SERUM IRON IN ACUTE MYOCARDIAL INFARCTION

THESIS

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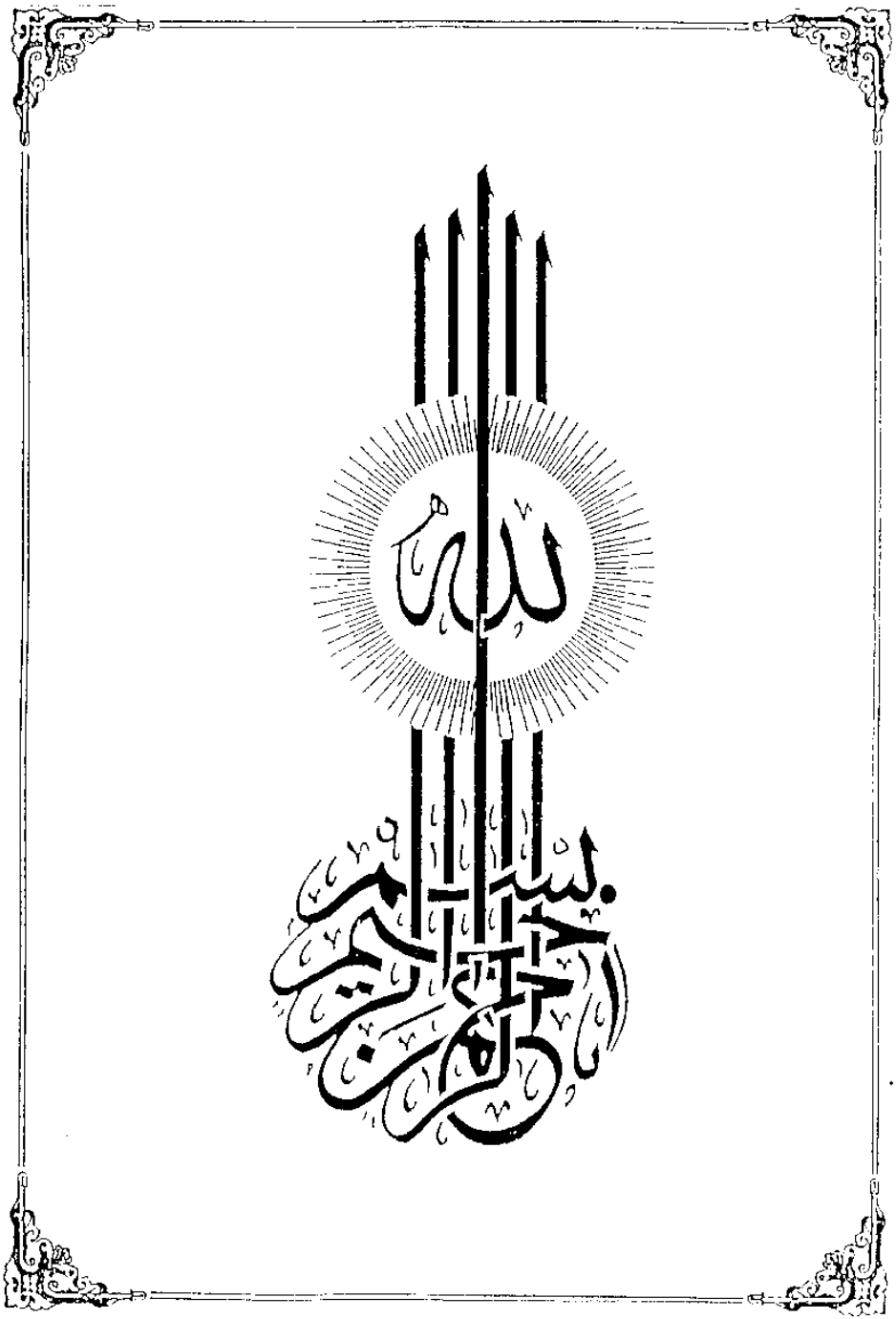

CONTENTS

INTRODUCTION AND AIM OF WORK

The serum iron concentration and total iron-binding capacity (TIBC) vary markedly in different physiological and pathological conditions (Laurell, 1952).

Sudden onset of occlusion of a coronary artery in acute myocardial infarction is usually associated with a well-defined series of metabolic, functional and ultrastructural changes that could disturb the iron metabolism especially the binding protein transferrin (Barash and Dyaldetti, 1975).

The day to day changes in serum iron concentration that are not due to exogenous factors, show a rapid decrease in serum iron concentration after acute myocardial infarction (A.M.I.). Feldthusen and Lassen reported in (1954), a decrease in serum iron in patients with AMI who did not have infection, chronic diseases, bleeding or conditions which could affect the iron metabolism.

Later, Myhrman and Wilander, (1955) found that the serum iron to be low in acute phase of mycardial infarction associated with chest pain, systemic reactions as fever, leucocytosis, elevation of sedimentation rate as well as cardiac enzymes. In most of the series the maximal decrease in the serum iron was noted at the third day after the infarction (Syrkis and Machtey, 1973).

The aim of the present work is to study serum iron concentration in acute myocardial infarction. A trial to discuss the significance of serum iron estimation relation to cardiac enzymes will be done.

IRON METABOLISM

1- Historical Review:

The basis for the systematic study of the metabolism of iron started when Hoppe-Seyler (1890) described the spectrum of haemoglobin and was able to crystalize it.

Barken (1927), published a series of important papers on iron metabolism, and described a method for the determination of iron circulating in the serum. Heilmeyer and Plotner (1937) reported an easy method for the determination of serum iron, and recommended a modern basis for the clinical study of iron metabolism.

Radioisotope techniques represent an original and essential, contribution to the clinical and experimental study of iron metabolism. The first experiments in animals with radioactive iron were made by Hahn, et al., (1949) who published the first work on iron metabolism using Fe^{59}.

2- Total Body Iron:

The normal body iron content in adult male is approximately 50 mg/Kgm body weight, whereas in adult women is about 35 mg/Kgm body weight. This male-female difference reflects the high incidence of iron deficiency in women but there are no differences in iron metabolism between both sexes (Bothwell, and Finch 1962).

3- Iron Content of Different Foods:

The iron content of food varies widely and its availability for human requirement depends on the physical and chemical nature of iron in food and the integrity of the gastro-intestinal tract. Iron absorption

is enhanced by many dietary animal proteins. Foods derived from grains in which iron forms a stable complex with phytates, contain only small amounts of such iron, that can be converted to the absorbable form (Cook, 1977).

4- Iron Requirements During Growth:

The iron requirements for the period of growth from birth to the age of seventeen years amounts to approximately 3-31/2 grams of iron. If growth is uniform, this would represent 200 mg. a year or, 0.6 mg. a day. This 0.6 mg. is additional to the basic requirements which ensure iron balance in the body apart from growth, (Saddi and Schapira, 1970).

The period of most rapid growth during extra-uterine life and the period of greatest vulnerability to nutritional deficiency is during the first two years of life.

5- Iron Balance:

Unlike other trace elements, iron homeostasis is regulated primarily by absorption and not by excretion. Normally, the body is in a state of positive iron balance. The amount of iron liberated by the normal destruction of senile red cells together with the amount absorped very slightly exceeds the amount required for haemoglobin synthesis and that lost by excretion (Jacob, 1973).

The average intake of iron is variable in different parts the world and under various circumstances. However, 10mg. enters the body to

balance the amount lost, only 5 - 10% of the dietary iron is absorped. This proportion can be increased three to five folds, if iron stores are depleted and decreases in states of iron overload (Jacob, 1973).

6- Physiological Chemistry:

Iron is essential to most living organisms in a variety of vital processes from cellular oxidative mechanisms to the transport of oxygen to tissues. It is a constituent of the oxygen-carrying chromoproteins, hemoglobin and myoglobin, as well as various enzymes. e.g. cytochrome oxidase, xanthine oxidase, peroxidase and catalase. The remaining body iron is present in the flavo-proteins (NADH dehydrogenase and succinic dehydrogenase), the small portion (less than 0.1%) carried by serum B_1-Globulin (transferrin) and 30% of body iron as storage iron (ferritin) and (Haemosiderin) (Bothwell and Finch, 1967).

7- Iron Absorption:

The normal process of iron absorption involves several stages; (Bothwell and Finch, 1962). Iron in food which for the most part is complexed in organic molecules is processed in the lumen of the gut to render it suitable for absorption. It then enters the mucosal cells and carried on the transferrin of plasma and is deposited selectively in certain tissues. It is helpful to consider each of these aspects individually.

- Iron availability:

It is apparent that not all the iron in food could be rendered available for absorption. There is considerable variation between one

food staff and another. For example the iron in eggs and leafy vegetables is poorly absorped by the normal subjects while iron in dietary animal proteins is well absorped (Moore and Dubach, 1956).

Haemoglobin is a good source of available iron and is absorped by a mechanism different from that operating for simple iron salts; (Turnbull et al., 1962). The iron in the storage complex, "ferritin" is relatively less available for human metabolism; (Bothwell and Finch, 1962).

- **Luminal factors:**

Mucosal cells throughout the intestines have the capacity to uptake iron. However, under normal circumstances, most of the absorption occurs in the duodenum and the absorptive capacity is much less in the more caudal intestinal segments ((Bothwell and Finch, 1962). This is related to the fact that the pH and redox potential are optimal in this area. (Wheby, 1970). The number of specific receptors in the brush border explain also the differnces in absorptive capacity in various sites (Linder and Munro, 1977). The physico-chemical form of iron affects iron absorption. Iron from animal origin is absorped more efficiently from food than inorganic iron (Weintraub et al., 1968). Ferrous iron is absorped in greater quantities than ferric iron; (Brise and Hallberg, 1962). Dietary constituents which solubilize iron may enhance absorption whereas compounds that cause precipitation or molecular aggregation of iron decrease absorption (Conrad et al., 1966). Ketosugars, amino acids and amines are examples of dietary ingredients which decrease both the precipitation and polymerization so help absorption of iron

in aqueous solution. Certain substances such as phytates and phosphates as well as oxalates, decrease absorption. Certain substances such as ascorbic acid and cystein even make ferric iron more available than ferrous iron over a wide range of pH (Crosby, 1968).

Various intra luminal factors influence non-heme iron absorption but have no effect on heme iron, which is derived from hemoglobin, myoglobin and hemoproteins in foods of animal origin. When this heme iron exposed to acid and proteases of gastric juice, they free the heme from its apoprotein, while the iron is oxidized to the ferric state, forming hemin. These molecules enter the intact mucosal cells to be metabolized (Weintraub, et al., 1968).

- **Effect of Gastro-Intestinal Secretions:**

Since iron taken by mouth is exposed to the effects of the gastrointestinal juice, a number of studies have been done to find out the effects of these secretions on the absorption of iron salts. Hydrochloric acid potentiates the absorption of ferric iron in human subjects, this is probably due to increased availability of iron resulting from reduction of polymerization and protein binding at low pH; (Jacob, 1968).

Recently it has been discussed that there is a factor in the gastric juice of normal jsubjects which binds iron and that marked reduction of this factor is found in subjects with idiopathic hemochromatosis and iron deficiency anaemia (Davis et al., 1966). This substance was called gastroferrin. However in recent studies, the iron-binding capacity of gastric juice was found to be similar in normal subjects and in patients with hemochromatosis and it was doubted wheather gastroferrin was an important regulator of iron absorption (Wynter and Williams, 1978).

Bile enhances iron absorption because it contains significant quantities of ascorbate and other reducing compounds (Conrad and Schade, 1968). While the results of studies done by Balcerzak et al., (1967) do not suggest that pancreatic secretions play a significant role in the control of iron absorption.

Intestinal motility is believed by Schade et al., (1969) to alter iron absorption by changing the interval during which iron is exposed to the absorptive surface of the gut.

- **Mucosal factor**

The quantity of iron in the body is maintained primarily by controlled absorption from the duodenum and to a lesser extent by excretion. There are many theories describing the regulation of iron absorption. Mucosal Block Theory by Hahn et al., (1943)postulated that, there are a limited number of iron acceptor sites within the brush border of intestinal mucosa. If these are saturated, either exogenously or endogenously, a block for further iron absorption will result. The actual metabolic changes which occur in mucosal cells during the absorptive steps are energy dependent through an active transport process (Wheby, et al., 1963). Although some have suggested that it is a non energy dependent but depends on carrier mechanism (Howard and Jacobs, 1972).

These can be divided into 2 steps mucosal uptake followed by transfer of iron to the lamina propria to be rapdily delivered to the transferrin of plasma. The nature of the complex or complexes involved in this phase of iron absorption is unknown. Most of the remaining iron taken up by the mucosal cells is deposited as ferritin, which is an intra cellular protein. When absorption is enhanced little or no ferritin is

is formed that the iron entering mucosal cells is rapidly delivered to the plasma. On the other hand, when absorption is depressed the iron is trapped in ferritin and is lost when the mucosal cells exfoliate (Linder and Munro, 1977). Therefore, for some years, the control of iron absorption may be related to the ability of cells to synthetize ferritin. It appears as if the deviation of iron into ferritin represents a mechanism of preventing excessive absorption from the gut. This will prevent the transfer of unwanted iron to the plasma (Granick, 1954). This theory gradually lost favor, however when it demonstrated that iron is absorped even when tissues are staturated with deposited iron. Ferritin in the bowel represent a storage form, as occurs in other tissues (Beutler et al., 1963).

When heme iron enters the cell, the porphyrin ring is cleaved by an enzyme called heme oxygenase and the liberated iron follows the same pathway as ionic iron (Raffin, et al., 1974).

Generally iron absorption can be related to the state of saturation of body iron stores. Enhanced absorption occurs with iron deficiency and decreased absorption with iron overloading; (Prizio-Birolio and Finch, 1960).

Factors which stimulate erythropoiesis enhance iron absorption, wheathereffective or ineffective (Bothwell et al., 1958).

- Corporeal factors:

Two factors are usually cited as imporatant stimuli to iron absorption. These are the rate of erythropoiesis and tissue iron stores; (Beutler

et al., 1963). Accelerated red blood cell production always seems related to enhanced iron absorption wheather the cause to be bleeding, haemolysis or hypoxia (Simpson, et al., 1983). Conversely, diminished erythropoiesis occuring with starvation, blood transfusion or return to seal level from high altitudes, decreases the absorption of iron; (Conrad et al., 1967).

Many investigators have searched for a humoral factor which signals the gut to enhance or diminsh iron absorption (Conrad, 1969). These are based on measurements of the iron content of the whole gut wall and seemed to show an inverse relationship between mucosal iron and iron absorption (Mattii, et al., 1973).

It appears that the mucosal cells are conditioned at an eraly stage of development to the handling of iron subsequently taken up from the lumen of the gut (Crosby, 1965). Thus the absorptive capacity of each mucosal cell is dtermined by the amount of iron incorporated into the cell, while it is being formed in the cryptes of Lieberkuhn. So, the subsequent absorptive behaviour of the mucosal cell is regulated by the amount of this "messenger iron". More than normal being incorporated when iron stores are excessive or erythropoiesis is depressed. While in iron defficiency states or during accelerated phase of erythropoiesis, there is a reduced amount of incorporated iron into mucosal cell (Worwood and Jacobs, 1971). This cannot however be the only facor of importance since manipulation of the dietary iron content can also affect absorption (Bannerman et al., 1962).

A more recent proposes by Cavill, et al., (1975) suggested that iron absorption is regulated by exchanges taking place between plasma and

the various cellular iron stores. Iron circulating in the plasma bound to transferrin exchanges with iron in all cells of the body. An exchangeable iron pool may be defined as iron available for binding by circulating transferrin. The propability of an iron atom from a given tissue being picked up on transferrin molecule is propoortional to the ratio of exchangeable iron in that tissue to the exchangeable iron in the whole body. The number of iron atoms picked up in this way per unit time is equal to the number cleared from the plasma. This is reflected in the experimentally measured plasma iron turnover.

Iron transfer from the intestinal epithelium to the plasma is therefore proportional to:

$$\frac{\text{Intestinal exchangeable iron}}{\text{Total exchangeable iron}} \times \text{plasma iron turnover}$$

In general the total exchangeable iron in the body is directly related to the level of storage iron and explains why low iron stores are associated with increased iron absorption and high stores are associated with reduced absorption. It could explaine that an incrase in iron absorption may follow an increase in plasma iron tunover as a result of erythroid overactivity (Walter, et al., 1975).

It is, therefore, necessary to postulate that the brush border binding uptake, enterocyte translocation and serosal transfer are formed with a basic pattern of absorptive behaviour. All are showing modulatory responses to iron defficiency or overload. While this concept is an attractive one, most of these studies have been done on animals and there is no assurance that the results apply equally to human subjects. (Schott and Peters, 1983).

8- Plasma Iron Transport

- **Synonymus** Siderophilin, $beta_1$ - metal binding globulin.

In general, iron exists in three states: in transit, in use, or in storage. Transferrin is a protein concerned with the distribution of iron in the body from intestinal sites of absorption and the sites of hemoglobin breakdown to the bone marrow and other parts of hemoglobin synthesis. In the pregnant animal transferrin also carries iron through the placenta to the fetus.

Surgenor et al (1949) isolated the specific iron binding fraction human plasma and called it "metal binding globulin", while Jaurell (1947) called it transferrin.

- **Synthesis:**

Transferrin is synthetized chiefly in the lvier by the rough endoplasmic reticulum of the parenchymal cells. Additional synthesis may occur in macrophages within lymphoid tissue and in such ectodermal glands as the submaxillary, mammary glands, as well as in the ovary and testis (Thorebeck , 1973).

- **Genetics:**

With available electrophoretic techniques, the transferrin band ($beta_1$ - globulin) sometimes appears reduplicated. The extra bands usually of the same concetration as the fraction in the normal location, may appear either anodal or cathodal to the usuall position. This will explain a genetic polymorphism of transferrin. At least 21 variants have been described (Giblett, 1969).