SERUM COPPER CHANGES
IN
TRIPHASIC PILL USERS

Thesis Submitted In Partial Fulfilment For The Degree
OF
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«وَفِي أَنفُسِكُمْ أَفَلَا تُبْصِرُونَ»

صدق الله العظيم

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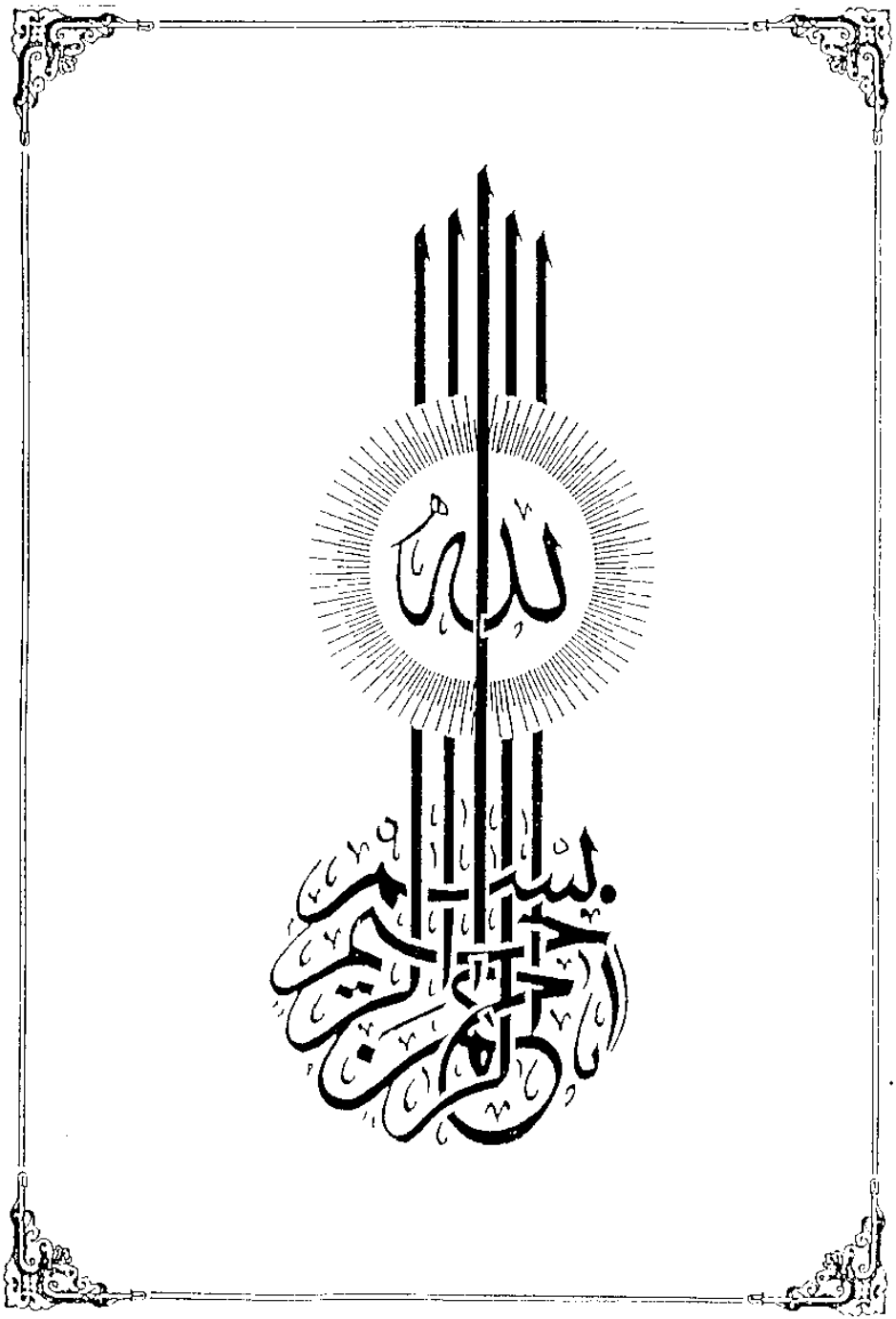

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INTRODUCTION

The biological value of Cu as a trace element was considered since 1925 (133). Methods for serum cu determination have been advanced to a great degree of accuracy. Thus the clinical importance of cu was fully understood (8, 58, 74, 79, 88, 132).

Serum cu concentration were noticed to rise in pregnancy , this was first reported in(1928) by Krebs (63) and later by others (21, 31, 57, 85, 103, 114).Correlation was observed between the elevation of copper levels following oral or parenteral estrogen administration. (98, 120).

Most if not all of side effects of estrogen containing contraceptive pills are attributed to the type and dosage of this componant (22, 36, 77, 78, 95, 125). Therefor, the search for an index of estrogenicity of the pills is a valiable goal for assessment of side effects and for prescribing a particular preparation to particular users.

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REVIEW OF LITERATURE

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BIOLOGICAL VALUE OF COPPER

The importance of copper in nutrition was first demonstrated by Hart and others at the university of Wisconsin in a series of studies that began in 1925. When rats and rabbits were given a milk diet they developed an anemia that was not alleviated by iron supplements, but they improved only when they were given the copper containg ash of certain foods.

From the standpoint of human health, copper is necessary for normal blood formation (haemopoiesis), maintenance of vascular and skeletal structures (blood vessels , tendons and bones) and the structure and functions of the central nervous system. (133).

The deleterious effects resulting from nutritional deficiency of copper in man have been demonstrated by many investigators in recent years. Vir and Love(1981) measured it in serum and hair during pregnancy to reflect the nutritional status of copper and its importance of adequate copper nutrition during pregnancy and for fetal development. (127).

There was elevation in serum copper levels during pregnancy which had been ascribed to increased estrogen

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levels (50, 103), and progesterone concentration (102). This observation was further strengthened by the observation that administration of estrogen and intake of estrogen containing oral contraceptives produce an increase in serum copper concentration. (18, 44, 104, 105).

Copper is very important for biological oxidations. It occurs in certain oxidases and possibly in other enzymes. It is now known that many enzymes and all oxidases contain copper. These are: cytochrome oxidase (a_3) , superoxide dismutase (hemocuprein), ferroxidase (ceruloplasmin), tyrosinase (melanomase), uricase (liver, kidney), dopamine oxidase, benzylamine oxidase, diamine oxidase and tryptophan 2,3 dioxygenase (tryptophan pyrrolase). Copper is present to the extent of about 0.34% in one of the plasma alpha 2 globulins, (ceruloplasmin) which apparently serves as a ferroxidase. (88).

Copper deficiency increase susceptibility to infection. This may partly be due to impaired immune responses observed in copper deprivation states. A common thread running through all copper deficiency states is the frequent occurrence of infection such as bronchopneumonia and bacterial septicemia with Escherichia coli

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and other organisms. Sepsis is a frequent terminal event.

Copper deficient animals show increased mortality when exposed to salmonella typhimurium and coxsakie B virus. Recent data implicate impaired immune response in the susceptibility of copper-deficient subjects to infection. (93).

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COPPER

* Sources of copper:

The occurrence of copper in several oxidative enzymes makes its presence in the diet essential. However a dietary copper deficiency is exceedingly rare except in infants and patients given parenteral feeding with deficient formulas. (79).

The richest dietary sources are: Cocoa powder, dry tea, beef and liver, pecans, walnuts, bran flakes, and peanut butter. Other foods like, apple raw, baked beans, bread, american cheese, eggs, flour, ice cream (vanilla), milk, orange juice, potato and tomato contain very small amounts of copper. (133).

* Daily requirement:

Human balance studies seem to indicate that an ordinary diet completely satisfies man's need for copper. It has been noted that adults maintain a copper balance on an intake of 2 mg/day. Preadolescent girls retained from 0.48 to 0.77mg, i.e the normal diet is enough for copper requirement (29,91). Children require about 0.05 to 0.7 mg/kg body weight daily (74).

Klevay et al in (1980) determined that the requirement for Healthy American men is 1.55 mg/day. And it is

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not affected by the type of source. This requirement substantially exceeds the amount of copper found in many convential diets. (61).

Metabolism

Copper metabolism has been studied less than that of other essential trace elements. This is due to the level of copper present in many tissues are too low to be measured by flam atomic absorption spectrophotometry, a common and relatively simple method of trace elements analysis.

Another reason for limited copper data is the lack of suitable isotopes to use as labels which are specially important in absorption studies. Turnlund in (1982) had used ^{65}Cu to study its absorption in elederly men. (119).

1. Absorption:

a) Site: About 25% of the ingested copper is absorbed from the upper alimentary tract and enhanced by acid and prevented by calcium. (74).

b) Mechanism of absorption: A mechanism of regulation of absorption of copper from gastrointestinal tract according to demand has not been established. But there are some factors which may affect copper absorption, e.g:

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egg albumin protein, may have an effect on copper absorption, the longer period of adaptation may have resulted in an increase in copper absorption and there may be individual differences between subjects. It is possible that with a lower level of dietary copper a higher percentage would be absorped. (119).

II. Transport and storage:

The transport of copper absorped either gastrointestinally or adminstrated intravenously has been studied with radioactive copper, ^{64}Cu. Ther is a transient initial rise in serum copper associated with the albumin fraction (direct), followed by a slower secondary rise associated with the alpha 2 globulin fraction, ceruloplasmin , (indirect). Ingested copper, loosely bound to serum albumin (direct) is transported rapidly to the liver, bone marrow and other organs where it is stored and becomes incorporated into cuproproteins. The slow secondry rise of serum radioactivity associated with ceruloplasmin can be taken to represent the incorporation of copper into this protein by synthesis and perhaps by exchange. The amino acid bound fraction in serum may be involved with the transport of copper across cell membranes. (74).

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III. Excretion:

The bile is the major pathway of copper excretion and small amount usually less than 30 ug/24h volume is excreted in the urine independant of the intake. Less than 5% of ingested copper is retained (74). Turnlund et al. in (1982) had determined the excretion of Cu into the gastrointestinal tract by injecting a labeled dose of ^{65}Cu and measured appearance in the faeces. In one study, recovery of intravenously adminstered radioactive copper, in the bile of patients with bile fistulas was 7.8% and an additional 2.1% was recovered in the stools, while in normal subjects resulted in recovery of an average of 12.4% and of 9 to 10% in the stools. (118).

IV. Normal values:

The average copper concentration of an adult vertebrate is of the order of 1.5 to 2.5 ug/gm fat free tissue. A total of 100 to 150 mg of copper is found in normal man. In general, the liver (10-15 mg), kidney, heart, hair and brain (10mg), they contain the highest concentration of copper. Spleen, lung, muscles, and bone contain intermediate, while pitutary, thyroid and thymus have the lowest concentrations. (74).

a) Serum: There is sex difference with females, showing higher levels than males (132).

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