BLOOD ZINC AND MAGNESIUM IN DIABETES MELLITUS

THESIS

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(General Medicine)

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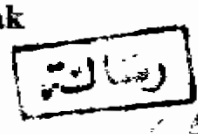

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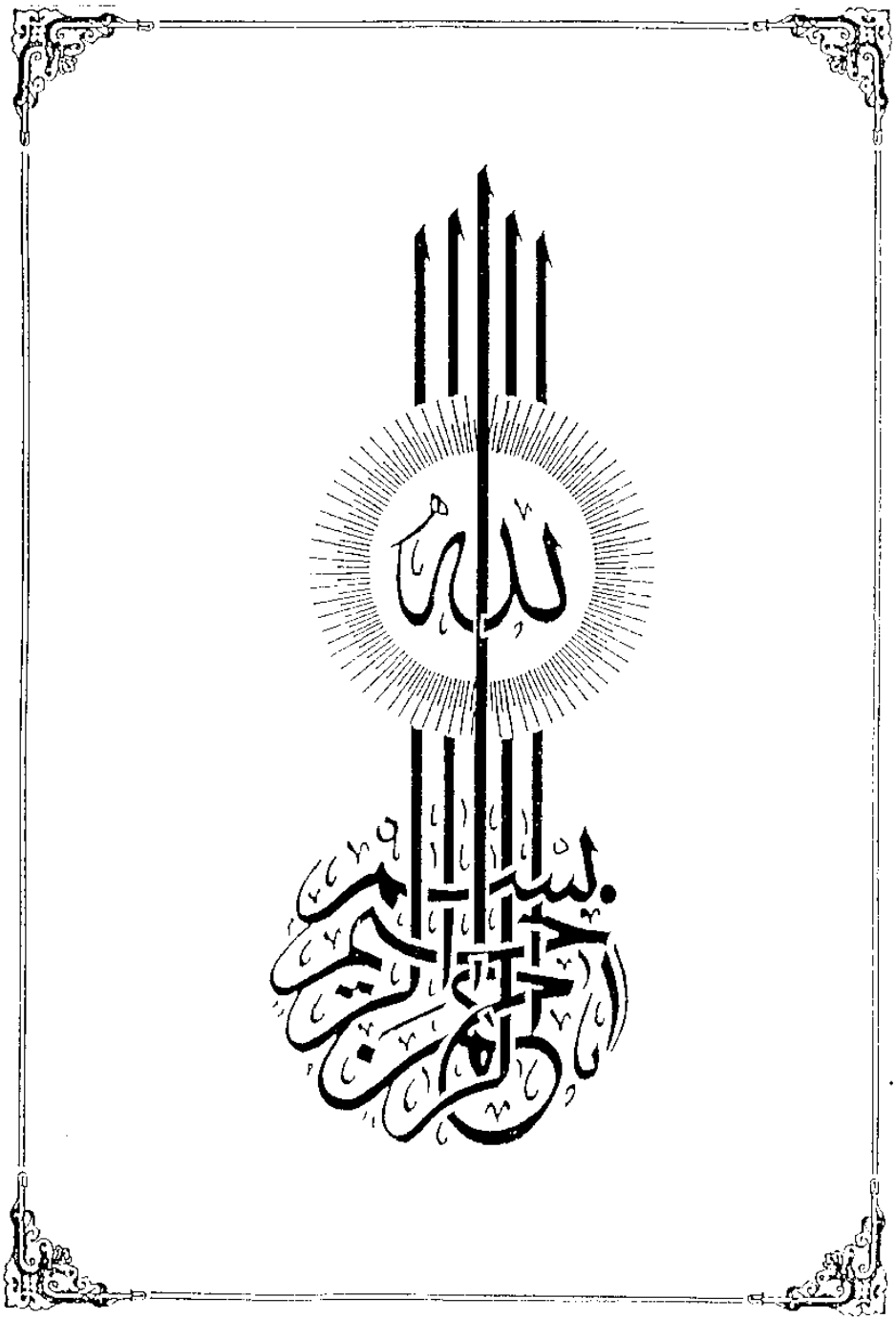

C O N T E N T S

AIM OF THE WORK

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Trace elements specially Zinc and Magnesium play some role in metabolism .

Zinc is an important trace element sharing in metalloenzymes and alkaline phosphatase .

Magnesium is an essential element in many steps of glycolysis and glucose oxidation and neuromuscular excitability

Many studies have been done on serum levels of Zinc and Magnesium in patients with diabetes mellitus . Some showed no difference between diabetics and normal controls .

Others demonstrated hypozincaemia and hypomagnesaemia in diabetes mellitus .

Also Zinc and Magnesium were measured in RBCs with no difference between diabetics and normal controls (Rosner and Gorfien I970)

Ghareeb et al (I973) reported hypozincaemia in diabetics who developed delayed failure of treatment with sulfonylurea drugs.

Hypomagnesaemia is reported as a causative agent in nocturnal muscle cramps in uncontrolled diabetics .

Moreover the same factor has been implicated in the pathogenesis of diabetic retinopathy (Mc Nair I979) .

The aim of this work is to prove or disprove the findings of the above mentioned authers in such important diabetic lesions .

REVIEW OF LITERATURE

ZINC

The normal adult human body contains from I.4 to 2.3 gm zinc, mostly present in muscle, bone and skin. Zinc is present within all body cells with the highest concentration being in the cells of liver then pancreas, kidney, heart, pituitary, adrenals and leucocytes.

Zinc was found to be essential for growth of tissues. The role of zinc in growth was first demonstrated by Raulin (I869) in the growth of Aspergillus niger . Todd et al (I934) demonstrated its role in growth and well being of rats.

Metabolic Balance of Zinc :

(I) Gastrointestinal factors :

The gastrointestinal tract appears to play a major role in regulating the body content of zinc through its capabilities of absorbing and excreting this trace element (Spencer, I965).

Studies using Zn^{65} as a tracer have shown that only 5-I5% of the ingested zinc is actually absorbed.(Spencer, I965), (Prasad, I966).

The intestinal mucosal cells seem to take up Zn from the intestinal contents and then regulate its subsequent transfar to plasma .

The mechanism of this zinc absorption is considered to be through specific binding to small transport protein molecules (Suso and Edwards , I970, I97I) , (Hahn and Evans , I973). The rate of flux from mucosal cells to plasma is regulated by body needs for zinc (Evans et al, I973).

Endogenous zinc is lost from the body via the gut .

Zinc is a component of pancreatic and biliary secretions .

Faecal losses of endogenous zinc may be twice the losses via the kidney (Spencer, I965), (Underwood, I97I) .

Well balanced diet supplies I0-I5 mg of zinc/day (Harper, I973). It is provided as meat, eggs, fish, cocoa, tea, nuts, grains, legumes, milk .

Cereals and most vegetables contain phytate, fibres which can bind zinc and reduce its biological availability.

(2) Renal factors :

Zinc is a normal component of urine, from 0.I to 0.7 mg of zinc/day are excreted by normal adults (Underwood,I97I).

Increased rates of loss of zinc via the urine have been noted in a variety of conditions including early viral hepatitis, trauma, convalesence from surgery . Excessive losses of body zinc via urine appear to accompany periods of acute tissue breakdown . The mechanism of excretion of zinc via the kidney is not known .

(3) Dermal Factors :

Zinc is a normal component of sweat, and considerable quantities of zinc as much as I mg/liter can be lost during copious sweat production . Zinc is also lost through desquamation of skin and via milk specially colostrum .

Distribution of zinc within the body

Studies employing zinc 65 showed rapid deposition and turnover of zinc in liver, pancreas, kidney, heart, pituitary, and adrenals in contrast to slower kinetic rates in muscles, bone, hair and RBCs .

The concentrations of zinc in RBCs and white cells are 6-8 times that of plasma because zinc is a component of metallo enzymes such as carbonic anhydrase and alkaline phosphatase .

The mean concentration of zinc in plasma is about I00 ug/I00 ml ± I0 ug/I00 ml (Pekarek et al , I972). Prasad et al (I975) found normal concentration of plasma zinc is II2 ± I2 ug/I00 ml .

Values may be somewhat lower in females and aged persons (Lindeman et al, I97I).

The reported values in literature of zinc in RBCs are I0 - I4 ug/ml of red cells . (Ross et al, I958),(Prasad et al, I965),(Mansouri et al, I970),(Mc Bean and Halsted I969).

However Prasad et al,(I975) , found that the level of zinc in RBCs to be 42±6 ug/gm haemoglobin .

Almost all zinc in plasma is bound either loosely or tightly to one of several proteins . The prirciple zinc binding protein of plasma is an α_2- macroglobulin that accounts for about 40 % of total zinc (Parisi and Vallee , I970) .

Small portions of zinc may also be bound to enzymes and specific serum proteins such as transferrin (Prasad and Oberleas, I970) .

Most of the remaining plasma zinc is relatively loosely-bound as a macro-molecular complex with plasma albumin . 7 % of plasma zinc is bound to certain amino acids for example histidine and cysteine (Prasad and Oberleas, I970),(Giroux and Henkin, I972).

Metabolic changes in Zinc Deficiency :

(I) Effect of Zinc Deficiency on growth and Nutrient Utilization :

In a study done by Prasad et al,(1963), on Egyptian dwarfs, who had both schistosomiasis, hook worm infestations, and negligible intake of animal protein and their food consisted mainly of bread and beans; in all these subjects bone ages were significantly retarded compared with their chronological ages .

After extensive studies, Prasad et al, (1963 a,b,c.) demonstrated that Egyptian patients had deficincy of zinc in addition to iron deficiency anaemia .

This conclusion was based on the facts that zinc concentrations in plasma, red cells, and hair were decreased, and radioactive Zn^{65} studies showed that plasma zinc turnover rate was greater in patients comared to controls, and the excretion of Zn^{65} in stools and urine was less than in controls (Prasad et al, 1963 b,c).

Liver function test and biopsy failed to show evidence of cirrhosis of liver .

Furthermore, in contrast to cirrhotic patients, who excrete abnormally high quantities of zinc in urine, these patients excreted less stable zinc compared with control subjects .

Other metals assayed in these patients revealed that serum copper was slightly increased and magnesium was normal .

The endocrine abnormalities in these patients resembled those of idiopathic hypopituitarism (Sandstead et al, I967).

Growth failure and hypogonadism were the most outstanding features .

In addition, in some cases decreased pituitary ACTH reserve and abnormal oral glucose tolerance were found . Some of these abnormalities have been described in zinc deficient animals,and therefore probably characteristic of organism rendered zinc deficient at a period of expected rapid growth.

Supplemental zinc given to these dwarfs produced a greater rate of growth compared with those who recieved iron only or protein only(Sandstead et al, I967).

Pubic hair appeared in all cases within 7 - I2 weeks after zinc supplementation . The size of genitalia became normal and secondary sexual characters developed within I2 - 24 weeks in all patients recieving zinc .

These changes were not observed in comparable group recieving iron or single protein diet .

The growth retardation observed in zinc deficiency does not seem to be due to decreased food intake .
In young pigs given a zinc deficient diet, the growth rate declined beforefood intake was affected (Miller et al, I968) .
Zinc deficiency impairs nutrient utilization, perhaps by changes in enzyme activity .

(2) Effect on Hormones :

A - Glucose tolerance :

Hove et al, (I937) and Hendricks and Mahoney (I972) found no difference in oral glucose tolerance between zinc deficient and zinc supplemented rats .
However, when glucose was injected intraperitoneally as done by Quarterman et al, (I966), the glucose tolerance of zinc deficient animals was depressed compared to controls .

B - Insulin :

Quarterman et al, (I966), demonstrated that zinc deficient rats exhibit a reduced concentration of plasma insulin compared to pair fed controls . They believe that the rate of insulin secretion in response to a glucose stimulation is reduced in zinc deficiency.
Furthermore, the zinc depleted ahimals were less sensitive

to hypoglycaemic coma and convulsions when soluble, zinc-free insulin was injected intraperitoneally, though there was no differances in blood glucose level .
Huber and Gershoff, (I973), noted that serum of zinc deficient rats contained less immunoreactive insulin compared with that of ad libitum control animal .
Total serum insulin-like activity measured by in vitro adipose tissue assay, was significantly lower in the zinc deficient group than the controls .
However, in further experiments no difference in plasma insulin levels between zinc difficient and zinc supplemented rats .
Boquist and Lernmark (I969) did not find a reduced serum insulin concentration before or after the i.v. glucose to zinc deficient hamsters, although they observed a lowered glucose tolerance .
Since a similar reduction in glucose tolerance was found after pancreatectomy (Boquist, I967) and after alloxan (Boquist, I968), they believe that zinc deficiency causes a "Prediabetic" condition .
Furthermore, B- cells of pancreas as examined by light and electron microscopy showed reduced granulation, and thus possibly a reduced insulin content .