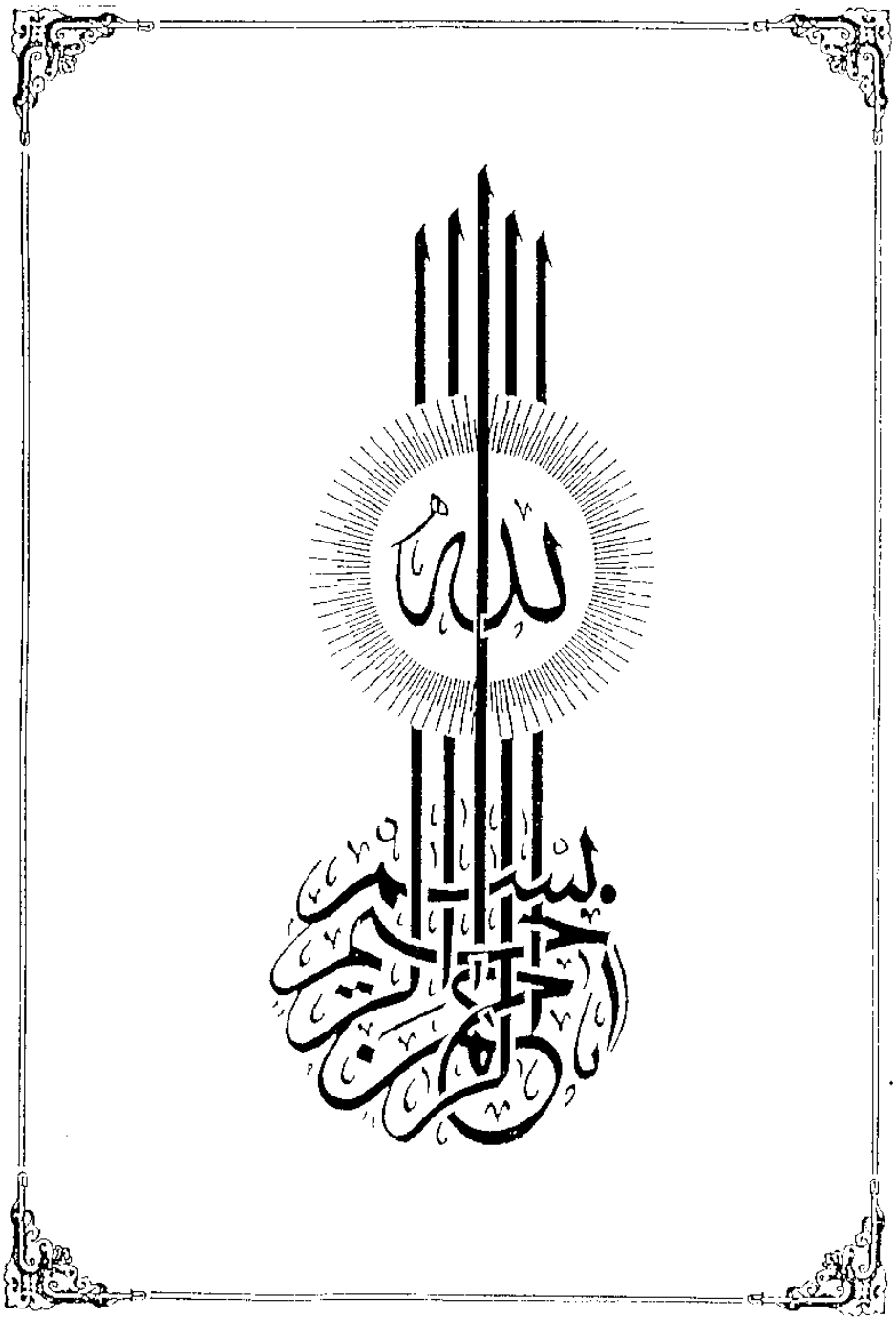

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TABLE OF CONTENTS

AIM OF THE WORK

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The aim of this work is to evaluate the effect of calcium supplementation during pregnancy on blood pressure behavior.

REVIEW OF LITERATURE

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CALCIUM HOMEOSTASIS

Calcium is an essential mineral for the human body (Martin, 1981). The body of a normal adult contains between 20 and 30 grams of calcium per kilogram body weight of which 98-99% is in the skeleton in the form of hydroxyapatite (Michael, 1991).

In addition to its role in bone crystal formation, the calcium ion plays an essential role in many biochemical processes, in neuromuscular transmission, membrane integrity and blood coagulation. It also acts as the intracellular second messenger for hormone action (Michael, 1991).

In serum, calcium exists in different forms with a total normal serum concentration varying between 9.0 and 11.0 mg/dl (Guyton, 1987).

The calcium present in the blood compartment is divided into non-diffusible and diffusible portions depending on its ability to pass across a semipermeable membrane. The non-diffusible or protein-bound fraction represents approximately 40% of the total plasma content; it is mainly bound to albumin with a small portion only attached to the globulins (Michael, 1991).

The diffusible fraction of plasma calcium is mainly in the ionized form (approximately 50% of the total). The remainder being in loose complex formation with a variety of molecules (bicarbonate, citrate, etc.). Thus the ionized and complexed forms together represent the diffusible fraction while protein bound calcium is non-diffusible (Michael, 1991). The ionized fraction is the physiological active portion (Guyton, 1987).

The total serum calcium level varies with the amount of serum protein present while the concentration of ionized

calcium is maintained within normal limits (Pitkin, 1975).

Factors causing a decrease in total calcium by lowering the serum albumin level do not result in obvious metabolic disturbance. By contrast, a fall in ionized calcium has dramatic consequences such as tetany (Pitkin, 1975).

Calcium homeostasis is a complex process involving calcium itself, other related minerals such as phosphorus, magnesium and three calcitropic hormones, parathyroid hormone, calcitonin and 1,25 dihydroxy vitamin D_3 (Pitkin, 1985).

It consists in essence of the relationship between a large pool of calcium in the extracellular fluid modified by input from the gastrointestinal tract and loss mainly from the kidney. The relationship is an extraordinary dynamic one with exchange regulated quite precisely so as to maintain the serum ionic calcium level within narrow physiologic limits (Pitkin, 1985).

Serum concentration of calcium and inorganic phosphorus tend to bear an inverse relationship and the "solubility product" - Ca x P- is relatively constant with calcium and phosphorus expressed in milligrams per 100 ml. The solubility product in the adult is 30-40 (Pitkin, 1975).

Magnesium ion homeostasis appears to be closely related to calcium homeostasis. Magnesium is required for the release of parathyroid hormone (Michael, 1991).

Calcium, magnesium and phosphorus play critical roles in many intracellular processes in addition to their structural function in crystal formation for bone mineralization (Michael, 1991).

Parathyroid hormone (PTH) is a single-chain polypeptide hormone (molecular weight 9500) which exerts its regulatory

role in calcium homeostasis through actions on bone, kidney and gastrointestinal tract. The prime function of PTH is control of the concentration of the ionized calcium fraction in the extracellular fluid compartment; its secretion rate is stimulated by a fall in its concentration and suppressed by an increase. The action of PTH on its target tissues (bone - kidney - gastrointestinal tract) have a common effect resulting in increased extracellular fluid calcium concentration (Michael, 1991).

The action of parathyroid hormone on bone is to mobilize calcium, which it does by stimulating the differentiation of precursor cells with a consequent increase in the number of osteoclasts - the bone resorbing cells. It increases renal tubular reabsorption of calcium and magnesium while decreasing renal reabsorption of phosphate and bicarbonate. Also, PTH activates the specific renal tubule 1α hydroxylase which promotes the synthesis of 1,25 dihydroxy vitamin D_3. PTH has a minor direct action on the gastrointestinal tract promoting calcium absorption and a major indirect action through its effect on 1,25 dihydroxy vitamin D_3 (Michael, 1991).

Calcitonin is a single-chain polypeptide hormone consisting of 32 amino acids (molecular weight 3000). It is synthesized in and secreted by the parafollicular cells (C-cells) of the thyroid gland. The secretion rate being stimulated by increased concentration of the serum ionized calcium fraction (Michael, 1991).

Calcitonin does not appear to be a hypocalcemic hormone but is probably more appropriately described as antihypercalcemic. Its main target tissues are bone and kidney. It has a direct inhibitory effect on bone resorption, inhibiting osteoclastic bone resorption and osteocystic osteolysis (Michael, 1991).

Pharmacological doses of calcitonin increase renal excretion of calcium, magnesium, phosphorus and potassium, but in contrast to the action of the hormone on bone, these effects are transient (Michael, 1991).

Vitamin D is really a group of steriod compounds that possess antirachitic properties. Cholecalciferol (vitamin D_3) is the naturally occurring compound. In humans it is formed in the skin from 7-dehydrocholesterol. It is metabolized to more polar compounds which act on intestine, kidney and bone. The first of these metabolites to be identified ,25 hydroxycholecalciferol, is the circulating form of cholecalciferol and is produced in the liver (Michael, 1991).

The ultimate polar metabolite of cholecalciferol -1,25 dihydroxy cholecalciferol-stimulates intestinal calcium transport, a process involving synthesis of a specific transport protein. It also appears to be active in mobilizing calcium from bone and transporting calcium in the renal tubules. The kidney is the sole site of hydroxylation of the intermediate compound 25 hydroxycalciferol to the highly active dihydroxy metabolite. The rate of renal 1,25 dihydroxycholecalciferol synthesis is stimulated by PTH and is dependent on changes in the concentration of the ionized plasma calcium fraction. This hormone link represents the adaptation mechanism to diet of differing calcium content and to variation in body calcium requirements (Michael, 1991).

Vitamin D forms are carried in the serum by a specific globulin known as D-binding protein (Guyton, 1987).

The calcium content of an average adult diet is between 600-1200 mg/day. Most food in the human diet contain calcium but in varying amounts. The main source of dietary calcium being milk, butter and cheese (Michael, 1991).

Calcium is absorbed throughout the length of the small intestine. Absorption is greater in the duodenum and

proximal jejunum than in the ileum. The mechanisms involved are simple passive ionic diffusion, facilitated diffusion and active transport. In the duodenum, calcium is transported by an active carrier-mediated energy dependent process. Whereas in the more distal segments the mechanisms seem to be passive transport and/or facilitated diffusion (Michael, 1991).

The rate of calcium absorption from the intestine depends on several factors including age, body requirements, previous dietary calcium intake, the absolute amount of calcium in the gut and the availability of calcium for absorption. 1,25 dihydroxycholecalciferol is the dominant factor regulating calcium absorption from the intestine (Michael, 1991). It has several effects on the intestinal epithelium to promote intestinal absorption of calcium. Probably, the most important of these effects is that it causes formation of calcium-binding protein in the intestinal epithelial cells. The rate of calcium absorption seems to be directly proportional to the quantity of this calcium binding protein (Guyton, 1987).

Other effects of 1,25 dihydroxy vitamin D_3 that might play a role in promoting calcium absorption are:

1. The formation of a calcium-stimulated ATPase in the brush border of the epithelial cells.

2. The formation of an alkaline phosphatase in the epithelial cells (Guyton, 1987).

The primary route of calcium excretion is through urine. The diffusible plasma calcium fraction is filtered by the glomerulus, approximately 98% of the filtered load is reabsorbed in the renal tubules. Urinary excretion is relatively constant for a particular individual and varies slightly in relation to intake (Michael, 1991).

Calcium is also lost from the body in faeces. Ultimately, faecal calcium content reflects dietary calcium intake minus the amount absorbed plus endogenous fecal calcium. The latter represents the calcium content of the various intestinal secretions (Michael, 1991).

CHANGES IN CALCIUM METABOLISM DURING PREGNANCY

About 25 to 30 grams of calcium is transferred from the mother to the fetus during gestation, about 300 mg/day being transferred in the third trimester (Pitkin, 1985).

In addition to the net transfer of calcium from the mother to the fetus there is a net loss of calcium into the urine because of the increased glomerular filtration (Maikranz et al, 1989).

A number of changes in maternal calcium homeostasis occurs during pregnancy that prevent the mother from going into markedly negative calcium balance (Maikranz et al, 1989).

The principle maternal adjustment during pregnancy is an increasing PTH secretion which maintains the serum calcium concentration in the face of a falling albumin level, an expanding extracellular fluid volume, an increasing renal excretion, and placental calcium transfer. The increased PTH levels then stimulate the conversion of 25-hydroxycholecalciferol to 1,25 dihydroxycholecalciferol, the biologically active metabolite of vitamin D. (Bouillon et al, 1981) (Gray et al, 1981).

Although the kidney is the predominant site of this 1 hydroxylation step, a significant amount of 1 hydroxylation of 25 hydroxycholecalciferol also occurs in the placenta (Gray et al, 1981).

Levels of vitamin D binding protein also increase during gestation but it appears that both the bound and free fractions of 1,25 dihydroxycholecalciferol increase that stimulates