TRACE ELEMENTS IN HYPERCHOLESTEROLAEMIA

THESIS

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By

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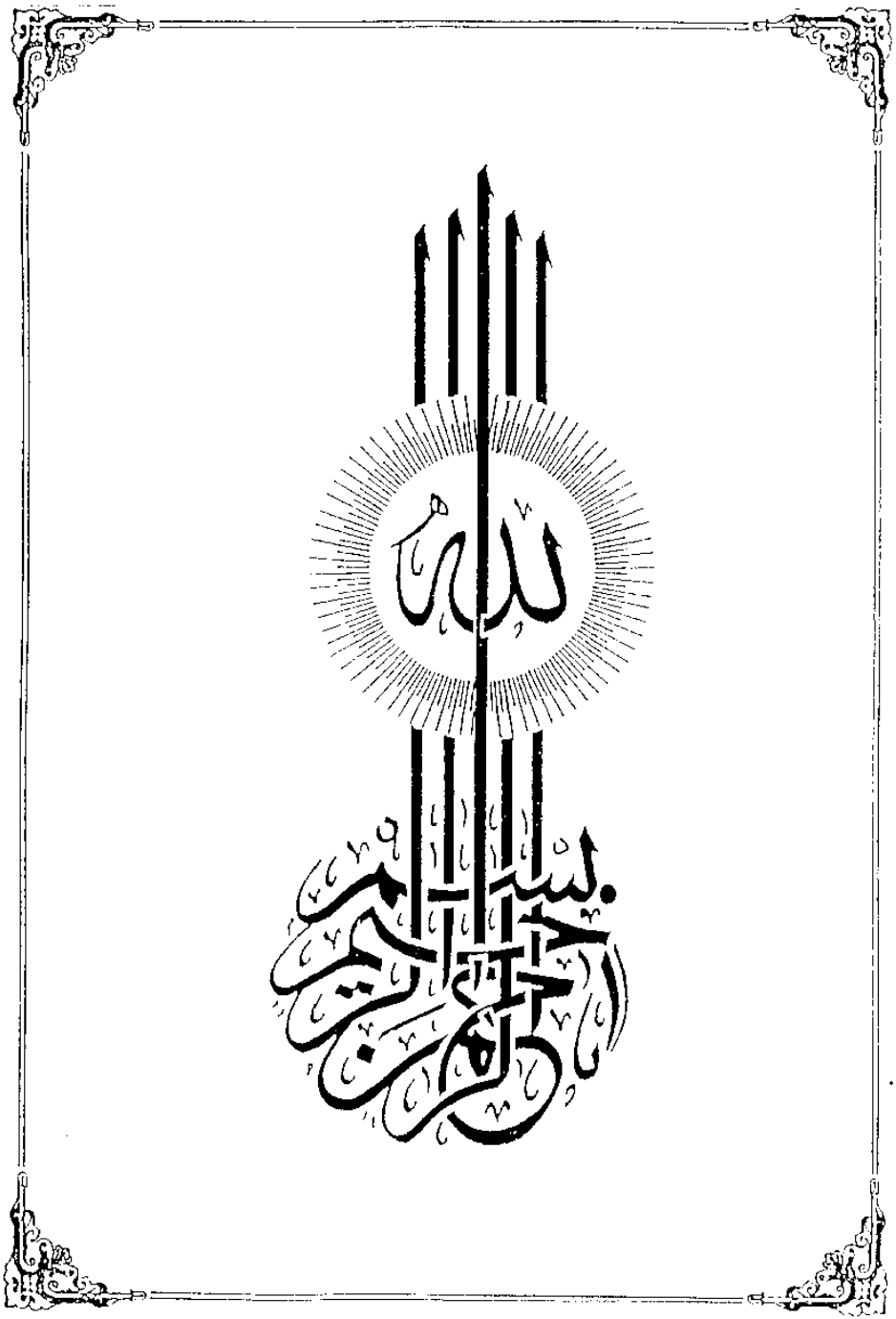

C O N T E N T S

THE AIM OF WORK

It has been observed by some workers that hypercholesterolaemia could be produced in rats by an increase in the ratio of zinc to copper in their diets (Klevay, 1973).

The W.H.O report on trace elements in human nutrition issued in 1973 contained this same fact as reported by Wooster P.O. (1965). It also stated that the ratio of zinc to copper in the tissues may influence lipid metabolism in rats.

Therefore it is the aim of this work to study the health significance of zinc to copper ratio in man by studying their levels in subjects with hypercholesterolaemia,, and to find any imbalance between the zinc and copper which may be a hidden contributary factor in the development of hypercholesterolaemia and other lipid metabolic disturbances.

INTRODUCTION

TRACE ELEMENTS

Certain elements although present in minute amounts in the tissues, are essential nutrients. Their presence was long overlooked and even after their identification, shortcomings of the methods available for analysis together with failure to recognise their importance led to their being reported as present in traces and therefore to their deprecatory designation as trace elements. They perform functions indispensable to maintenance of life, growth, and reproduction. Inadequate intake of trace elements may impair cellular and physiological functions and often causes illness.

Zinc :

Raulin in 1869 first showed that Zn was essential for growth of Aspergillus niger. This was confirmed 40 years later by Bertrand & Javillier (1911), and in 1926 its essentiality for higher forms of plant life was established Sommer and Lipman (1926). In 1934 Todd et al., proved that zinc was essential for the growth of the rat but recognition that lack of zinc could be a limiting factor in nutrition under non-experimental conditions was delayed for another 20 years until Tucker & Salmon

(1955) found that an increased zinc intake corrected parakeratosis in swine. Subsequently lack of zinc was proved to be responsible for a syndrome of hypogonadal dwarfism in adolescence encountered in Iran Prasad et al (1961) and Egypt Prasad et al (1963).

Availability and absorption:

A well balanced diet supplied from 10 to 15 mg. of zinc daily. However, only 20-30% of it is absorbed. Zinc is widely distributed in foods such as meat, eggs, fish, cocoa, tea, nuts, grains, legumes, oysters, cow's milk and water from galvanized pipes.

All cereals and most vegetables contain phytate and fibers, which can bind zinc, particularly in the presence of calcium and reduce its biological availability Cartwright et al. (1960), also an increased copper content of the diet causes decrease in zinc absorption Carter et al. (1969).

Zinc is absorbed from the small intestine. The mechanism of absorption is unknown. However absorption does not take place by simple diffusion. There are at least two proteins in the intestinal mucosa that bind zinc Van Campen and Nowalski (1971), but it is not clearly evident

that those proteins are involved in zinc absorption. Evans et al. (1973), showed that zinc absorption is inversely related to intestinal mucosal zinc content and they suggest that the latter may be regulated by zinc content of plasma. The mechanism of this regulation is unknown.

Excretion:

The primary excretory pathway for zinc is the gastro-intestinal tract, by way of the pancreatic secretion Spencer et al (1965) though which a maximum of 1.5 mgm. can be excreted daily. The mechanism of excretion is unknown. Small amounts of zinc may be lost in the urine "300-700 ug/24 hr". Zinc excretion in urine may increase markedly under conditions of stress, e.g. prolonged Starvation Spencer (1970) or traumatic injury Pell et al (1973), and as much as 1 mg/liter may be lost in Sweat Prasad et al (1963). It is also partly excreted through desquamation of skin and via milk specially colostrum. A small amount is excreted through menstrual blood which is about 308-616 ug/menses. Schroeder et al (1967).

Distribution of zinc in body:

An adult 70 kgm. human body contains 1.4 to 2.3 grams of zinc. The choriod of the eye in all species of mammals has high levels of zinc Underwood (1962). Also a high concentration of zinc is present in the uveal

tract and the prostate. Relatively high concentrations are present in the skin, while the visceral organs contain approximately 30-50 ug/gm. of fresh tissue. Muscle contains approximately Tucker (1955), 50 ug/gm. Most of the body zinc is stored in the bones, where the concentration is approximately 200 ug/gm. Hair contains 125-250 ug/gm. in the adult Hambidge et al (1972).

In blood serum, zinc exists in at least two forms either firmly bound or loosely bound to a protein fraction. The firmly bound zinc is coupled with alpha globulin and satisfies the criteria of metalloproteins, whereas the loosely bound zinc protein is defined as a metal-protein complex, and appears to be concerned primarily with zinc transport Vallee (1959). As yet no specific plasma protein has been definitely identified as a transport protein for zinc like transferrin for iron and ceruloplasmin for copper Bresel (1964). Plasma zinc concentration of healthy persons is about 95 ± 12 ug/100 ml. Plasma zinc concentration of children tends to be slightly lower than adults Sandstead et al (1965). A decline of plasma zinc concentration occurs with advancing age, amounting to 5 ug/100 ml. per decade Lindeman et al (1971).

Concentration of zinc in serum are higher by 5 to 15 ug/100 ml. than those in plasma, mainly because zinc is released from platelets during clot formation Foley et al (1968).

Erythrocytes contain 12-14 ug/100 ml., so erythrocytes contain 75-85% of blood zinc, primarily in the zinc metaloenzyme carbonic anhydrase. Plasma contains 12-22%, and leukocytes contain 3% of zinc in whole blood of human Vallee (1959).

Recent studies on human blood by Parisi and Vallee (1970) indicate that 30-40% of the serum zinc is firmly bound to alpha$_2$ macroglobulin. The remaining zinc is apparently loosely bound to albumin. Despite the relatively large amounts of zinc in tissues, it appears that the exchange of zinc from one tissue to another is limited and for this reason, the organism is dependent upon a regular exogenous supply to meet daily needs for growth and for unusually high localized tissue needs, as in wound healing Carter et al (1969). Zinc is transferred from plasma to body cells by an unknown mechanism Carter et al (1969).

By using radioactive $Zn^{(65)}$ it has been found that liver, kidney spleen, intestinal mucosa, lung, pancreas, thyroid, pituitary, testes, and adrenals show rapid uptake as well as turnover of $Zn^{(65)}$.

The turnover rate of $Zn^{(65)}$ is relatively slow in brain, muscle, and erythrocytes Carter et al.(1969). Hair and bone have very slow $Zn^{(65)}$ turnover rates Carter et al. (1969).

Metabolic role:

Numerous zinc metalloenzymes as well as zinc dependent enzymes have been described since the initial discovery of carbonic anhydrase in 1939 Keilin and Mon (1940). Also zinc is known to be as essential component of nicotinamide dinucleotide-dependent dehydrogenases Vallee (1959), pancreatic carboxypeptidase, liver and yeast alcoholic dehydrogenase, alkaline phosphatase, glutamic dehydrogenase, malic dehydrogenase, glutamic dehydrogenase and probably other pyridine nucleotide-dependent metalloldehydrogenases Sinha et al (1970). In addition, zinc increases the activity of a number of other enzymes apparently as cofactor in a non-specific manner Vallee (1959).

Zinc has been shown to have a role in the metabolism of nucleic acids and proteins Underwood (1962). Experimentally, produced zinc deficiency leads to a prompt decrease in food consumption Mills and Chesters (1970). Growth diminishes , in part because of decreased food

intake, but also because of an extensive impairment of the processes of metabolism. Decreased synthesis of DNA Fujioka (1964) and RNA Fernandez et al. (1963) have been demonstrated. Synthesis of connective tissue protein is impaired Mac Clainet (1973).

In alcoholic liver cirrhosis, plasma zinc is lowered Vallee et al. (1956), Halsted (1970). Hepatic zinc is decreased, as are activities of the urea cycle enzyme Dipton et al(1966), an effect that may enhance the production of ammonia, characteristic of terminal hepatic cirrhosis.

Influence of Zn on lipid metabolism was reported by Klevay ., in 1973. They obtained hypercholesterolaemia in rats by adjusting dietary zinc/copper ratio in the diet to 40. The same effect of Zn/Cu ratio on the blood lipids can be produced by increasing the zinc to copper ratio in drinking water of rats Quarterman (1967).

Zinc and diabetes mellitus:

Diabetics have been shown to have hyperzincuria as compared with a control group Pidduck et al. (1970), but their average serum level is within normal range Pidduck et al. (1970).

The hyperzincuria is out of proportion to zinc that may be administered with insulin. So the hyperzincuria here may be due to the polyurea of diabetes Meltzer et al (1962).

The zinc content was determined in blood, plasma, and urine of diabetic patients by many investigators. The mean level of plasma zinc did not differs from that of healthy persons Gatsko (1965), Reusch and Bunch (1969), Rosner and Gonzien (1970). Also Pidduck et al 1970 indicated that leukocyte zinc levels were not significantly different in both groups, Shustov, 1963 and Turin, 1958 showed that the whole blood zinc content was near normal but in some cases of ketonuria, the zinc content in the blood was higher, while it was lower in diabetic patients without ketone bodies-excretion. Blood and plasma zinc levels did not depend on age, sex, length of illness, blood sugar level, or the effectiveness of insulin therapy, but in patients resistant to insulin therapy, zinc content in the plasma tended to be low Shustov (1963).

Connection between zinc metabolism and diabetes:

At the alkaline pH within the pancreas, insulin can be crystallized only in presence of zinc, cadmium, cobalt and nickel ions Scott and Fisher (1935).

Zinc is not chemically incorporated into the insulin molecule, but crystalline insulin is coated with zinc. The more zinc can be made to adhere to insulin molecule the longer the duration of action of the insulin. Insulin containing small amounts of zinc is very resistant to digestion by proteolitic enzymes. The possibility has been raised by considered that zinc has a functional role in the enzymatic conversion of pro-insulin to insulin within B cells Grant and Cobbs (1970).

There is evidence that zinc is used in the Beta cells of the pancreas to store and release insulin as required Logothata et al. (1961). Degranulation of B cells and release of insulin is accompanied by loss of zinc from B cells, and regranulation of B cells is accompanied by an increase in zinc content of B cells as demonstrated histochemically Logothata et al (1961).

With regard to the peripheral action of zinc insulin, some recent work has suggested that in vitro zinc stimulates glucose uptake by adipose tissue independent of similar action by insulin. In addition, zinc deficiency reduces the uptake of glucose by adipose tissue Quarterman (1968).

Many workers have demonstrated differences of zinc content and handling between diabetic and control pancreatic tissue. In 1938 Scott and Fisher demonstrated that the pancreatic tissue of diabetics contains about only 1/3 the normal concentration of zinc and less than the third of the insulin activity as control pancreatic tissue.

Zinc Deficiency:

Signs of zinc deficiency in man include hepatosplenomegaly, geophagia, hypogonadism, and dwarfism. This syndrome was first related to zinc deficiency by Prasad et al.(1961), in Iran. Prasad et al., (1963) described also the same syndrome in a group of Egyptian males but they were not geophagics Proof that lack of zinc is responsible has been provided by the work of Sandstead et al.(1967), and Halsted (1968). Administration of zinc to affected dwarfs resulted in a dramatic stimulation of growth and sexual development. The Egyptian and Iranian diets do not lack zinc, but deficiency develops because of interference with zinc up-take from the intestine by phytate and fibre Trowell 1972 which are present in the bread. In Iran geophagia is also an important contributing factor, Prasad et al. (1961), as in chronic loss of blood by parasitic infestation Prasad et al. (1963).