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Original Article

Relationship between indices of iron status and metabolic syndrome in an Iranian population

Niloofar Tavakoli-Hoseini[1], Majid Ghayour-Mobarhan[2], Seyed Mohammad Reza Parizadeh[3], Seyed Reza Mirhafez[4], Shima Tavallaie[4], Gordon Ferns[5], Amir Ghorbanihaghjo[6], Nadereh Rashtchizadeh[*7]

[1] *MSc Student, Department of Biochemistry and Clinical Laboratories, International Campus-Aras, Tabriz University of Medical Sciences, Tabriz, Iran*
[2] *Associate Professor, Cardiovascular Research Center, Biochemistry of Nutrition Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3] *Professor, Department of Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[4] *Department of Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[5] *Professor, Division of Medical Education, Brighton and Sussex Medical School, Mayfield House, Falmer, Brighton, UK*
[6] *Associate Professor, Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[7] *Professor, Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

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Abstract

Introduction: Iron overload may contribute to the pathogenesis of metabolic syndrome (MS). A growing body of evidence indicates that the oxidative stress that results from excess tissue iron can leads to insulin resistance, tissue damage, and other complications observed in MS. The objective of this study was to investigate indices of iron status including serum ferritin, iron, total iron binding capacity (TIBC) levels, and full blood cell count, together with demographic and anthropometric characteristics, lipid profile components, and other biochemical parameters in subjects with and with-out MS.

Methods: A total of, 385 individuals (176 with and 209 subjects without MS) according to the International Diabetes Federation's (IDF) criteria were recruited. Indices of iron status and other clinical and biochemical parameters were determined in MS patients and healthy controls using standard methods.

Results: Higher serum iron and ferritin values were observed in subjects with MS in compared to healthy controls ($P < 0.001$). TIBC did not differ significantly between healthy controls and MS patients ($P > 0.050$). Among the other indices, only red blood cell (RBC) was associated considerably with the presence of MS ($P < 0.050$).

Conclusion: Our data indicate that even in a country with a comparatively high prevalence of iron deficiency, serum iron and ferritin values in MS patients are higher than healthy controls. The reason why ferritin and iron are higher in MS patient may be related to dietary factors.

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Introduction

Iron is an essential trace element that is not also involved in several important cellular functions, but is a key component of various enzymes. On the other hand, due to its ability to transfer electrons between ferrous and ferric forms, the excess of iron can be toxic. This process may produce reactive oxygen species[1] by Fenton and Haber-Weiss reactions,[2] resulting oxidative stress and the oxidation of organic biomolecules. This may be involved in neurodegenerative disorders,[3]

*** Corresponding Author:** Nadereh Rashtchizadeh, Email: rashtchizadeh@rocketmail.com

cardiovascular diseases[4] or cancer.[5-7]

Ferritin, a key protein regulating iron homeostasis, is used as a clinical biomarker to assess iron status and is an important indicator for iron deficiency. Basically, in healthy individuals, the ferritin value in blood reflects the iron stored in the body. However, elevated serum ferritin concentrations have been involved in the pathogenesis of several chronic inflammatory diseases including the metabolic syndrome (MS).[8-11]

The MS consists of a group of numerous physiological and metabolic abnormalities, including impaired glucose regulation, dyslipidemia, hypertension, and obesity. Due to its association with an increased risk of developing Type 2 diabetic mellitus and atherosclerotic cardiovascular disease, it has become a subject of great interest.[12-17] During the past decades, various international organizations have proposed several working definitions.[18-23]

There is no report on the relationship between indices of iron status and MS in an Iranian population, based on our research in the literature. Therefore, in continuation of our previous studies on MS,[24-29] and the lack of studies evaluating indices of iron status in MS, in this paper, we have investigated iron, serum ferritin, total iron binding capacity (TIBC) levels and also full blood counts (FBC) including red blood cell (RBC), white blood cell (WBC), mean corpuscular volume (MCV), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet (PLT) in individuals with MS with age/sex-matched healthy controls in an Iranian population.

Methods

A total of 385 individuals comprising 176 individuals with MS and 209 healthy subjects aged 35-65 years, were selected by a cluster-stratified method from Mashhad in Khorasan Razavi province, Iran. Subjects were assessed for iron indices, hematological and biochemical parameters and also anthropometric and demographic measures. Clinical examinations were carried out by trained nurses.

After a 12-h fasting, the blood samples were collected by venepuncture of the ante cubital vein. Blood samples were collected into plain vacutainer tubes (Becton-Dickenson, Cowley, Oxford, UK), to allow for clotting and then serum removed to avoid possible elemental contamination.

All chemicals were purchased from Sigma (Sigma Chemical Co, Dorset, UK) unless stated otherwise. Data on socioeconomic factors were collected using an interviewer-administered questionnaire including information on gender, age, and smoking status.

Anthropometric parameters such as weight, height, hip circumference (HC), body mass index (BMI), waist circumference (WC) and Mid Arm Circumference (Mid Arm C) were measured. Height (cm) was measured with a portable, telescopic stadiometer to the nearest millimeter while the participant's head was in the Frankfurt plane. After an overnight fasting, the subjects dressed in light clothing were weighed using a standard scale. Using measuring tape at the maximum circumference of the hips, the HC (cm) was measured. BMI was calculated by weight (kg)/height (m^2). The WC (cm) was measured at the midpoint between the iliac crest and last rib.

Using a mercury sphygmomanometer with adjustable cuff size for each individual on two occasions (separated by an interval of 15 min) while subjects were in a sitting position, the blood pressure was measured. The average of two values of Phase IV was recorded for diastolic blood pressure (DBP) and the average of the two measurements of Korotkoff Phase I was considered as systolic blood pressure (SBP).

For each subject, a complete lipid profile, comprising triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (HDL-C) was determined. Fasting blood glucose and serum lipid concentrations were enzymatically measured using commercial kits, i.e., the BT-3000 auto analyzer machine (Biotechnica, Rome, Italy). By polyethylene glycol-enhanced immunoturbidimetry using a Bayer Advia 1650 analyzer (Bayer, Newbury, UK), highly

sensitive C-reactive protein concentrations were determined.

Hematological parameters FBC were measured using an automated blood cell counter (Sysmex KX-21N, Japan). Separated serum and whole blood were kept frozen at -80 °C until analysis. TIBC and iron concentrations were enzymatically measured by commercial kits using the BT-3000 auto-analyzer machine (Biotechnica, Rome, Italy). Serum ferritin levels were assayed with the using of commercial kits by standard enzyme-linked immunosorbent assay (Stat Fax 2100).

According to the International Diabetes Federation's (IDF)[30] definition, MS is defined central obesity (defined as a WC of at least 94 cm in men or 80 cm in women) and meeting at least two of the following criteria:

• Fasting serum TG: 1.70 mmol/l (150 mg/dl)

• HDL-C: 1.04 mmol/l (40 mg/dl) in men or 1.30 mmol/l (50 mg/dl) in women

• BP: 130/85 mmHg

• Fasting glucose: 6.11 mmol/l (100 mg/dl).

The software SPSS for Windows (version 16, SPSS Inc., Chicago, IL, USA) was used for data analysis. The Kolmogorov-Smirnov test was used to assess normality. Descriptive statistics (frequency, mean, and standard deviation) determined were determined for all variables. Values are reported as mean ± standard deviation for normally distributed variables (or median and interquartile range for non-normally distributed variables). Baseline demographics and clinical features were compared among groups using t-test, one-way ANOVA test, chi-square test, and/or Fisher exact test as appropriate. Kaplan-Meier test is SPSS has been used for survival analysis. $P < 0.050$ was regarded as statistically significant.

Results

Socio-demographic, anthropometric characteristics, and biochemical parameters in the group with and without MS are shown in table 1.

Table 1. Socio-demographics, anthropometric characteristics, and biochemical parameters in the group with and without MS

Parameters	Variable	MS (−) (n = 209)	MS (+) (n = 176)	P
Socio-demographics	Age (years)	52.7 ± 9.7	54.0 ± 7.9	0.144
	Sex (%)			
	Male	108 (51.7)	90 (51.1)	0.916
	Female	101 (48.3)	86 (48.9)	
	Smoking (%)			
	Yes	47 (22.5)	53 (30.1)	0.333
	No	162 (77.5)	123 (69.9)	
Anthropometric characteristics	Height (cm)	161.4 ± 9.2	162.1 ± 8.2	0.460
	Weight (kg)	67.6 ± 12.7	77.9 ± 12.8	< 0.001
	HC (cm)	101.3 ± 8.7	107.0 ± 7.0	< 0.001
	BMI (kg/m^2)	25.9 ± 4.4	29.5 ± 3.8	< 0.001
	WC (cm)	93.1 ± 12.5	103.3 ± 8.7	< 0.001
	Mid Arm C (cm)	29.9 ± 4.3	31.5 ± 3.0	< 0.001
Biochemical parameters	TG (mg/dl)	128 (90-177)	172 (118-223)	< 0.001
	TC (mg/dl)	193.1 ± 37.3	200.0 ± 40.8	0.099
	HDL-C (mg/dl)	42.8 ± 8.4	38.7 ± 8.3	< 0.001
	LDL-C (mg/dl)	119.4 ± 32.8	126.2 ± 36.4	0.070
	HSCRP (mg/dl)	1.4 (0.9-3.1)	1.9 (1.1-4.2)	0.039
	FBG (mg/dl)	93.9 ± 47.1	97.7 ± 35.6	0.012
	SBP (mm Hg)	126.0 ± 19.5	136.6 ± 18.4	< 0.001
	DBP (mm Hg)	80.2 ± 11.1	87.2 ± 11.0	< 0.001

MS: Metabolic syndrome; HC: Hip circumference; BMI: Body mass index; WC: Waist circumference; Arm C: Arm circumference; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein-cholesterol; HSCRP: High-sensitivity C-reactive protein; FBG: Fasting blood glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Values are expressed as mean ± standard deviation (for normally distributed data) or median and interquartile range (for non-normally distributed data)

Independent samples T test and Mann-Whitney U test were performed for normally and non-normally distributed variables, respectively

Among this study's total population of 385 individuals, 176 (45.7%) individuals had MS (51.1% men and 48.9% women) meeting the IDF criteria. No considerable difference was observed in the average age, sex distribution and smoking habit (P = 0.144, P = 0.916 and P = 0.333, respectively). The MS group were significantly more adipose, and with higher HC, BMI, WC, and Mid Arm C (P < 0.001) respectively, than the control group. Subjects with MS also had significantly higher TG, SBP, and DBP (P < 0.001) than subjects without MS. By contrast, serum HDL-cholesterol levels values were significantly lower in individuals with MS (P < 0.001).

The relationships between FBC and iron indices and the presence of MS are shown in table 2. All FBC indices including WBC, RBC, HCT, MCV, MCH, MCHC, and PLT were higher in subjects with MS than the healthy controls. Among these indices, however, only the difference in RBC was significant (P = 0.021). No significant relation between TIBC and the presence of MS was found (P = 0.431), while the subjects with MS exhibited significantly higher serum iron (P <0.001) and Ferritin (P < 0.001) than the control group (Table 2).

Table 3 summaries the relationship between iron indices (iron, TIBC, and ferritin) and components of the MS in the group with and without MS. A significant positive correlation was found between iron and TIBC in MS (+) (r = 0.565, P < 0.001), whilst there was weaker positive relationship between iron and ferritin in MS (+) (r = 0.177, P = 0.019). Negative associations were found between ferritin and HDL-C (r = -0.226, P = 0.006) and also between TIBC and HDL-C in MS (+) (r = -0.169, P = 0.041).

Univariate and multivariate analysis with Pearson correlation coefficients were applied to assess the association between iron indices (iron, TIBC, and ferritin) and MS. The results are shown in table 4. As shown, a strong correlation was found between iron and MS in both univariate and multivariate analysis (P < 0.001). Ferritin was also strongly associated with MS in univariate analysis (P < 0.001), but weaker correlation was found between ferritin and MS in multivariate analysis (P = 0.004). There was a non-significant association between TIBC and MS in both univariate and multivariate analysis (P = 0.431 and 0.480 respectively).

Discussion

Published data have shown the prevalence of MS in females was significantly higher compared to males, and this also appears to be the case in Iran.[31-34] However, in recent years, it appears that the prevalence of MS among men is increasing.[35,36] The results of the present study showed that although there was no meaningful difference, the proportion of males with MS was slightly higher compared to females.

Table 2. Comparison of FBC and iron indices in MS group with healthy controls

Indices	MS (−) (n = 209)	MS (+) (n = 176)	P
WBC (10^3/ul)	6.0 ± 1.9	6.2 ± 1.6	0.388
RBC (10^6/ul)	4.7 ± 0.8	4.9 ± 0.6	0.021
HCT (%)	41.0 ± 7.3	42.2 ± 5.2	0.102
MCV (FL)	84.0 ± 13.6	84.2 ± 8.8	0.835
MCH (pg)	28.3 ± 4.7	28.5 ± 3.3	0.609
MCHC (gr/dl)	32.9 ± 5.2	33.6 ± 3.0	0.154
PLT (10^3/ul)	217.0 ± 71.0	225.0 ± 58.7	0.282
Iron (µg/dl)	102.4 ± 44.7	133.2 ± 64.8	< 0.001
TIBC (µg/dl)	537.8 ± 267.5	560.5 ± 297.5	0.431
Ferritin (ng/ml)	93.5 ± 73.7	125.6 ± 97.8	< 0.001

MS: Metabolic syndrome; WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; HCT: Hematocrit; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PLT: Platelet count; TIBC: Total iron binding capacity; FBC: Full blood count

Values are expressed as mean ± standard deviation

Independent samples T test was performed for blood count and iron indices variables

Table 3. Correlation between iron indices and other clinical and biochemical parameters including components of the MS in individuals with and without MS

Variable	MS (−)			MS (+)		
	Iron	TIBC	Ferritin	Iron	TIBC	Ferritin
TIBC (µg/dl)						
r	0.545	-	-	0.565	-	-
P	< 0.001	-	-	< 0.001	-	-
Ferritin (ng/ml)						
r	0.108	-0.140	-	0.177	-0.059	-
P	0.120	0.043	-	0.019	0.435	-
BMI (kg/m^2)						
r	0.089	-0.016	0.092	-0.011	-0.159	0.069
P	0.204	0.822	0.189	0.893	0.054	0.405
WC (cm)						
r	0.185	0.032	0.120	-0.107	-0.108	0.003
P	0.008	0.643	0.084	0.197	0.191	0.969
HC (cm)						
r	0.104	0.053	-0.003	-0.020	-0.100	-0.089
P	0.135	0.447	0.971	0.808	0.233	0.287
TG (mg/dl)						
r	0.090	0.125	-0.017	0.129	0.050	0.121
P	0.200	0.074	0.812	0.120	0.552	0.143
TC (mg/dl)						
r	0.067	0.037	-0.003	0.040	-0.013	-0.113
P	0.338	0.603	0.961	0.632	0.877	0.173
HDL-C (mg/dl)						
r	-0.053	0.014	-0.138	-0.127	-0.169	-0.226
P	0.453	0.838	0.049	0.125	0.041	0.006
LDL-C (mg/dl)						
r	0.099	-0.012	0.081	0.019	0.025	-0.151
P	0.159	0.863	0.251	0.822	0.768	0.068
FBG (mg/dl)						
r	-0.090	0.001	0.021	-0.082	-0.106	0.105
P	0.201	0.993	0.770	0.325	0.199	0.206
HSCRP (mg/dl)						
r	0.024	0.029	0.002	0.073	0.153	-0.079
P	0.738	0.690	0.977	0.38	0.065	0.344
SBP (mm Hg)						
r	-0.011	-0.022	0.317	-0.047	-0.078	-0.027
P	0.880	0.750	< 0.001	0.568	0.348	0.750
DBP (mm Hg)						
r	0.001	-0.047	0.286	-0.001	0.030	0.060
P	0.986	0.504	< 0.001	0.988	0.720	0.470

MS: Metabolic syndrome; TIBC: Total iron binding capacity; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; TG: Triglyceride; TC: Total cholesterol; FBG: Fasting blood glucose; HSCRP: High-sensitivity C-reactive protein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 4. Association between Iron indexes and MS by univariate and multivariate analysis

Metabolic syndrome	Iron				TIBC				Ferritin			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	β	P*	β	P*	β	P*	β	P*	β	P*	β	P*
MS (−)**	0	-	0	-	0	-	0	-	0	-	0	-
MS (+)	30.8	< 0.001	32.7	< 0.001	22.7	0.431	22.6	0.480	32.1	< 0.001	27.9	0.004

*In present of age, sex, smoking and TIBC, **Reference category

β: Coefficient regression; MS: Metabolic syndrome; TIBC: Total iron binding capacity; HSCRP: Highly sensitive C-reactive protein

Since many western food sin particular, contain refined carbohydrates and iron, excessive consumption of these foods can increase the risks of insulin insufficiency and iron overloading.[37] The association between MS and anthropometric parameters such as weight, HC, BMI, and WC, is possibly related to diet and high dietary intake of iron may related to a high meat intake that is often also associated with a high calorie intake and adiposity. Also, in several studies, serum ferritin levels have been found to be associated with increased fasting serum insulin and blood glucose as well as decreased insulin sensitivity, these abnormalities may result in increased adiposity which increases the risk of MS.[38,39]

The appropriate balance of dietary trace elements has long been accepted as important for optimum health. The clinical significance of trace elements is still somewhat controversial. Among the trace elements, iron is of particular interest. In this study, the association of iron status in subjects with and without MS in an Iranian population was examined. The present study showed a significant association between MS and indices of iron status in Iranian subjects. Subjects with MS had higher iron and ferritin status. These finding do not accord with those of some studies that have examined the relationship between MS and indices of iron status.[40,41] These studies demonstrated a negative association between MS and iron status. However, other studies have shown a positive relation between the presence of MS and iron status.[42,43] This positive relationship can increase the risk of iron overload.[44,45] We found no statistically significant relationship between the presence of MS and TIBC index. The subjects in the MS group had considerably higher levels of iron and ferritin than the control group. However, the TIBC level was not significantly different between two groups.

Among the FBC indices, only RBC exhibited a significant correlation with MS. In MS (+), positive correlations were found between iron and TIBC, and also between iron and ferritin, whilst the associations between ferritin and HDL-C and also between TIBC and HDL-C were negative. It has been theorized that elevated iron may intervene with hepatic insulin extraction (leading to peripheral hyperinsulinemia) despite the fact that the mechanisms for the effect of iron on the risk of MS are not clear.[46,47] Other researchers have suggested that iron might catalyze the hydroxyl radicals' formation contributing to the development of insulin resistance.[48,49]

The iron deficiency anemia indices-induced MS can be explained by three proposed mechanisms via insulin resistance, hepatic dysfunction, and B-cell oxidative stress. Clinical finding concludes that iron likely play a role in the pathogenesis of insulin resistance.[50] This hypothesis has been noted in clinical studies including those determining a relation between iron stores with increased ferritin and insulin resistance and amelioration of insulin resistance after iron depletion therapy.[51,52]

Insulin resistance mechanisms involve the likelihood of iron overload resulted in resistance directly or by hepatic dysfunction.[53] In one study, the patients with unexplained hepatic iron overload were mostly found to be insulin resistant.[54] This suggests a common etiologic correlation among insulin resistance, hepatic iron, and hepatic dysfunction. Oxidative stress and elevated iron mediate pancreatic islets' apoptosis with a resultant decrease in insulin secretory capacity.[55]

Conclusion

Correlation between indices of iron status (including iron, ferritin and TIBC) and also FBC indices, demographic and anthropometric characteristics, lipid profile components, and other biochemical parameters with MS in an Iranian population was investigated. The subjects in the MS group had considerably higher levels of iron and ferritin ($P < 0.001$), than the control group, while no significant relationship between TIBC and MS was observed. Among the socio-demographics, anthropometric characteristics, biochemical parameters, and FBC indices, weight, HC, BMI, WC, Mid Arm C, TG, HDL-C, SBP, DBP, and RBC exhibited

significant correlation with MS.

Conflict of Interests

Authors have no conflict of interest.

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