Original Article

Association between dietary iron, iron stores, and serum lipid profile in reproductive age women

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ABSTRACT

Background: Some studies have shown that increased rate of iron stores even in a normal range may increase cardiovascular diseases (CVDs) in some individuals. Lipid disorders are also the risk factors for CVDs. Therefore, the question is whether or not iron store is correlated with lipid profile, this study evaluates the association between dietary iron, iron stores and serum lipid profiles. **Materials and Methods:** This cross-sectional study was done on 82 healthy university students and university staff females in Isfahan University of Medical Sciences who were in reproductive age and announced their readiness to participate in the study. Serum ferritin concentration, components of lipid profile, blood glucose, and insulin were measured in all the subjects. Dietary intake was assessed by semi-quantitative food frequency questionnaire. Data analysis was done through SPSS software, version 18. **Results:** Pearson correlation test showed a positive and significant correlation between serum ferritin concentration levels with triglyceride ($r = 0.278$; $P = 0.006$), total cholesterol ($r = 0.267$; $P = 0.008$), and blood glucose ($r = 0.275$; $P = 0.006$); however, the correlation between serum ferritin, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and insulin was not significant. After adjustment of confounding factors, only the significant correlation occurred for blood glucose ($P = 0.016$). Before and after adjustment of confounding factors, there was no significant correlation between hemoglobin and hematocrit with concentration of lipid profile components, glucose and insulin. Before and after adjustment of confounding factors, there was no significant correlation between total amount of iron, heme iron, and non-heme dietary iron with concentration of lipid profile components, glucose and insulin. **Conclusion:** According to the current study, serum ferritin is directly and significantly correlated with concentration of fasting blood glucose, which emphasized on the amount of iron store with blood glucose even in healthy people. The results of the present study indicate no significant correlation between iron store and dietary iron intake with lipid parameters and insulin. Conducting more extensive epidemiologic studies in men and other age groups is recommended.

Key words: Iron intake, iron store, lipid profile, reproductive age women

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INTRODUCTION

Nowadays cardiovascular diseases (CVD) are recognized as the main cause of morbidity and mortality in the world and they comprise 50% of all mortalities in the developing countries and more than 25% of them in the developed

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countries.[1] CVDs are also the first and most common cause of mortality in Iran.[2] According to the report of the World Health Organization in 2005, 41.3% of mortalities in Iran have been due to CVD and it is predicted to reach to 44.8% until 2030.[3] Many risk factors, such as diabetes, hypertension, hyperlipidemia, smoking, family history of CVD, sedentary lifestyle, and inappropriate diet have been related to CVD.[4] Other factors also have been considered during recent years, including serum homocysteine, serum fibrinogen, iron stores levels, and inflammatory factors.[5-8]

Iron is one of the essential elements for many cellular functions. Comprehensive iron function can be attributed to its ability in electron reception and donation and accordingly participation in reduction oxidation (Redox) reactions.[9] Ferritin is the major iron storage protein in the body; serum ferritin in normal people is directly associated with body iron stores.[10] The accumulation of iron in the body after menopause may increase the incidence of CVD in women.[11]

For the first time Sullivan has suggested that lower incidence of CVD in premenopausal women compared with men of the same age and also increased incidence of this disease in postmenopausal women is due to increased iron stores.[12,13] Since then, several studies have been conducted in this regard. In some of them, increased iron store lower than that observed in hemochromatosis and even in normal range of iron store caused individual prone to chronic diseases such as diabetes and CVDs;[14-16] however, in some other studies, there was no correlation between iron stores and CVDs.[17-19] Dietary iron intake is one of the determinant factors of body iron stores.[20] Findings of studies about association between dietary iron intake and incident risk of CVD were also inconsistent; in some of them a significant direct association was observed between dietary iron intake and risk of CVD,[21,22] but in others, there was no such relationship.[23]

However, anemia was also recognized as a potential risk factor for CVD.[24] Chronic anemia increases cardiac output,[25] which on long term, causes left ventricular hypertrophy (LVH); LVH is also a known risk factor for CVDs.[26]

Lipid disorders such as increased total cholesterol, triglyceride, and low-density lipoprotein-cholesterol (LDL-C) and decreased high-density lipoprotein-cholesterol (HDL-C) are the major risk factors of CVD.[27-29] Although assessment of these indicators (lipid profile and iron stores) can provide important information about preventing CVD, all these factors would put together in human body; therefore investigating their interaction, certainly is preferable to examine each of them separately. For example, studies have shown that poor iron diet can influence on lipid metabolism in mice.[30] Some studies also evaluated the association of iron deficiency anemia and lipid metabolism; in some of them, lipid parameters in those with iron deficiency anemia were higher than those in healthy people, whereas in some others, these parameters were lower in those with iron deficiency anemia and they increased following the supplementation with iron.[31,32] Hence, some studies have reviewed the association between iron stores and lipid profile. In some studies, there was a significant positive correlation between iron stores and lipid profile;[33] however, it was not so in others.[34]

Moreover, most of the studies about the association between body iron status and CVD risk factors have been done in Western communities and the number of conducted studies in Asian countries, particularly Iran is very limited. Therefore, given the multitude of contradictions, unanswered questions, and also difference between Iranian genetics and diet, which can cause difference in iron intake and body iron stores, implementing such a study seems highly necessary in order to assess the correlation between iron stores and dietary iron intake with lipid profile in reproductive-age women in Isfahan, Iran.

MATERIALS AND METHODS

This cross-sectional and descriptive–analytical study conducted on 82 reproductive-age women in order to determine the association between iron stores and dietary iron intake with lipid profile. This study was approved by the Department of Clinical Nutrition in Isfahan University of Medical Sciences. The current study carried out in university students and staff of Isfahan University of Medical Sciences who announced their readiness to participate in the study. The inclusion criteria included female gender at the age range of 15-49 years. Those with a history of CVDs, diabetes, hypertension, gastrointestinal and hepatic diseases, or those consumed mineral multivitamin, iron supplements, and specific medications (blood glucose or lipid lowering drugs), or were pregnant and smoked, did not enter the study. Basal metabolism rate (BMR) was calculated through standard equations based on weight, age, and gender.[35] Thereafter, the ratio of energy intake (EI) to BMR (EI/BMR) was calculated for each individual. Underreporting and overreporting of energy intake were defined as EI/BMR lower than 1.35 and equal to or greater than 2.4.[36,37] One of the study subjects had underreported and two study subjects had overreported who did not enter in the study. The exclusion criteria included triglyceride (TG) concentration greater than 400 mg/dL. All the study subjects completed the informed written consent.

Usual dietary intake was assessed by semi-quantitative food frequency questionnaire (FFQ) including a list of 168 food items with a standard serving size. The studied subjects were asked to mention the consumption frequency of each food given to its amount in the past year. The mentioned amounts and values were converted to *gram* through the manual for household measures.[38] Then, each food was encoded according to the Nutritionist Software version 4 (N4). Dietary heme iron intake calculated through multiplying the number 0.4 in total iron content of all meat items. Non-heme iron was also calculated through multiplying the number 0.6 in total iron content of all the meat items plus iron in nonmeat items,[39-42] although validity and reliability of the FFQ in this study have been proved in Tehran.[43,44]

The weight of participants was measured using an analog scale with minimal clothing and without shoes with a precision of 0.1 kg and their height using a fixed tape meter on wall in standing position and no shoes while their shoulders were in normal position with 1 cm precision. Body mass index (BMI) was calculated through weight (kg) divided by squared height (m^2).

Venous blood samples were collected after 12 h fasting. Two milliliters of the blood samples placed in tube containing ethylenediaminetetraacetic acid in order to implement complete blood count and the rest were placed in tubes without anticoagulant. Thirty minutes after keeping them at the room temperature, the second series of tubes were centrifuged for 15 min at 2000 rpm until the serum is separated. Then, the separated sample serums were stored in freezer at −70°C until the laboratory analysis. Measuring fasting blood sugar (FBS) conducted through colorimetric method, which measures the activity of the enzyme glucose oxidase. Measuring total cholesterol and TG also were done through colorimetric method. To measure HDL-C, first cholesterol in LDL-C and very-low-density lipoprotein was brokendown through cholesterol oxidase enzymes then cholesterol of HDL-C was measured by colorimetric method. To measure the serum ferritin concentration, the concentration of agglutinated latex particles was measured through turbidimetry. Measurement of the above-mentioned items conducted through quantitative detection kits made by Biosystem Co. in Spain. LDL-C was calculated by Friedewald formula (the TG concentration of none of the study subjects was greater than 397 mg/dL). Serum insulin was measured by enzyme-linked immunosorbent assay and using AccuBind® ELISA Kit (Costa Mesa, CA 92627 USA).

The participants were asked to report their average daily physical activity. Then physical activity was calculated based on metabolic equivalent.[45]

Statistical analysis was carried out through SPSS Software version 18. Normal distribution of variables evaluated through Kolmogorov–Smirnov test and the distribution of variables was normal. Descriptive statistics were used to calculate the mean and standard deviation (SD) of the variables. Pearson correlation test was used to determine the relationship between serum ferritin, hemoglobin, hematocrit and total iron, heme iron, non-heme dietary iron intake with serum lipid parameters, blood glucose, and serum insulin. Multivariate regression was used for adjustment of confounding factors (eg, age, BMI, physical activity, family history of chronic diseases, total energy intake, fat, protein, and saturated fatty acids intake).

RESULTS

Demographic characteristics of participants are shown in Table 1. Mean age of the studied subjects was 28.54 ± 8.51 years and their mean BMI was 23.48 ± 3.71.

Metabolic characteristics of the participants are shown in Table 2. The mean serum ferritin and blood glucose were 47.2 ± 41.7 μg/L and 98.6 ± 13.65 mg/dL, respectively.

The mean energy intake was 2349.52 ± 951.5 kcal per day and mean percentage of energy intake from protein, carbohydrate, and fat was 13.4%, 58.35%, and 28.25%, respectively. The mean total iron intake was 14.88 ± 8.17 mg/d, which was lower than recommended daily allowance for reproductive-age women [Table 3].

As indicated in Table 4, before adjustment of confounding factors, there was a positive and significant correlation between serum ferritin levels and triglycerides, total cholesterol, and blood glucose; however, correlation of serum ferritin was not significant with HDL-C, LDL-C, and serum insulin. There was not any correlation between hemoglobin and hematocrit with these variables. After adjustment of the

Table 1: Basic characteristics of the study subjects

Variable	Mean	SD
Age (years)	28.54	8.51
Height (cm)	161.59	5.4
Weight (kg)	61.04	10.22
BMI (kg/m^2)	23.48	3.71
Physical activity (metabolic equivalent h/d)	34.8	7.2
Family history of chronic diseases (%)	37	-

SD: Standard deviation

Table 2: Metabolic characteristics of participants

Variable	Mean	SD
Blood glucose (mg/dL)	98.60	13.65
TG (mg/dL)	124.34	77.17
Total cholesterol (mg/dL)	178.52	36.47
HDL-C (mg/dL)	47.41	8.22
LDL-C (mg/dL)	106.12	29.30
Ferritin (μg/L)	47.20	41.70
Insulin (mIU/mL)	6.80	3.6
Hemoglobin (g/dL)	12.25	1.12
Hematocrit (%)	39.91	2.79

SD: Standard deviation, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol

Table 3: Dietary profile of the study subjects

Variable	Mean	Standard deviation
Energy (kcal)	2349.52	951.59
Protein (g/d)	78.7	42.88
Percentage of energy	13.4	
Carbohydrate (g/d)	342.73	195.82
Percentage of energy	58.35	
Fat (g/d)	73.74	35.32
Percentage of energy	28.25	
Cholesterol (g/d)	296	202.62
Saturated fatty acids (g/d)	31.62	16.68
Dietary fiber (g/d)	23.37	18.23
Total iron intake (mg/d)	14.88	8.17
Non-heme iron (mg/d)	14.22	7.95
Heme iron (mg/d)	0.66	0.71

confounding factors (such as age, BMI physical activity, family history of chronic diseases, energy, protein, fat, and saturated fatty acids intake) as shown in Table 6, only correlation between serum ferritin and blood sugar levels remained significant ($P = 0.016$).

Total, heme iron, and non-heme dietary iron intake were not correlated with components of lipid parameters, glucose, and insulin before and after adjustment of confounding factors (in Tables 5 and 6, respectively).

DISCUSSION

A significant positive correlation between serum ferritin level with concentration of TG and total cholesterol was observed; however, after adjustment of confounding factors, this correlation disappeared. In this study, the correlation between serum ferritin level with the concentrations of LDL-C and HDL-C was not significant. The available evidences in this regard are inconsistent; thus the results of our study sometimes were in accordance and sometimes differed from other previous studies.

In a study Williams *et al.*[34] conducted on 26-year-old men and women in Dunedin Multidisciplinary study, the results were in accordance with the results of the present study, that is, there was no significant correlation between serum ferritin levels with concentration of total cholesterol,

Table 4: Correlation between serum ferritin, hemoglobin, and hematocrit with components of the lipid parameters, glucose, and insulin in a simple correlation model

	TG (mg/dL)	Total cholesterol (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Blood glucose (mg/dL)	Insulin (mIU/mL)
Ferritin (μg/L) g/L)						
r	0.278	0.267	0.171	0.05	0.275	0.167
P value *	0.006	0.008	0.062	0.319	0.006	0.067
Hemoglobin (g/dL)						
r	0.021	0.149	0.112	0.213	0.157	0.147
P value	0.426	0.091	0.158	0.082	0.08	0.09
Hematocrit (%)						
r	0.048	0.179	0.109	0.304	0.162	0.15
P value	0.334	0.054	0.166	0.07	0.07	0.089

LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, TG: Triglyceride. **P* value less than 0.05 considered as significant

Table 5: Correlation of total, heme, and non-heme dietary iron intake with components of lipid parameters, glucose, and insulin in a simple correlation model

	TG (mg/dL)	Total cholesterol (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Blood glucose (mg/dL)	Insulin (mIU/mL)
Total iron (mg/dL)						
r	0.063	0.167	0.154	0.072	0.137	0.049
P value *	0.286	0.066	0.084	0.26	0.11	0.331
Heme-iron (mg/dL)						
r	0.073	0.2	0.24	0.195	0.075	0.17
P value	0.258	0.072	0.09	0.078	0.253	0.06
Non-heme iron (mg/dL)						
r	0.072	0.154	0.136	0.056	0.134	0.066
P value	0.261	0.08	0.111	0.3	0.115	0.279

LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, TG: Triglyceride. **P* value less than 0.05 considered as significant

Table 6: *P* values* in multivariate regression between ferritin, hemoglobin, hematocrit, total iron, heme and non-heme dietary iron intake with components of the lipid parameters, glucose and insulin after adjustment of confounding factors**

	TG (mg/dL)	Total cholesterol (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Blood glucose (mg/dL)	Insulin (mIU/mL)
Ferritin (μg/L)	0.064	0.17	0.5	0.99	0.016	0.34
Hemoglobin (g/dL)	0.28	0.37	0.46	0.41	0.5	0.405
Hematocrit (%)	0.79	0.44	0.8	0.09	0.3	0.533
Total iron (mg/d)	0.525	0.86	0.72	0.435	0.45	0.196
Heme iron (mg/d)	0.16	0.809	0.502	0.16	0.43	0.268
Non-heme iron (mg/d)	0.525	0.86	0.72	0.435	0.45	0.196

LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, TG: Triglyceride. * *P* value less than 0.05 considered as significant. **Age, body mass index, physical activity, family history of chronic diseases, total energy intake, fat, protein, and saturated fatty acids intake

HDL-C, apolipoprotein B, Lp (a), and blood pressure in women. In men also, there was no significant correlation between serum ferritin levels with concentration of total cholesterol, apolipoprotein B, Lp (a), and blood pressure. Serum ferritin level in men and women had a direct and significant correlation with TG concentration and in men had an inverse and significant correlation with HDL-C concentration. However, these significant correlations disappeared after adjustment of confounding factors. Allissa *et al.*[46] in a study conducted on 270 Saudi men found that there was no significant correlation between serum ferritin level with concentration of TG, HDL-C, and blood pressure. In these individuals, serum ferritin level had a significant and direct correlation with total cholesterol and LDL-C. After adjustment of confounding factors, the ferritin correlation with LDL-C disappeared. Vari *et al.*[33] evaluated the correlation between serum ferritin with prevalence and incidence rate of metabolic syndrome, also investigated the correlation between serum ferritin level and components of the metabolic syndrome in three groups of men, menopausal women, and reproductive age women who participated in D.E.S.I.R. (Data from an Epidemiological Study on the Insulin Resistance Syndrome) study. Serum ferritin level in each three groups was directly correlated with TG concentration. This correlation was stronger in menopausal women and men ($P < 0.001$) than in reproductive-age women ($P < 0.05$). Serum ferritin was inversely correlated with HDL-C only in menopausal women. The observed difference in the results of the mentioned study with the present study might be due to high sample size (n = 900) in that study. Ramakrishan *et al.*,[47] in NHANSE III study on 20- to 49-year-old women found that after adjustment of confounding factor in non-Hispanic black women and Mexican women, there was a direct and significant correlation between ferritin level with concentration of total cholesterol, TG, and blood pressure. However, this correlation in non-Hispanic white women did not remain significant. The researchers attributed different obtained results due to heterogeneity and racial differences in people; however, the precise mechanism is still unknown.

Most studies in this regard conducted in Western and European countries and studies in Asian countries are very limited. Sheu *et al.*[48] showed that in Chinese women, there was a direct correlation between serum ferritin level with concentration of total cholesterol and TG; however, it was not significant between ferritin and HDL-C, in Chinese men also there was no correlation between serum ferritin levels with component of lipid profile. In this study, different obtained results in men and women may be attributed to higher number of Women population which was twice as much as men. In this study nearly more than half of women were of menopause age and the correlation between ferritin levels with components of lipid parameters in all the women reported together; if this correlation was evaluated in menopause-age women and reproductive-age women separately, the results had been more comparable. Although the findings of some studies were not in accordance with the results of the present study, the differences in the participants, their metabolic status, racial and genetic differences also should be taken into account. Perhaps, some of these differences can be attributed to gender, age, BMI, and different amounts of iron intake in the participants of these studies. In most studies there was a significant association between serum ferritin and lipid profile components, the age, BMI and serum ferritin levels were higher than the present study. It is also worth mentioning that most of these studies investigated the correlation between serum ferritin and component of lipid profiles as marginal and subsidiary and did not give a special attention to remove confounding factors and other factors influencing on the correlation.[33,48,49] In this study, before adjustment of confounding factors, there was a significant correlation between serum ferritin level and concentration of TG and total cholesterol; however, this was not significant anymore after adjustment of confounding factors. Therefore, provided that the mentioned studies appropriately considered confounding factors and adjusted the confounding variables, various results could be obtained.

The results of the present study indicated a significant positive correlation between serum ferritin level and concentration of FBS. This correlation remained significant even after adjustment of confounding factors. There was no significant correlation between serum ferritin level and insulin concentration, which was in accordance with the results of other studies in this regard. Bozzini *et al.*[49] conducted a study to compare the serum ferritin level in those with metabolic syndrome and healthy individuals. The correlation between serum ferritin level and component of metabolic syndrome also was investigated and the results showed that there was a significant direct correlation between serum ferritin level and FBS; however, it was not significant between serum ferritin level and insulin concentration. Vari *et al.*[33] found that there was a significant positive correlation between serum ferritin level with blood glucose and insulin in menopausal women, reproductive-age women, and men. Sheu *et al.*, Halle *et al.*, and Ramakrishan *et al.* found similar association between serum ferritin and blood glucose.[47,48,50] The correlation between serum ferritin level and insulin has not been assessed in these studies.

Although the precise molecular mechanism in association between iron stores with blood glucose has not been well understood, it appears that because iron can act as an oxidant in the body, it would be able to catalyze the reactions leading to the production of active oxygen species and finally increase the oxidative stress that is associated with type II diabetes.[51] Furthermore, iron may interfere in glucose uptake by adipose tissue and muscle cells too.[52,53]

There was no correlation between total, heme, and non-heme iron intake with the components of lipid profile, glucose, and insulin levels. To our knowledge, only one study investigated the correlation between total iron intake and component of lipid parameters. In this study,[46] (Alissa *et al.*) the correlation between dietary iron intakes was

not significant with blood sugar level, blood pressure, HDL-C, and TG. After adjustment of confounding factors, dietary iron intake only significantly correlated to the total cholesterol concentration (nevertheless, the name of adjusted confounding factors was not mentioned in this study and it is not clear whether or not the effect of total energy intake and the amount of saturated fatty acid (SFA) have been adjusted). According to our knowledge, no study has ever assessed the correlation of iron intake separated by *heme* and *nonheme* with components of lipid parameters, glucose and insulin; therefore, more attention to this subject in future studies is recommended.

Obviously, lipid disorders are major risk factors of CVDs and glucose intolerance and impaired insulin sensitivity are also the risk factors of diabetes. Studies that investigated the correlation between total, heme, and nonheme dietary iron intake and the risk of CVDs and diabetes and their correlation has been found that only heme iron was directly correlated with incidence risk of these diseases (it was still significant even after adjustment of SFA effect); however, there was no significant correlation between total iron and nonheme iron with incidence risk of CVDs and diabetes.[21,54,55] In these studies, the amount of iron intake, particularly heme iron, which has the major negative effect, was more than heme iron intake in the present study, which is not very surprising; because, meat intake and heme iron in our diet is lower than the diet of people in Western countries and our major iron intake supplied from nonheme iron resources. Perhaps it can be concluded that heme iron in higher amounts can be harmful and the amounts consumed by the current study participants cannot be associated with risk factors of CVDs and diabetes.

The limitations of the study included cross-sectional nature of the study, low sample size, lack of assessing the amount of tea intake, lack of adjustment for effects of inflammatory factors on ferritin level, possibility of recall bias in completing the FFQs, implementation of the study only on reproductive-age women and lack of a proper software to analyze Iranian food intake. Moreover, validity and reliability of the FFQ in this study have been proved only in Tehran.[43,44]

Therefore, it is recommended to evaluate these findings in larger epidemiological studies, in men, menopausal women and other age groups as well. The level of α-1 acid glycoprotein should also be measured to adjust inflammation effect on ferritin levels. The light subunit of ferritin (l-ferritin), which is more sensitive to body's iron level, should also be measured.

In conclusion, serum ferritin level was directly correlated with concentration of FBS. Although the findings of this study indicated lack of a significant correlation between iron store and dietary iron intake with components of lipid parameters and insulin, implementation of larger epidemiological studies in men, menopausal women, and other age groups is recommended to confirm or reject the findings of the present study.

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