ZINC METABOLISM IN PATIENTS WITH DIABETIC KETOACIDOSIS BEFORE & AFTER TREATMENT

THESIS

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BY

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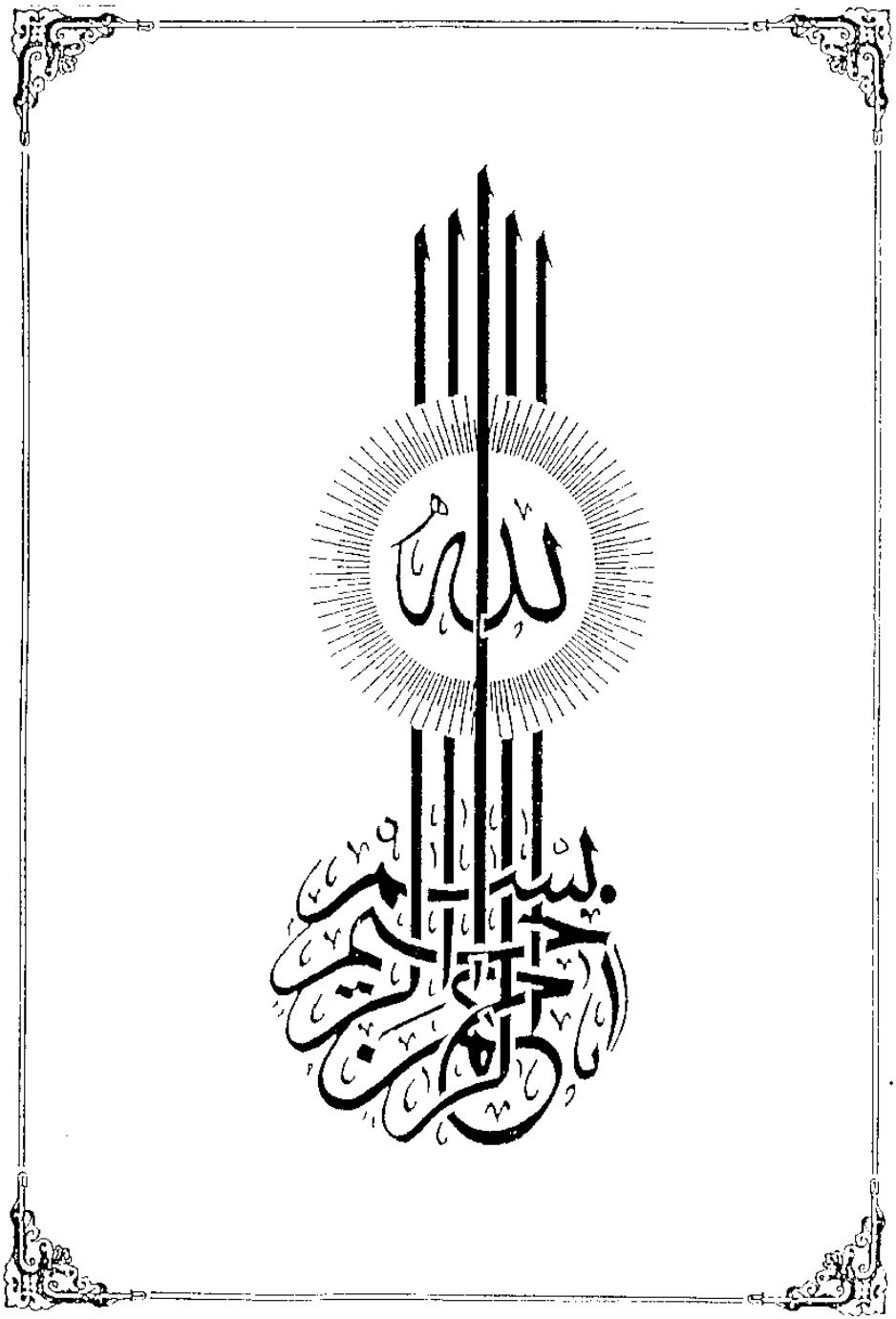

ABBREVIATIONS

AcAc	Acetoacetate
AMP	Adenosine Monophosphate
BoHB	B-hydroxybutyrate
B.P.	Blood pressure
B.R.	Background Retinopathy
CAS	Carbohydrate Active Steroids
DKA	Diabetic Ketoacidosis
D.M.	Diabetes Mellitus
E.C.F.	Extracellular Fluid
FBG	Fasting Blood Glucose
G-6-P	Glucose-6-phosphate
HDL	High Density Lipoprotein
I.D.D.M.	Insulin Dependent Diabetes Mellitus
I.H.D.	Ischemic Heart Disease
N.I.D.D.M.	Non-Insulin Dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
PCWP	Pulmonary Capillary Wedge Pressure
P.R.	Proliferative Retinopathy
PRL	Prolactin
R.B.S.	Random Blood Sugar
RDA	Recommended Daily Allowance
r.p.m.	Revolutions per minute
S.Z.	Serum Zinc
TRH	Thyrotrophin Releasing Hormone
U.Z.	Urinary Zinc
VLDL	Very low density lipoprotein
Z.cl.	Zinc clearance

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Introduction

Diabetic ketoacidosis is one of the acute metabolic complications of a diabetic patient. It remains relatively common and is still associated with an average mortality rate of 15% **(Conaglen and Sonksen, 1989).**

Zinc is an essential trace element that is directly involved in the physiology of insulin. There are several reasons to suspect that abnormal zinc metabolism could play a role in the pathogenesis of diabetes mellitus and some of its complications **(Kinlaw et al., 1983).** Also, **May and Contoreggi (1982),** have reported that zinc can inhibit stimulated lipolysis.

Studies on zinc metabolism in diabetic patients have shown contradictory results **(Mc Nair et al., 1981).** However, **Hagglog et al. (1983),** have found that serum zinc concentration was reduced significantly at onset of insulin-dependent diabetic children in various degrees of metabolic control (i.e. blood and urine glucose, degree of ketoacidosis, dehydration and weight loss).

Aim of the Work

The aim of this work is to investigate zinc metabolism in diabetic patients with ketoacidosis before and after treatment.

REVIEW OF LITERATURE

ZINC AS A TRACE ELEMENT

In recent years, trace elements have attracted attention because they play an important role in many aspects in health and diseases **(Ghareeb et al., 1984).**

Mclaren (1986), divided trace elements into 3 groups:

(A) Trace elements known to be essential for man: Zinc, Copper, Iron, Iodine, Cobalt, Manganese, Molybdenum, Selenium, Fluorine, and Chromium. These are required in amounts of no more than a few mg/day and sometimes a few µg.

(B) Trace elements essential for animals but not proved necessary for man: tin,nickle, silicon, and most recently, arsenic and possibly cadmium and lead.

(C) Trace elements with no known function: mercury, barium, strontium, aluminium, lithium, beryllium, rubidium, gold, silver and others.

I. Zinc Biophysiology

Zinc is essential for many biological functions in man and animals. The biochemical functions in which zinc has been implicated as necessary include: enzyme and enzymatic functions, protein synthesis, and carbohydrate metabolism (Halsted et al., 1974).

Zinc and Enzymes

Vallee (1955), defined a zinc metalloenzyme as a catalytically active metalloprotein containing small amounts of zinc firmly bound at its active site. In zinc metalloenzyme, metal is located at the active site and participates in the actual catalytic process and zinc serves in both catalysis and stabilization of structure (Drum et al., 1967).

Zinc metalloenzymes participate in wide variety of metabolic processes including lipid, protein, and nucleic acid synthesis or degradation. They include several dehydrogenases, aldolases, peptidases, and phosphatases (Vallee and Wacker, 1970).

There are now over 70 metalloenzymes known to require zinc for their functions (Riodran and Vallee, 1976).

One of the most important enzymes of which zinc forms an integral part is carbonic anhydrase enzyme which

is present in highest concentration in red blood cells. This enzyme is responsible for rapid combination of carbon dioxide with water in red blood cells forming carbonic acid which dissociates into bicarbonate and proton, the equilibrium is toward the dissociation. The following equation explains this reaction:

$$Co_2 + H_2O \xrightarrow[\text{carbonic anhydrase}]{} H_2CO_3 \xrightarrow{\text{spontaneous}} HCO_3^- + H^+$$

(Adapted from Martin and Jr., 1985)

Also, zinc may have a regulatory role as in aspartate - transcarbamylase **(Rosenbusch and Weber, 1971).** There are three enzymes, alkaline phosphatase, carboxypeptidase and thymidine kinase, which appear to be most sensitive to zinc restriction in that their activities are affected adversely within three to six days of institution of a zinc - deficient diet to experimental animals **(Prasad, 1983).**

Zinc and Protein Metabolism

Riodran and Vallee (1976), have reported that zinc is also present in DNA and RNA polymerases, in reverse transcriptase of avian myeloblastosis which may indicate relation between zinc metabolism and cancer. Also, zinc has a critical role in nucleic acid and protein metabolism,

so, its deficiency adversely affect the cell mediated immune system **(Malave et al., 1983).**

It has been found by **Fernandez et al. (1973),** that there is a significant reduction in total collagen in the connective tissue of zinc deficient rats in comparison with pair-fed controls. Also, the RNA/DNA ratio was significantly lower in zinc deficient connective tissue. So, the effect of zinc deficiency on collagen deposition was a generalized effect on protein synthesis and nuclei acid metabolism more than specific effect on collagen metabolism.

Zinc and Lipid Metablism

Klevay and Allen (1977) have reported that one of the crucial determinants underlying the pathogenesis of atherosclerosis is a relative deficiency of copper or a high ratio of zinc to copper in the diet and according to this hypothesis, an imbalance in copper and zinc metabolism results in decreased activity of lysyloxidase at a young age, causing decreased cross-linking of connective tissue in the coronary arteries.

Recently, the possible link between ingestion of certain trace minerals and the development of atherosclerosis has been reviewed by **Mertz (1982),** who concluded that no evidence can link trace elements status directly to cardiovascular disease, but that a number of

trace elements have been shown to influence individual risk factors for cardiovascular diseases. Zinc supplementation in rats on a copper and zinc deficient diet was associated with substantial increases in serum cholesterol. Increasing the copper content of the diet partially counteracted the hypercholesterolemic effect of zinc (Klevay, 1973). Also, it has been found that there is a significant interaction between zinc intake and physical activity in their effect upon the level of HDL-cholesterol. This suggested that zinc could negate the effect of exercise on HDL-cholesterol and cessation of zinc supplements was associated with a small but significant increase in serum HDL-cholesterol (Goodwin et al., 1985).

Zinc and Carbohydrate Metabolism

It was discovered by Scott (1934) that crystalline insulin prepared by various procedures contained zinc and that amorphous insulin would not crystallize without the presence of this element. Furthermore, Hendricks and Mahoney (1972) postulated that the reduced glucose tolerance of zinc deficient animals is caused by an increased rate of insulin degradation. Also, zinc has been shown to enhance the action of insulin in promoting uptake of glucose by adipose tissue (Edward et al., 1978).

Zinc and Hormones

Prasad et al. (1969) reported that growth hormone

given to zinc deficient pigs did not improve growth or food intake and had no influence on serum zinc level or serum alkaline phosphatase activity.

Many studies have been done to investigate the serum prolactin (PRL) response to an oral zinc challenge *in vivo*. One of these studies which was done by **Login et al. (1983)** has shown that the suppression of prolactin release by zinc, *in vitro*, displays the following characteristics: It is dose dependent over a range of physiological zinc concentrations. Physiological concentrations of zinc inhibits secretion to a greater extent than synthesis, and pharmacological concentrations inhibit both synthesis and secretion. Also, both basal and *TRH-stimulated* secretion are reversibly inhibited and the process is specific for prolactin **(Judd et al., 1984)**.

These observations are consistent with the hypothesis that prolactin is a zinc-regulating hormone and that zinc induced inhibition of prolactin secretion is closure of a negative feedback loop **(Koppelman, 1988)**. However, **Koppelman et al. (1989)** were unable to demonstrate an acute suppressive effect of oral zinc on basal or TRH-stimulated PRL secretion in either normal or hyperprolactinemic women.

It has been found that patients with untreated