Iron as a Risk Factor in Ischemic Heart Disease

Thesis

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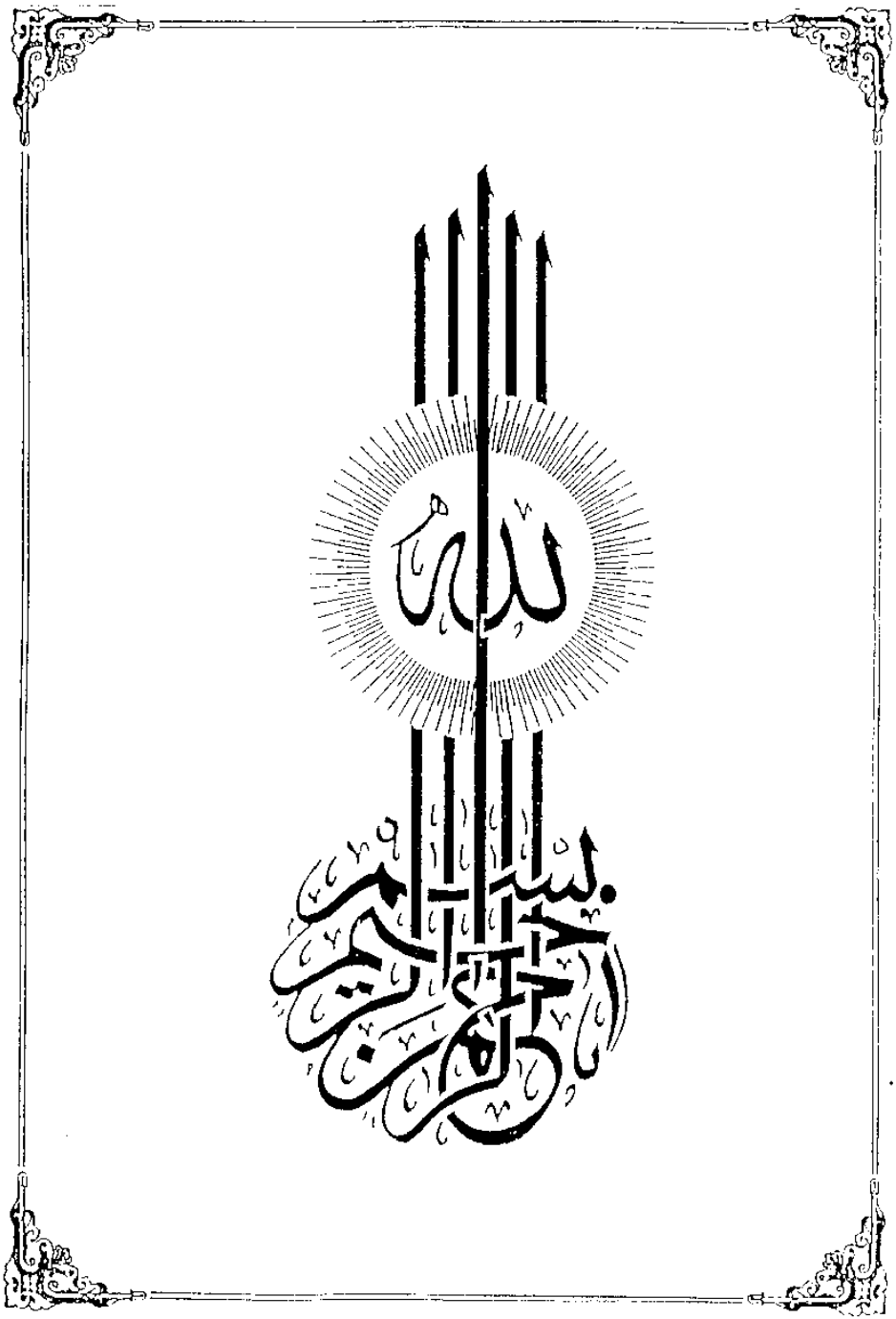

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INTRODUCTION AND AIM OF WORK

Introduction and Aim of the Work

Despite the best efforts of the health sciences, the cardiovascular diseases particularly coronary heart disease (CHD) remain the major source of mortality and morbidity among men in the affluent societies while premenopausal females seem to be protected from the disease **(Gordon et al, 1978; Sullivan, 1981).**

The risk of CHD doubles in menopausal women whether the menopause was natural or surgically induced irrespective to the age at which menopause occurs **(Gordon et al., 1978).**

The mechanism by which premenopausal females are protected from CHD is not yet fully clarified and has been studied by several authors **(Parish et al., 1967; Manchester et al., 1971; Shelton ID, 1982).**

The relationship between the menopause and the risk factors for CHD is complex.

The most surprising change is the rise of serum lipids, cholesterol and triglycerides **(Lindquest et al., 1985).** This increase though significant is too small to be biologically meaningful and is opposed by the changes in the blood pressure and weight observed in these patients **(Lindquest et**

al., 1985). The argument that estrogen could be a protective factor is complex: many observations make it unlikely that estrogen is responsible for the sex difference in CHD (Sullivan, 1981), this is supported by the fact that in surgical menopause, there is an excess incidence of CHD whether the ovaries were removed or not. Postmenopausal women on hormones have even double risk of CHD (Gordon, 1978).

Sullivan, 1981 proposed that the higher risk of CHD among men and postmenopausal women can be attributed to higher levels of stored iron, this is supported by the fact that iron is a known cardiotoxic and arrhythmogenic element in iron storage diseases.

In this study we aim to study the iron as a risk factor for the occurrence of CHD.

REVIEW OF LITERATURE

Review of the Literature

Iron is the fourth most abundant element in the earth crust, only oxygen, silicon and aluminium are more common. Nevertheless, man is extremely vulnerable to disturbances in iron balance and iron deficiency seems almost universal in some populations. This seeming paradox is the result of iron being almost exclusively in the oxidized ferric state, it is therefore highly insoluble at neutral PH and consequently has very little bioavailability.

The poor availability of most of environmental iron led to an evolution of adaptive biological means for acquiring this crucial nutrient. **(Finch, 1985; Pippard, 1985).**

Body Iron:

The total body iron in healthy subjects remains constant within relatively narrow limits, the iron loss is counterbalanced by the iron absorption from food. The total body iron in an adult male ranges between 50-55 mg/kg body weight while in females it is about 35-40 mg/kg B.Wt. **(Kushner, 1985).** For convenience body iron may be divided into that which is essential for normal functions and iron reserves that are useful in times of urgent iron needs. Essential iron includes a variety of heme compounds, enzymes

with iron sulphur complexes and other iron dependent enzymes **(Finch, 1982).**

Hemoglobin and Myoglobin:

Hemoglobin is a readily available major protein in the human body and carries a well known function, the transport of oxygen.

Quantitavely hemoglobin amounts the essential fraction of body iron being 69.6% of total body iron in males, about 2670 mg in an adult male (70 kg body weight) and 73.1% of total body iron in females, about 1500 mg in an adult female (50 kg body weight).

Each molecule of hemoglobin contains 4 heme subunits thus 4 atoms of iron per molecule amounting to 1.1 mg of iron per millimeter of RBC, **(Dallman, 1974)**, normally hemoglobin molecule (Molecular weight 64, 450) is made up of 4 subunits, each one contains a heme moiety conjugated to a polypeptide. Heme is an iron containing porphyrin derivative. The polypeptides are referred to collectively as the globin portion of the hemoglobin. There are 2 pairs of polypeptides in each hemoglobin molecule. One pair is of alpha chains containing 141 amino acid residues and the other is of beta chain, each of which contains 146 amino acid

residues, thus hemoglobin A normally present in adults is designated A_2 B_2. Not all the hemoglobin in the blood of normal adults is hemoglobin A. About 2.5% of hemoglobin is hemoglobin A_2, in which B chains are replaced by delta chains, each is formed also of 146 amino acid residues 10 of them differ from those of B chain. There are small amounts of 3 hemoglobin A derivatives closely associated with hemoglobin A that probably present glycosylated hemoglobins. One of these, hemoglobin AIc (HbIc) has a glucose attached to the terminal valine in each B chain and is of special interest because its quantity in the blood increases in poorly controlled diabetes mellitus. There is evidence that the quantity in the circulation is reduced after 5-6 weeks of good diabetic control **(Ganong, 1985)**. It is particularly valuable in some insulin dependent diabetics to obtain strict control. For example before conception and during pregnancy. It is also useful in long term studies of the relationship of diabetic control to micro- and macrovascular complications **(Wright and Northam, 1982)**.

The other form of essential iron involves myoglobin amounting for 9.1% of the total body iron in adult males (about 350 mg) and 10.7% in females (about 220 mg) **(Dallman, 1974)**. Myoglobin is found in skeletal muscles with greatest content in muscles specialized for sustained contraction. The muscle blood supply is compressed during such

contractions, and myoglobin may provide O_2 when blood flow is cut off. There is also evidence that myoglobin facilitates the diffusion of O_2 from the blood to mitochondria, where the oxidative reactions occur. **(Ganong , 1985).**

The enzymes containing iron: They are of 2 types:

1- Heme enzymes including:

a- Cytochrome C: with a molecular weight 13,200, its amount is 14 grams and contains 0.007 grams iron, its function is oxidation.

b- Cytochromes a, a3, b: their molecular weight, their amount in grams and their iron content is not yet measured, the function is oxidation.

c- Catalase: mol. weight 225,000, amount in grams is 5 grams, contains 0.004 grams iron, its function is H_2O_2 decomposition.

2- Non Heme enzymes: or iron sulphur compounds. They include flavoproteins, oxidases and hydroxylases; their molecular weight, amounts in grams and iron content is not yet measured **(Martin, 1983).**

The Transferrins:

They comprise a class of 2 sited, single chain, metal binding proteins widely distributed in physiological fluids and cell of vertebrates. They are glycoprotein in nature containing 6% carbohydrate. There are 3 major types:

a- Serum transferrin: referred to as serotransferrin or siderophillin.

b- Lactoferrin: the distinctive iron binding protein of milk, tears and leukocytes, sometimes named lactotransferrin.

c- Ovotransferrin, old name is conalbumin.

They originate from a common ancestral gene. Each of the transferrins consists of a single polypeptide chain of molecular weight in the range 76,000 to 81,000 and called apotransferrin, on which disposed 2 similar but not identical binding sites. Under physiological conditions iron is bound so tightly to transferrin that spontaneous dissociation of the metal from the protein is effectively precluded, this binding capacity requires presence of suitable anions, mainly bicarbonate but in its absence other anions as oxalate, EDTA, malonate and others can substitute it. (Asien

and Listowsky, 1980).

The iron binding capacity of transferrin is normally about 20-33% **(Martin, 1983).** Normal plasma level is 130 microgram/dl (23 micro mol./L) in men and 110 microgram/dl (19 micro mol/L) in women **(Ganong, 1985).** Recent studies have shown that plasma iron pool is composed of three different molecular species, two monoferric and one diferric transferrin. The 2 monoferric species donate iron similarly in vivo but are inferior to the diferric moiety in their iron donating capacity **(Cazzola et al, 1985).**

Ferritin:

It is the primary and most available iron storage protein present in most of tissues especially mammalian liver, spleen and bone marrow which are rich of it, it is also present in the serum and circulating blood cells. It has a characteristic electron-dense appearance so conjugates of ferritin have been employed as markers for morphological localization of tissues. Monitoring its level can give informations about the reticulo endothelial iron stores or the presence and progress of some malignant diseases **(Aisen and Listowsky, 1980).**

It is formed of apoferritin molecule of molecular weight about 500,000 and composed of 24 identical 18,000 mol. weight subunits. Apoferritin can assimilate 4300 iron atoms in a single molecule to form ferritin, ferritin can become denatured loosing apoferritin and polymerizing into hemosiderin **(Hoy and Jacob, 1981).**

The normal serum level is 11-120 ng/ml for women and 25-250 ng/ml for men **(Arosio, 1981).** In interpreting these values it has been assumed that 1 microgram of ferritin per liter represents 8-10 mg of storage iron. Although this is a fair approximation in adults, it seems clear that the relationship is actually one of concentration, in which 1 ug of ferritin per liter is equivalent to about 140 ug of storage iron per kilogram of body weight **(Finch and Huebers, 1982).** In liver the ferritin iron is found in a concentration of 61.6 ug $\pm$ 32.4/gram liver tissue in males and 60.6 $\pm$ 26.4 ug/gram liver tissue in females **(Wong and Saha, 1985).** The iron stores of the liver have been recently estimated non invasively using nuclear resonance scattering (NRS) **(Weilopolski et al, 1985).** Reticulocytes can take up liver ferritin by a saturable time and temperature dependent process. Up to 70% of iron taken up by the cells enter the iron cycle and utilized in heme synthesis comparing directly with iron derived from transferrin **(Blight and Morgan, 1983).** Ferritin is also available in reticulo endothelial