Association between Body Iron Stores and Coronary Artery Disease

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Abstract

Background- Animal studies have indicated the effects of iron stores in the process of the formation of free radicals and low density lipoprotein (LDL) oxidation. Oxidation of lipids, especially LDLs, by oxidants such as iron plays a central role in atherogenesis. As a result, an evaluation of the iron stores of the body in patients with coronary artery diseases is of utmost importance.

Methods- In this prospective study, 112 patients with coronary artery disease (CAD) and 63 individuals without this disease were investigated. The coronary condition of the subjects was determined with coronary angiography. The amount of iron, ferritin, total cholesterol, triglycerides, LDL, and HDL was measured in both groups. The patients were also evaluated for known CAD risk factors, including diabetes mellitus, hypertension, smoking, family history of CAD, and hyperuricemia. Patients suffering from anemia, renal and hepatic diseases, and those with a history of malabsorption, hemochromatosis, chronic infections, or immunological and inflammatory disorders and patients with neoplastic diseases and cardiac failure were excluded from the study. Moreover, all the subjects had a similar socio-economic status.

Results- Mean serum iron was 12.9±4 micromoles/liter and 10.8±5 micromoles/liter in the group with CAD (case) and the group without CAD (control), respectively, which were significantly different ($P<0.001$). Mean serum ferritin was 126±75 microgram/liter in the case group, while it was 101±75 microgram/liter in the control group, the difference also being significant ($P<0.005$).

Conclusion- The findings indicated that the serum level of iron and ferritin - excluding other known risk factors - in patients with CAD is higher compared to the subjects without CAD. It may, therefore, be possible that iron stores in the body can play a role in the atherosclerotic process ***(Iranian Heart Journal 2006; 7 (2):37-41)***.

Key words: ferritin ■ coronary atherosclerosis ■ serum iron

Atherosclerotic disease of the coronary arteries is one of the most common causes of mortality. A number of known risk factors have been recognized for this disease, but less known factors such as the serum level of lead and zinc, the deficiency of antioxidants such as vitamin E and oxidants like free radicals have also been considered.[13,15,18]

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The relationship between body iron stores and coronary artery diseases (CAD) was first considered by Sullivan, who believed that free iron catalyzes the production of free radicals in the peroxidation of lipids and myocardial ischemic damage.[17]

In another study, daily iron intake was found to have a significant relationship with increased infarction risk.

Evidence shows that the oxidative transformation of LDL is important in the pathogenesis of atherosclerosis and dysfunction of vascular endothelium.[2,14,16]

The oxidation of LDL cholesterol often occurs in the layers under the endothelium of the arteries prone to atherosclerosis. Lysolecithin is a product of lipid peroxidation, which plays a role in leading to the arterial response. Free iron catalyzes the production of free radicals, which have a role in the oxidation of lipids and the atherosclerotic process of coronary arteries.[1,2,14,18] Serum ferritin also reflects the iron stores of the body. On the other hand, ferritin acts as the scavenger of iron and is likely to reduce the production of free radicals due to reperfusion injury. Ischemia increases the myocardial ferritin, which is associated with the intensity of ischemia.[11] Prevention being crucial in atherosclerosis, it is very important that causes be recognized and the said factors be controlled so that the disease can be prevented or its severity can be reduced. The present research was conducted to take a step in determining the causes of this disease, especially concerning body iron and ferritin stores.

Methods

In this prospective study, 112 patients (72 males and 40 females) with CAD (case group) and 63 individuals (40 males and 23 females) with normal epicardial coronary arteries (controls) on coronary angiography were investigated. The participants were all between 45 and 65 (mean, 61±2) years old. The serum level of iron and ferritin was measured twice in both groups within a one-week interval and was averaged to determine the iron and ferritin levels meticulously. Trace laboratory kits were used with units of micromoles per liter (µm/l) and ELISA kits with micrograms per liter (µg/l) measurement to determine the serum levels of iron and ferritin, respectively. All these measurements were conducted in the central laboratory of Shaheed Rajaei Cardiovascular Medical Center by an experienced technician. Meanwhile, lipoproteins and lipid profiles were measured twice during a one-week interval, and the mean of both measurements was used in the study. The subjects of both groups were investigated in terms of the known risk factors of CAD such as diabetes mellitus, hypertension, smoking and family history of CAD to make sure none of the patients was suffering from these diseases. Moreover, all the subjects had a moderate-to-high socio-economic status. Patients suffering from anemia, renal and hepatic diseases and those with a history of malabsorption, hemochromatosis, chronic infections or immunological and inflammatory disorders and patients with neoplastic diseases and cardiac failure were excluded from the study.

The collected data were reported in the form of mean and standard deviation. The data were analyzed using t-test with a significance level of $P<0.05$.

Results

The lipoprotein (a) level in both groups was 20-35 milligrams per deciliter and that of HDL was 35-60 milligrams per deciliter. The LDL cholesterol level in the case group was less than 130 milligrams per deciliter (mean, 108±15 mg/dl), and in the control group it was less than 130 milligrams per deciliter (mean, 116±15 mg/dl), with no significant difference ($P<0.05$).

One hundred seventy-five subjects took part in this study. One hundred twelve subjects had CAD (case group), 40 (35.7%) of whom were females and 72 (64.3%) were males. The control group (subjects with normal epicardial coronary arteries) comprised 23 (36.5%) females and 40 (63.5%) males. 27% of the subjects in the case group were suffering from single vessel disease (SVD), another 27% were suffering from 2VD, and the rest had 3VD. The

serum iron level of the groups was 5-35 micromol/l. The serum iron level in the case group was 8.1±5 micromol/l, while it was 12.9±4 micromol/l in the control group, the difference being significant (P<0.001). The mean serum level of iron in patients with SVD, 2VD, and 3VD was 11.3±4, 12.6±5, and 14.8±4 micromol/l. The difference between these groups was not statistically significant (Fig. 1).

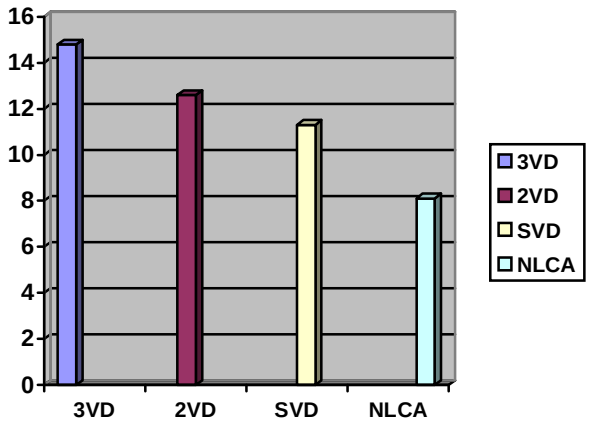

Fig. 1. Mean serum iron levels in subjects without CAD (control) and patients with different severities of CAD.
SVD: one coronary artery is involved
2VD: two coronary arteries are involved
3VD: three coronary arteries are involved
NLCA: normal epicardial coronary artery

The serum ferritin level in the whole group was 5-216 micrograms/l. The serum ferritin level in the case group was 126±75 micrograms/l on average, and this was 101±75 microgram/l in the control group. This difference was statistically significant (P<0.005). The mean serum ferritin in patients with SVD, 2VD, and 3VD was 115±70, 119±70, and 135±70 microgram/liter. The difference between these groups was not statistically significant (Fig. 2).

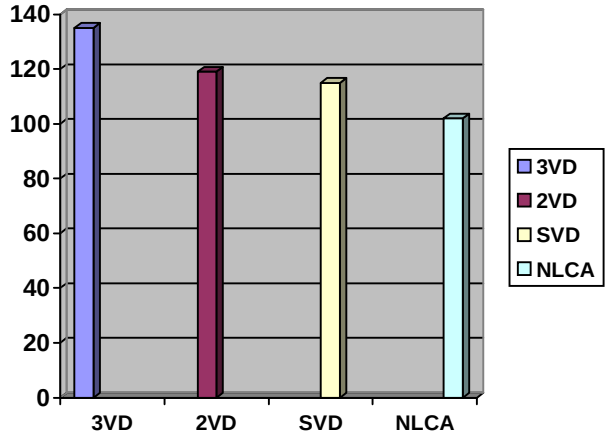

Fig. 2. Mean serum ferritin in subjects without CAD and patients with different severities of CAD.
SVD: one coronary artery is involved
2VD: two coronary arteries are involved
3VD: three coronary arteries are involved
NLCA: normal epicardial coronary arteries

Discussion

The most important finding of this study was the noticeable increase in the serum level of iron and ferritin in the patients with severe coronary artery disease. The iron level of the body, determined by serum ferritin, increases after menopause in females and after maturity in males.[19] All the serum iron is bound to proteins except when it is increased. Iron should be separated from proteins in order for the free radicals to form. Oxidative agents can create iron for the formation of free radicals.

These agents act through separating iron from ferritin or breaking down the protein-bound irons. The reduced iron plays a role in the peroxidation of lipids.[16] Much research has indicated that the increase of iron in the pathogenesis of atherosclerosis acts through creating free radicals of oxygen and oxidation of lipids.[9, 12, 13, 15, 19]

Sullivan et al. claimed that the high prevalence of coronary artery diseases among men and women after menopause is due to the high amount of iron store in these people. Moreover, the decrease of iron stores can prevent ischemic heart diseases through restraining the oxidative transformation of LDL-cholesterol.[10,17,18] In a study, Ascheivo et al. found a relationship between iron consumption and infarction risk among men who did not have vitamin E in their diet. This risk was even higher among men with a history of diabetes mellitus and smoking. In this study the severity of coronary disease was higher among men who had a higher iron store.[2, 3, 7, 17] In a research conducted by Auer et al. on 100 patients who had coronary angiography, the high level of ferritin and transferrin had nothing to do with the extent of atherosclerosis.[4] There may be some reasons for the conflict between this study and the present research. First, the age of the subjects of this study is higher (63.7±11). Second, the amount of serum iron and its relationship with the severity of atherosclerosis have not been taken into account in this study. Furthermore, epidemiological studies have shown that the amount of body iron stores has a positive relationship with the prevalence of CAD in humans.[1, 5, 6, 16] In a study by Heidari et al., the amount of ferritin in men with CAD was remarkably high and it was suggested that the increased serum ferritin may be a predictor for premature CAD among Iranian men.[8] In this study, the iron store of the body was considerably high in both men and women suffering from CAD. Also, serum ferritin was used as an index of the amount of iron store in the body, and the amount of iron was used as an index of the serum iron. Moreover, in this study the mean serum iron and ferritin was substantially higher than that in subjects without coronary atherosclerosis. It is also of note that in the group with CAD, the serum level of iron and ferritin had a significant relationship with the severity of coronary artery disease in SVD, 2VD, and 3VD subgroups; consequently, the amount of serum iron and ferritin was higher in group of patients with 3VD than that in the other groups. The findings of this study were in line with those of Heidari and Sullivan, who indicated the high prevalence of coronary artery disease among individuals who had a high level of iron storage.[16, 18] The present research is important in that the case group dis not have the other known risk factors of atherosclerosis and the role of body iron was studied without the interference of other factors. The findings of this research suggested that the increased level of iron stores in the body can have a role in the severity of coronary atherosclerosis. Based on these findings, it is suggested that the serum level of iron be tested in patients with CAD without other risk factors at least once. A diet low in iron will help if serum iron is too high. Phlebotomy can also help to decrease the serum iron through decreasing the density of serum ferritin. This has no complications, is cost effective and easily accepted by the patients.[8, 19] Finally, measuring serum iron and determining its normal mean in at-risk adolescents is recommended.

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