Iron Status and Coronary Risk in Rheumatic Heart Children

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Summary This study aimed at clarifying the relationship between iron status and atherogenic lipid profile in normal and chronic rheumatic heart as well as congenital heart defect children. The study included 31 children, 16 cases with chronic rheumatic heart disease (10 males and 6 females) and 6 with congenital heart disease. Nine children with normal hearts were taken as the control. Serum iron and total iron binding capacity were higher in both chronic rheumatic and congenital heart disease children than in the controls; but the increase was only significant in the second case. Serum low-density lipoprotein cholesterol (LDL-ch) and high-density lipoprotein-cholesterol (HDL-ch) were not significantly changed in either disease. In relation to sex, no significant changes were noticed in iron status of chronic rheumatic heart children. Serum LDL-ch and LDL-ch to HDL-ch ratio were significantly higher in females than in males. A correlation study was also done between lipid profile and iron status.

Key Words: rheumatic heart, congenital heart, serum iron, lipoproteins, children

In recent years there has been growing interest in the risk factors predisposing to coronary heart disease. Although studied intensively, the problem seems to bear a different perspective in developing countries. Sullivan [1] reported that cardiovascular disease seems to be an inevitable concomitant of prosperity and that poverty protects the heart. However, others [2] presented evidence that children of low socio-economic areas had the most unfavourable risk factor profile for coronary heart disease. Two of the commonest medical problems in Egypt are malnutrition [3] and parasitosis [4] and are commonly associated with iron

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deficiency anaemia. Sullivan [1] suggested that there is a definite relationship between iron status and heart disease risk based on the following observations: myocardial failure in patients with iron storage diseases [5], the accumulation of stored iron with age in men after adolescence and the accumulation of stored iron after menopause or hysterectomy with a two-fold increase in heart disease [6]. So that it is unlikely that estrogen alone could be responsible for the sex differences in heart disease.

The above data, in addition to the conflicting issue of the relationship of nutritional status to coronary risk, prompted us to uncover some facts pertaining to the iron status in our community and the atherogenic lipid profile in normal children and in children affected with chronic rheumatic as well as congenital heart disease.

MATERIALS AND METHODS

Twenty-two children aged 7 to 14 years, 16 cases with rheumatic heart disease and 6 with congenital heart disease, were selected from the Pyramids Rheumatic Heart Centre in Giza, Egypt. Nine age-matched controls with normal hearts were taken as a reference group. The 16 rheumatic heart cases consisted of 10 males and 6 females and included 8 cases with double mitral valve lesion, 4 cases with mitral incompetence, 2 cases with mitral stenosis, and 2 cases with mitral incompetence and aortic incompetence. The cases did not show signs of activity, and were not receiving any medication apart from prophylactic long acting penicillin. The 6 congenital heart patients included 3 cases with congenital cyanotic heart disease and another 3 with ventricular septal defect.

Blood samples were drawn and serum was separated. Estimation of serum iron and total iron binding capacity was carried out as described [7, 8]. HDL-ch and LDL-ch were also determined as described [9-11].

Statistical analysis was performed by Student's *t*-test. A correlation study was also done between iron status (serum iron and total iron binding capacity) and lipid profile (LDL-ch and HDL-ch).

RESULTS

Serum iron, iron binding capacity, and percentage saturation

There was a significant ($p < 0.05$) increase in the serum iron of children with congenital heart disease ($19.78 \pm 2.360 \mu\text{mol/liter}$) when compared with the control value ($13.33 \pm 2.103 \mu\text{mol/liter}$). Total iron binding capacity was also significantly higher ($p < 0.01$) in congenital heart patients ($144.68 \pm 11.454 \mu\text{mol/liter}$) than in controls ($107.85 \pm 6.5 \mu\text{mol/liter}$). Percentage saturation did not differ significantly between the two groups. In chronic rheumatic heart children, the mean serum iron ($15.87 \pm 1.665 \mu\text{mol/liter}$), mean total iron binding capacity ($112.44 \pm 6.8 \mu\text{mol/liter}$), and mean percent saturation ($15.12 \pm 1.925\%$) were in-

creased, but not significantly so, over the values for the control patients (Table 1).

The percent saturation was below 16 (i.e., an indication of Fe deficiency anaemia) in 7 (77.78%) of the control cases, 10 (62.5%) of rheumatic heart disease children, and 4 (66.67%) of congenital heart cases. So, of the 31 cases studied, 21 (67.74%) of them showed biochemical evidence of Fe deficiency anaemia.

In relation to sex (Table 2), the serum iron and total iron binding capacity in chronic rheumatic heart children were higher in males (16.89 ± 1.983 and 116.29 ± 7.293 $\mu\text{mol/liter}$, respectively) than in females (14.18 ± 2.834 and 105.93 ± 13.001 $\mu\text{mol/liter}$, respectively), but these differences were insignificant ($p > 0.05$). The mean percentage saturation did not differ significantly: $15.69 \pm 2.587\%$ for males and $14.17 \pm 2.752\%$ for females.

Table 1. Comparison of serum iron, iron binding capacity, and % saturation in control cases and in rheumatic heart and congenital heart children.

		Serum Fe ($\mu\text{mol/liter}$)	Total iron binding capacity ($\mu\text{mol/liter}$)	Saturation (%)
Control	$n=9$	13.330 ± 2.013	107.850 ± 6.500	12.660 ± 2.033
Rheumatics	$n=16$	15.870 ± 1.665	112.440 ± 6.800	15.120 ± 1.925
Congenital heart	$n=6$	$19.780 \pm 2.360^*$	$144.680 \pm 11.454^{**}$	13.460 ± 0.972

Values significantly different from the control: $*p < 0.05$; $**p < 0.01$.

Table 2. Sex differences in serum iron, total iron binding capacity (TIBC), % saturation, LDL-ch, HDL-ch, and LDL-ch : HDL-ch ratio in rheumatic heart patients.

	Male rheumatic heart children $n=10$	Female rheumatic heart children $n=6$
Iron ($\mu\text{mol/liter}$)	16.890 ± 1.983	14.180 ± 2.834
TIBC ($\mu\text{mol/liter}$)	116.290 ± 7.293	105.930 ± 13.001
Saturation (%)	15.690 ± 2.587	14.170 ± 2.752
LDL-ch (mmol/liter)	1.450 ± 0.168	$2.830 \pm 0.184^{**}$
HDL-ch (mmol/liter)	0.840 ± 0.164	0.630 ± 0.133
LDL-ch : HDL-ch ratio	1.800 ± 0.563	$5.300 \pm 0.853^*$

Values significantly different from corresponding male value: $*p < 0.005$; $**p < 0.0005$.

Table 3. Comparison of lipid profiles; LDL-ch, HDL-ch, and LDL-ch : HDL-ch ratio in controls, rheumatic heart and congenital heart children.

		HDL-ch (mmol/liter)	LDL-ch (mmol/liter)	LDL-ch : HDL-ch ratio
Control	$n=9$	0.570 ± 0.060	2.120 ± 0.230	3.900 ± 0.457
Rheumatic hearts	$n=16$	0.760 ± 0.118	1.970 ± 0.210	3.120 ± 0.638
Congenital hearts	$n=6$	0.570 ± 0.139	2.040 ± 0.433	5.620 ± 1.690

No values differ significantly from the control.

Table 4. Correlative studies between LDL-ch or LDL-ch : HDL-ch ratio and iron, total iron binding capacity (TIBC), and percentage saturation in rheumatic heart patients of either sex.

		Iron		TIBC		Saturation (%)	
		Male <i>n</i> =10	Female <i>n</i> =6	Male	Female	Male	Female
LDL-ch	<i>r</i>	0.12	0.85	0.13	-0.40	-0.05	0.81
LDL-ch : HDL-ch ratio	<i>r</i>	-0.42	0.77	0.13	0.07	-0.35	0.43

Table 5. Correlative studies of LDL-ch and LDL-ch : HDL-ch ratio with serum iron, total iron binding capacity (TIBC), and percentage saturation in control (C) cases and congenital heart patients (Cong.Hrt).

		Iron		TIBC		Saturation (%)	
		C <i>n</i> =9	Cong.Hrt <i>n</i> =6	C	Cong.Hrt	C	Cong.Hrt
LDL-ch	<i>r</i>	-0.57	-0.26	0.31	-0.54	-0.57	0.54
LDL-ch : HDL-ch ratio	<i>r</i>	-0.65	0.06	-0.32	0.54	-0.61	-0.29

Lipid profile, LDL-ch, HDL-ch, and LDL-ch : HDL-ch ratio

As seen in Table 3, the HDL-ch mean serum levels in controls (0.57 ± 0.06 mmol/liter), rheumatic heart cases (0.76 ± 0.118 mmol/liter), and congenital heart cases (0.57 ± 0.139 mmol/liter) were not significantly different from one another ($p > 0.05$).

Nor were the mean serum levels of LDL-ch: controls, 2.12 ± 0.23 mmol/liter; rheumatic heart cases, 1.97 ± 0.21 mmol/liter and congenital heart cases, 2.04 ± 0.433 mmol/liter ($p > 0.05$). Thus the LDL-ch to HDL-ch ratio of either group did not differ significantly from that of the other.

In relation to sex, the mean serum LDL-ch was significantly higher ($p < 0.0005$) in chronic rheumatic heart females (2.83 ± 0.184 mmol/liter) than in corresponding males (1.45 ± 0.168 mmol/liter). Also, the LDL-ch to HDL-ch ratio was significantly higher ($p < 0.005$) in the females (5.3 ± 0.853) than in the males (1.8 ± 0.563). While the HDL-ch level in males (0.84 ± 0.164 mmol/liter) was not significantly higher than that in females (0.63 ± 0.133 mmol/liter) (Table 2).

Correlative studies

There were significant positive correlations between Fe and LDL-ch ($r = +0.85$, $p < 0.05$), Fe and LDL-ch to HDL-ch ratio ($r = +0.77$, $p < 0.05$), and percent saturation and LDL-ch ($r = +0.81$, $p < 0.05$) in rheumatic heart patients of the female sex, but no significant relationships were seen between Fe and LDL-ch in the male sex (Table 4).

For controls, correlative studies between Fe and LDL-ch (-0.57) and Fe and LDL-ch : HDL-ch ratio (-0.65) were significant at $p < 0.05$. The % saturation with LDL-ch (-0.57) and with LDL-ch to HDL-ch ratio (-0.61) was also significant

at $p < 0.05$. No significant relationship was seen between serum Fe or % saturation and LDL-ch to HDL-ch ratio in congenital heart patients (Table 5).

DISCUSSION

This study reflects the high prevalence of iron deficiency anaemia in our community. According to Zilva and Pannall [12], percent saturation is a better index of iron deficiency anaemia than iron alone; and when it is below 16%, iron deficiency is likely to be present. Accordingly we found iron deficiency to be commoner in the control cases (78%) than in the cases with rheumatic heart (62%) and congenital heart (67%). Overall iron deficiency was a common feature in all the cases. In a survey carried out on Egyptian children [3], iron deficiency was found to affect an estimated 1.4 million. Said *et al.* [13] reported low haemoglobin mean levels in school-aged children. Abul-Fadl [4] found the serum iron level significantly reduced in children with parasitic infestation. Iron deficiency in heart disease is a serious finding. Iron deficiency anaemia induces cardiac hypertrophy with a defective mitochondrial population, potentially placing the heart in an energy imbalance [14].

In congenital heart patients the higher mean serum iron is due to the associated hypoxia, which enhances mucosal iron uptake by a mechanism that is independent of the stimulated erythropoiesis. Also, the changes in the rate of erythropoiesis have an additional effect, particularly on the transfer phase of iron absorption [15].

There was tendency for rheumatic heart disease children to show a higher mean serum iron and percent saturation than control cases. Although the nutritional status may be similar and the chronic disease process may further impair the absorption and utilization of nutritive elements, yet the lack of physical exercise may account for the differences encountered in the iron metabolism. Other studies [16, 17] have shown that iron deficiency anaemia develops more in active children. Rheumatic heart disease children may develop cardiac cirrhosis in which iron levels may be high [12].

Sex differences in chronic rheumatic heart patients were found in the serum iron and TIBC, both of which were higher in males. The difference is probably hormonal in origin and becomes evident around puberty before significant menstrual iron is lost. Androgens tend to increase plasma iron concentration; and estrogen tends to lower it [12].

On examining the correlation between the LDL-ch to HDL-ch ratio in the control group and their serum iron or percent saturation, we found a significant negative correlation. Thus, the iron deficiency in this group was accompanied by an increase in the LDL-ch to HDL-ch ratio; i.e., it encouraged an atherogenic profile. The anaemia may depress the metabolic processes affecting the conversion of LDL and HDL in the liver [18].

The lipid profile in the heart patients was comparable to that in the control

group. However, the females with chronic rheumatic heart disease had a significantly higher LDL-ch and LDL-ch to HDL-ch ratio than the corresponding males. This unfavourable risk factor profile was also accompanied by significant positive correlations of the ratio with serum iron and percent saturation. This suggests that the atherogenic lipid profile in females is closely related to the iron status. A direct relationship between iron and heart disease has been suggested by Sullivan [1], who believes that the differences reported in coronary heart disease risk cannot be solely attributed to hormonal factors and that the increases in iron stores in the body may also play a role. His hypothesis is backed by the findings of other workers [19] of the equal incidence of coronary risk in men and women undergoing surgical menopause inspite of intact ovaries. However, we found no significant correlations between lipids and iron in males. The absence of such finding in males could be due to the protective effect of testosterone on the development of a lipid atherogenic profile prepubertally [20].

The relationship between atherosclerosis and iron can be explained by the hydroxyl radical formed in the process of transformation of iron from the ferric to ferrous form [21]. The hydroxyl radical is the most toxic of univalent reduction products derived from oxygen, and it is able to attack or destroy membranes [22]. Sparrow *et al.* [18] showed that LDL can be oxidatively modified by cultured endothelial cells or by cupric ions resulting in increased macrophage intake of lipoprotein. The oxidative powers of iron may mimic in the same way the effects of cupric ions. Hence the mechanism whereby iron is atherogenic could operate via the formation of macrophage-derived foam cells characteristic of early atherosclerotic lesions.

In conclusion, our findings indicate that although iron deficiency anaemia is common in rheumatic and congenital heart disease children, yet they appear to be better off than heart disease-free Egyptian children. Of considerable interest was the finding of significant positive correlations between the lipid profiles and serum iron and percent saturation. The risk of atherosclerosis, whose natural history starts from childhood, appears to be linked with both iron deficiency in heart disease-free subjects and iron level elevation in heart patients. Such findings urge us to be more cautious in prescribing iron to such patients. More studies should be directed towards defining the levels of iron in the body that would be biologically harmless.

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