Acossiation of 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 free radical formation and low density lipoproteins (LDL) oxidation. Oxidation of the lipids especially LDLs by oxidants such as iron has a central role in atherogenesis. As a result, evaluating the amount of iron stores in patients with coronary artery diseases may be of importance.

Methods- In this prospective study, 112 patients with coronary artery disease (CAD) and 63 normal individuals were investigated. The coronary condition of the subjects was determined by coronary angiography. The amounts of iron, ferritin, total cholesterol, triglyceride, LDL and HDL were measured in both groups. The subjects were also evaluated for known CAD risk factors including diabetes mellitus, hypertension, smoking, family history of CAD and hyperuricemia. The subjects suffering form 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 socioeconomic status.

Results- Mean serum iron was 12.9±4 μmol/l and 10.8±5 μmol/l in the group with CAD (case) and in the group without CAD (control), respectively, which was significantly different ($p<0.001$). Mean serum ferritin was 126±75 μgram/l in the case group, while it was 101±75 μgram/l in the control group: this was also significantly different ($p<0.005$).

Conclusion- The findings indicate that serum levels of iron and ferritin - excluding other known risk factors - in patients with CAD are higher compared to the subjects without CAD. Consequently, iron stores in the body may play a role in the atherosclerotic process ***(Iranian Heart Journal 2005; 6 (3): 54-58).***

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 implicated.[13,15,18]

The relationship between the iron stores of the body and coronary artery disease (CAD) was first considered by Sullivan, who believed that free iron catalyzed the production of free radicals in peroxidation of lipids and myocardial ischemic damage.[17] In another study, the daily iron intake was found to have a significant relationship with increased infarction risk.

There is evidence indicating that the oxidative transformation of LDL is of importance in the pathogenesis of atherosclerosis and dysfunction of endothelium.[2,14,16]

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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 arterial response. Free iron catalyzes the production of free radicals, which have a role in the oxidation of lipids and 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] Since prevention is crucial in atherosclerosis, it is very important to recognize the causes. Controlling the above-mentioned factors can prevent the disease or reduce its severity. The present research was conducted to take a step in determining the causes of this disease, including 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 (control) in coronary angiography were investigated.

The participants were all 45-65 (mean 61±2) years old. The serum levels of iron and ferritin were measured twice in both groups at a one-week interval and averaged to determine the iron and ferritin levels meticulously. Trace laboratory kits (micromoles per liter, µmol/l) and ELISA kit (micrograms per liter, µg/l) were used to determine the serum level of iron and ferritin, respectively. All these measurements were conducted in the central laboratory of SRCMC by an experienced technician.

Meanwhile, lipoproteins and lipid profiles were measured twice at 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 were suffering from these diseases. Moreover, all the subjects were of a moderate-to-high socio-economic status. The subjects 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 and analyzed using t-test with a significance level of $p<0.05$.

Results

The lipoprotein (a) level in both groups was 20-35mg/dL, and that of HDL was 35-60mg/dL. The LDL cholesterol level in the case group was less than 130mg/dL (mean 108±15mg/dL). It was also less than 130mg/dL in the control group (mean 116±15mg/dL). Thus, there was no significant difference ($p<0.05$). 27% of the subjects in the case group were suffering from single-vessel disease; another 27% were suffering from two-vessel and the rest had three-vessel disease. The serum level of iron in the case group was 8.1±5µmol/L, while it was 12.9±4µmol/L in the control group. This difference was 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±4µmol/L, respectively. The difference between these groups was not statistically significant (Fig. 1).

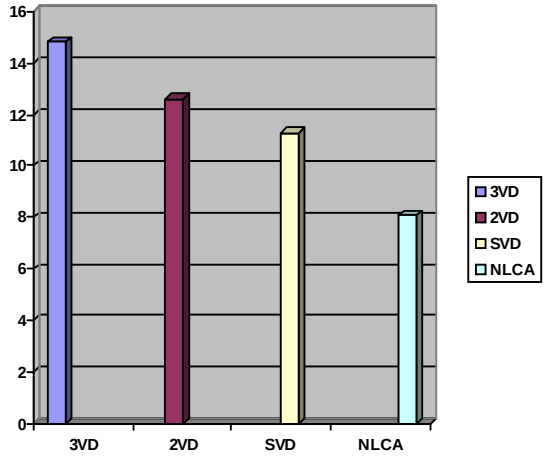

Fig. 1. Comparison between the mean serum iron in subjects without CAD (controls) and patients with different severity of CAD.
SVD: single vessel disease, 2VD: two vessel disease, 3VD: three vessel disease, NLCA :normal epicardial coronary artery

The serum ferritin level in the case group was 126±75 microgram/liter on average and 101±75 microgram/liter 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).

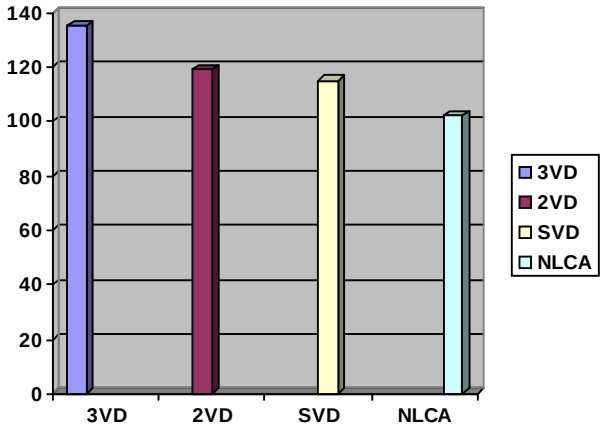

Fig. 2. Comparison between the mean serum ferritin in subjects without CAD and patients with different severity of CAD.
SVD: single vessel disease, 2VD: two vessel disease, 3VD: three vessel disease, NLCA :normal epicardial coronary artery

Discussion

The most important finding of this study was the noticeable rise 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 peroxidation of the lipids.[16] Many researchers have 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 disease among men and women after menopause was due to the high amount of iron stores in these people. Moreover, the decrease in iron stores can prevent ischemic heart disease through restraining the oxidative transformation of LDL-cholesterol.[10,17,18] Ascherio 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 has 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 stores of the body was considerably high in both men and women suffering from CAD. Also, serum ferritin was used as an index for the amount of iron stores in the body, and the amount of iron was used as an index for the serum iron. The mean serum iron and ferritin was substantially higher than that of subjects without coronary atherosclerosis. Furthermore, 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, such that the amount of serum iron and ferritin was higher in the group of patients with 3VD than that in the other groups. The findings of this study are 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.[17,18] The present research is important in that the case group did not have the other known risk factors of atherosclerosis and that the role of body iron was studied without the interference of other factors. Therefore, the findings of this research suggest 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.[18,19] Finally, the measurement of serum iron and determining its normal mean in adolescents at risk is recommended.

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