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Association of elevated serum ferritin concentration with insulin resistance and impaired glucose metabolism in Korean men and women

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Abstract

Increased serum ferritin concentrations in nonpathologic conditions, reflecting subclinical iron overload, have been reported to be associated with insulin resistance and an increased risk of type 2 diabetes mellitus (DM). However, serum ferritin concentrations differ significantly according to sex and ethnicity; and data concerning the relationship between serum ferritin concentrations and glucose metabolism abnormalities in Asian men and women are conflicting. This cross-sectional study investigated the association of serum ferritin concentrations with insulin resistance and impaired glucose metabolism in a large number of subjects with normal fasting glucose (NFG) level, impaired fasting glucose (IFG) level, or type 2 DM. We analyzed clinical and laboratory data from 12 090 subjects (6378 men and 5712 women; age, 20-89 years) who underwent general medical checkups. The study population included 1054 subjects with type 2 DM, 3783 subjects with IFG level, and 7253 subjects with NFG level. Serum ferritin, hemoglobin A_{1c}, fasting glucose, lipid, and insulin levels were measured. Insulin resistance and β-cell function indices were derived from a homeostasis model assessment. Serum ferritin concentrations were highest in the DM group, followed by the IFG group and the NFG group, in both men and women (186 ± 127, 176 ± 108, and 156 ± 92 ng/mL, respectively, in men; 85 ± 62, 75 ± 55, and 59 ± 47 ng/mL, respectively, in women). After adjustment for other variables using multiple regression analysis, homeostasis model assessment of insulin resistance was independently associated with serum ferritin concentration in men, but not in women. When the fourth quartile of ferritin was compared with the first quartile, the age-adjusted odds ratio (OR) for type 2 DM was 1.71 (95% confidence interval, 1.38-2.12) in men and 1.50 (1.05-2.13) in women. The OR in men was attenuated to 1.27 (1.01-1.60) but remained significant after adjustment for body mass index (BMI), waist circumference, blood pressure, serum lipids, liver enzymes, and high-sensitivity C-reactive protein (hsCRP). In nondiabetic subjects, the age-adjusted OR for IFG in the fourth quartile of ferritin was 1.82 (1.56-2.13) in men and 1.68 (1.40-2.02) in women. The OR was attenuated to 1.31 (1.11-1.55) in men and 1.45 (1.19-1.78) in women after adjustment for BMI, waist circumference, blood pressure, serum lipids, liver enzymes, and hsCRP. In NFG subjects, the age-adjusted OR for metabolic syndrome in the fourth quartile of ferritin concentration was 2.85 (1.99-4.07) in men and 1.21 (0.82-1.79) in women. In men, the OR was attenuated to 1.58 (1.06-2.37) after adjustment for BMI, liver enzymes, and hsCRP. Increased serum concentrations of ferritin are associated with insulin resistance, type 2 DM, IFG, and metabolic syndrome in men, but only with IFG in women. These results suggest that iron overload is associated with insulin resistance in men, but not in women.

1. Introduction

Iron is a transition metal that can convert poorly reactive free radicals (eg, H_2O_2) into highly reactive moieties (eg, the hydroxyl radical), which can cause oxidative damage to cells and tissues [1,2]. Increased accumulation of iron in patients with hemochromatosis or hematologic diseases affects the synthesis and secretion of insulin by the pancreas [3,4] and compromises insulin action in target tissues [5-7]. Recent reports have linked increased serum ferritin concentrations in nonpathologic conditions, reflecting subclinical iron overload, to insulin resistance [8-11] and an increased risk of type 2 diabetes mellitus (DM) [12,13].

Serum ferritin concentrations differ significantly according to sex and ethnicity. Asian men and women were reported to have higher adjusted mean serum ferritin

The study protocol was approved by the Institutional Review Board of the Asan Medical Center, Seoul, Korea.

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concentrations compared with their white counterparts [14]. A study examining the association of diabetes with serum ferritin concentration in 6 racial/ethnic groups found that serum ferritin concentrations were significantly higher in women with diabetes than in women without diabetes in all racial/ethnic groups, but serum ferritin concentrations were significantly lower in Asian men with diabetes than in those without diabetes [15]. As serum ferritin concentrations differ significantly between men and women, it is thought that ferritin plays a different role in insulin resistance in each sex [16]. However, conflicting data have been reported with regard to the relationship between iron overload and glucose metabolism in Asian men and women [16-20]. The relationships between serum ferritin concentrations and insulin resistance [16] and risk of diabetes [19] have been reported in Chinese women, but not in men. Another Chinese study [17] found that serum ferritin concentrations of healthy, glucose-tolerant, first-degree relatives of type 2 DM patients were significantly higher than those of healthy control subjects in men, but not in women. However, Sun and colleagues [20] showed a strong positive association between elevated serum ferritin concentration and the risks of type 2 DM, impaired fasting glucose (IFG), and metabolic syndrome in both men and women aged 50 to 70 years. Therefore, the role played by ferritin in insulin resistance in men and women, particularly in Asian populations, remains poorly understood. Few studies have examined the relationship between serum ferritin concentration and glucose regulation status in large numbers of subjects with normal fasting glucose (NFG), IFG, and type 2 DM. The present study was performed to examine the association of serum ferritin concentrations with glucose metabolism abnormalities and insulin resistance and to determine if the association differed between men and women in a Korean population of varied glucose regulation status.

2. Subjects and methods

2.1. Subjects

Clinical and laboratory data were collected from 13 848 adults (47% women) who visited the Health Promotion Center at Asan Medical Center (Seoul, Korea) for regular health checkups in 2008. The health checkup recipients came voluntarily from all over South Korea; but most of them were middle-aged office workers, professionals, or housewives living in Seoul or the nearby urban area of Gyeonggi province. Each subject completed a standard questionnaire that detailed medical history, family history of diabetes and/or ischemic heart disease, and regular medications. A total of 821 subjects were excluded because of missing history, serum glucose, or ferritin data. Subjects with acute or chronic inflammatory or infectious diseases (n = 504), liver cirrhosis or chronic liver diseases (n = 33), major cardiovascular events (n = 267), neoplastic diseases (n = 189), and history of transfusion or iron therapy in the previous year (n = 117) and those with hsCRP greater than 5 mg/L (n = 423), serum liver enzyme (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) activities above 2 times of the upper normal limits (n = 335), and increased serum creatinine (>1.4 mg/dL) (n = 60) were excluded from the study. After excluding 1758 subjects (some subjects met more than 2 exclusion criteria), data for 12 090 adults (6378 [52.7%] men and 5712 [47.3%] women) with an average age of 51.3 ± 9.2 (SD) years (range, 20-89 years) were analyzed. The study protocol was approved by the Institutional Review Board of the Asan Medical Center.

2.2. Measurements

Height and weight were measured in subjects wearing light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference was measured midway between the costal margin and the iliac crest at the end of a normal expiration. Blood pressure was measured with a mercury sphygmomanometer on the right arm with subjects in the sitting position after a 5-minute period of rest. Blood samples were obtained in the morning after an overnight fast. Plasma concentrations of glucose (assayed by the hexokinase method), total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using an autoanalyzer (Toshiba, Tokyo, Japan). C-reactive protein (hsCRP) was measured by a high-sensitivity assay, using a latex particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany). Serum ferritin was measured by direct chemiluminescent 2-site sandwich immunoassay (Siemens Medical Solutions Diagnostics, Tarrytown, NY), and insulin levels were measured using an immunoradiometric assay (TFB, Tokyo, Japan). Insulin resistance (HOMA-IR) and β-cell function (HOMA%B) indices were derived from homeostasis model assessment [21].

2.3. Definitions

Diabetes was defined by fasting plasma glucose levels of at least 7.0 mmol/L or by treatment with antidiabetic medications. *Impaired fasting glucose* was defined as fasting plasma glucose levels of at least 5.6 mmol/L and less than 7.0 mmol/L. *Hypertension* was defined as systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or treatment with antihypertensive agents. In accordance with the 2005 revised National Cholesterol Education Program–Adult Treatment Panel III criteria [22], *metabolic syndrome* was defined as the combination of 3 or more of the following measures: fasting plasma glucose levels of at least 5.6 mmol/L or antidiabetic treatment, blood pressure of at least 130/85 mmHg or antihypertensive treatment, waist circumference greater than 90 cm in men and greater than 80 cm in women, plasma triglyceride levels of at least 1.7 mmol/L,

and plasma HDL cholesterol levels less than 1.03 mmol/L in men and less than 1.29 mmol/L in women.

2.4. Statistical analysis

Data were expressed as means ± SD. Variables that were not distributed normally, such as blood concentrations of glucose, triglycerides, and hepatic enzymes, were log-transformed before analysis. Serum ferritin concentrations were divided into quartiles because the distribution of serum ferritin concentration was highly skewed and we could not assume that there was a linear relationship between serum ferritin and the other clinical and biochemical variables. Quartiles were used rather than quintiles to get sufficient statistical power in logistic regression analysis because the number of diabetic subjects in the lowest quintile was quite small.

One-way analysis of variance with post hoc analysis using the Scheffe method was used to compare differences between groups. Pearson correlation coefficients between serum ferritin concentrations and variable parameters were determined. Multiple regression analysis with forward selection method was performed to identify factors that were independently associated with HOMA-IR. Multivariate logistic regression analyses were used to estimate the odds ratios (ORs) for type 2 DM, IFG, and metabolic syndrome after adjusting for other clinical and biochemical variables. Statistical analyses were performed using the SPSS 14.0 for Windows software package (SPSS, Chicago, IL). P values < .05 were considered statistically significant.

3. Results

Among the 12 090 subjects, 1054 had type 2 DM, 3783 had an IFG level, and 7253 had an NFG concentration. The average serum concentration of ferritin was much higher in men (167 ± 103 ng/mL) than in women (65 ± 51 ng/mL). Ferritin concentrations were highest in the DM group, followed by the IFG group and the NFG group, in both men and women (186 ± 127, 176 ± 108, and 156 ± 92 ng/mL, respectively, in men; 85 ± 62, 75 ± 55, and 59 ± 47 ng/mL, respectively, in women) (Table 1). Table 2 shows the

Table 1
Clinical and laboratory characteristics of study subjects according to glucose regulation status

	NFG	IFG	Type 2 DM
A. Men			
n	3384	2267	727
Age (y)	50.4 ± 9.5	52.2 ± 8.3†	55.3 ± 8.6†,§
BMI (kg/m^2)	24.4 ± 2.6	25.1 ± 2.6†	25.2 ± 2.8†
Systolic BP (mmHg)	116 ± 12	120 ± 13†	121 ± 13†,‡
Fasting glucose (mmol/L)[a]	5.1 ± 0.3	6.0 ± 0.3†	8.0 ± 2.1†,§
Fasting insulin (mIU/L)[a]	5.6 ± 3.3	7.4 ± 4.1†	8.3 ± 15.9†,‡
ALT (IU/L)[a]	30 ± 15	32 ± 17†	34 ± 18†,‡
GGT (IU/L)[a]	33 ± 24	41 ± 29†	42 ± 30†
hsCRP (mg/L)[a]	1.3 ± 1.2	1.5 ± 1.4	1.5 ± 1.2
HOMA-IR[a]	1.28 ± 0.80	2.01 ± 1.20†	2.88 ± 1.94†,§
Ferritin (ng/mL)[a]	156 ± 92	176 ± 108†	186 ± 127†,‡
B. Women			
n	3869	1516	327
Age (y)	49.5 ± 8.9	53.3 ± 8.8†	58.1 ± 8.2†,§
BMI (kg/m^2)	22.4 ± 2.7	23.8 ± 3.1†	24.6 ± 3.4†,§
Systolic BP (mmHg)	110 ± 13	117 ± 14†	121 ± 16†,§
Fasting glucose (mmol/L)[a]	5.0 ± 0.3	6.1 ± 0.3†	7.8 ± 2.2†,§
Fasting insulin (mIU/L)[a]	5.3 ± 3.0	7.9 ± 4.1†	8.7 ± 6.1†,§
ALT (IU/L)[a]	21 ± 10	24 ± 12†	28 ± 16†,§
GGT (IU/L)[a]	16 ± 12	19 ± 14†	24 ± 19†,§
HOMA-IR[a]	1.20 ± 0.71	2.10 ± 1.14†	3.15 ± 2.31†,§
hsCRP (mg/L)[a]	0.9 ± 0.8	1.4 ± 1.1†	1.8 ± 1.4†,‡
Ferritin (ng/mL)[a]	59 ± 47	75 ± 55†	85 ± 62†,§

Data are shown as means ± SDs. BP indicates blood pressure.
$^{\dagger}P < .001$ vs NFG group; $^{\ddagger}P < .05$, $^{\S}P < .01$ vs IFG group by analysis of variance with post hoc analysis using Scheffe method.
[a] Nontransformed data are presented in this table; however, statistical analyses were performed on log-transformed data.

Table 2
Clinical characteristics of study subjects according to quartile of serum ferritin concentration

A. Men

	Ferritin quartile (range, ng/mL)				
	1st (3-98)	2nd (99-145)	3rd (146-208)	4th (209-976)	P for trend[a]
Age (y)	53.0 ± 8.9	51.7 ± 9.1	51.0 ± 9.0	50.7 ± 9.3	<.001
BMI (kg/m^2)	24.2 ± 2.6	24.5 ± 2.6	24.9 ± 2.5	25.4 ± 2.7	<.001
Systolic BP (mmHg)	117 ± 12	118 ± 13	118 ± 12	119 ± 13	.004
Glucose (mmol/L)	5.6 ± 1.1	5.6 ± 0.9	5.7 ± 1.1	5.9 ± 1.5	<.001
ALT (IU/L)	26 ± 10	28 ± 11	30 ± 13	35 ± 15	<.001
GGT (IU/L)	28 ± 20	32 ± 24	38 ± 27	48 ± 32	<.001
hsCRP (mg/L)	1.1 ± 0.8	1.3 ± 1.2	1.4 ± 1.2	1.8 ± 1.5	<.001
Fasting insulin (mIU/L)	5.6 ± 3.4	6.5 ± 4.8	6.6 ± 3.8	7.4 ± 4.5	<.001
HOMA-IR	1.4 ± 1.0	1.6 ± 1.6	1.7 ± 1.1	2.0 ± 1.4	<.001

B. Women

	Ferritin quartile (range, ng/mL)				
	1st (1-29)	2nd (30-54)	3rd (55-85)	4th (86-508)	P for trend[a]
Age (y)	46.1 ± 7.8	49.7 ± 8.8	53.1 ± 9.0	55.1 ± 8.3	<.001
BMI (kg/m^2)	22.3 ± 2.8	22.7 ± 2.9	23.1 ± 2.9	23.5 ± 2.9	<.001
Systolic BP (mmHg)	110 ± 13	111 ± 14	114 ± 15	115 ± 14	<.001
Glucose (mmol/L)	5.2 ± 0.7	5.3 ± 0.9	5.4 ± 0.9	5.6 ± 1.1	<.001
ALT (IU/L)	18 ± 8	20 ± 9	22 ± 9	25 ± 11	<.001
GGT (IU/L)	14 ± 10	15 ± 11	17 ± 12	22 ± 18	<.001
hsCRP (mg/L)	0.7 ± 0.5	1.0 ± 0.9	1.1 ± 1.1	1.6 ± 1.3	<.001
Fasting insulin (mIU/L)	5.8 ± 3.3	5.9 ± 3.4	6.2 ± 3.7	7.0 ± 4.4	<.001
HOMA-IR	1.4 ± 0.9	1.4 ± 0.9	1.5 ± 1.1	1.8 ± 1.3	<.001

Data are shown as means ± SDs.
[a] Determined by a regression model with the covariate as the dependent variable and an indicator variable equal to the median level of ferritin for the quartile that the observation falls into as the independent variable.

Table 3
Multiple regression analysis of the relationship between HOMA-IR and clinical/biochemical parameters

	Coefficient			R^2	Change of R^2	P value
	β	Standard error	95% CI			
Men						
BMI	.300	.010	.281~.319	.204	.204	.000
Glucose	.346	.014	.318~.374	.358	.154	.000
ALT	.158	.009	.139~.177	.389	.032	.000
Triglyceride	.129	.026	.077~.181	.412	.023	.000
HDL	−.103	.012	−.127~−.079	.421	.009	.000
Systolic BP	.095	.008	.080~.110	.429	.008	.000
Ferritin	.038	.010	.018~.058	.430	.001	.000
Age	.001	.010	−.019~.021			.998
hsCRP	.012	.010	−.008~.032			.210
Women						
Glucose	.354	.011	.332~.376	.228	.228	.000
BMI	.241	.011	.219~.263	.331	.103	.000
Triglyceride	.185	.019	.148~.222	.380	.049	.000
HDL	−.086	.013	−.112~−.060	.385	.005	.000
Systolic BP	.089	.009	.071~.107	.390	.005	.000
Age	.081	.012	.057~.105	.393	.003	.000
ALT	.053	.012	.028~.078	.399	.006	.000
Ferritin	.015	.010	−.005~.036			.199
hsCRP	.015	.010	−.005~.035			.153

characteristics of study subjects according to quartile of serum ferritin concentration.

Serum ferritin concentrations in men correlated with BMI ($r = 0.165$), waist circumference ($r = 0.186$), and the levels of fasting glucose ($r = 0.142$), triglycerides ($r = 0.203$), ALT ($r = 0.257$), γ-glutamyl transferase (GGT) ($r = 0.278$), fasting insulin ($r = 0.176$), and HOMA-IR ($r = 0.196$) (Pearson correlation analysis, $P < .001$ for all). In women, serum ferritin concentration correlated with age ($r = 0.300$), waist circumference ($r = 0.170$), and levels of fasting glucose ($r = 0.147$), triglycerides ($r = 0.167$), ALT ($r = 0.230$), GGT ($r = 0.185$), fasting insulin ($r = 0.127$), and HOMA-IR ($r = 0.150$) ($P < .001$ for all). The HOMA%B was not significantly correlated with serum ferritin concentrations in men or women. After adjustment for other variables using multiple regression analysis, HOMA-IR was independently associated with serum ferritin concentration in men, but not in women (Table 3). Hemoglobin A_{1c} was significantly correlated with serum ferritin concentration in men ($r = 0.074$, $P < .001$), but not in women ($r = 0.004$, $P = .73$), after adjustment for age, BMI, blood pressure, ALT, GGT, triglycerides, and hsCRP.

When the fourth quartile of ferritin was compared with the first quartile, the age-adjusted OR for type 2 DM was 1.71 (95% confidence interval [CI], 1.38-2.12) in men and 1.50 (1.05-2.13) in women (Table 4). The OR in men was attenuated to 1.27 (1.01-1.60) but remained significant after adjustment for BMI, waist circumference, blood pressure, AST, ALT, GGT, triglyceride, HDL cholesterol, and hsCRP. The age-adjusted OR for IFG in the fourth quartile of ferritin concentration was 1.82 (1.56-2.13) in nondiabetic men and 1.68 (1.40-2.02) in nondiabetic women (Table 5). The OR was attenuated to 1.31 (1.11-1.55) in men and 1.45 (1.19-1.78) in women after adjustment for BMI, waist circumference, blood pressure, AST, ALT, GGT, triglyceride, HDL cholesterol, and hsCRP. In NFG subjects, the age-adjusted OR for metabolic syndrome in the fourth quartile of ferritin was 2.85 (1.99-4.07) in men and 1.21 (0.82-1.79) in women (Table 6). In men, the OR was attenuated to 1.61 (1.08-2.41) but remained significant after adjustment for BMI, AST, ALT, GGT, and hsCRP. To investigate whether the associations differed significantly according to sex, we included ferritin × sex interaction term in the logistic regression analyses. There was significant interaction for type 2 DM ($P = .001$) and metabolic syndrome ($P = .026$), but not for IFG ($P = .206$).

4. Discussion

Our findings confirm that serum ferritin concentrations are significantly increased in prediabetic subjects as well as in type 2 DM patients and that serum ferritin concentration is positively associated with components of metabolic syndrome in both Korean men and women. However, men and women differ with regard to the role of ferritin in insulin

Table 4
Odds ratios (95% CI) for type 2 DM according to quartile of serum ferritin concentration in men and women

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Men					
Model 1	1.00	0.97 (0.77-1.23)	1.20 (0.96-1.51)	1.71 (1.38-2.12)	<.001
Model 2	1.00	0.92 (0.72-1.16)	1.11 (0.88-1.40)	1.42 (1.14-1.78)	<.001
Model 3	1.00	0.90 (0.71-1.14)	1.06 (0.84-1.33)	1.27 (1.01-1.60)	.028
Women					
Model 1	1.00	1.01 (0.70-1.49)	1.04 (0.74-1.47)	1.50 (1.05-2.13)	.004
Model 2	1.00	0.98 (0.66-1.45)	0.90 (0.61-1.32)	1.30 (0.89-1.89)	.070
Model 3	1.00	0.96 (0.65-1.43)	0.86 (0.58-1.27)	1.12 (0.76-1.63)	.371

Model 1: adjusted for age. Model 2: adjusted for age, BMI, waist circumference, systolic and diastolic blood pressure, triglyceride, HDL cholesterol, hsCRP, smoking, alcohol use, and menopause status in women. Model 3: adjusted for the factors in model 2 as well as AST, ALT, and GGT.

Table 5
Odds ratios (95% CI) for IFG according to quartile of serum ferritin concentration in nondiabetic men and women

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend
Men					
Model 1	1.00	1.21 (1.04-1.41)	1.33 (1.14-1.55)	1.82 (1.56-2.13)	<.001
Model 2	1.00	1.14 (0.97-1.33)	1.17 (1.00-1.38)	1.40 (1.18-1.64)	.001
Model 3	1.00	1.12 (0.96-1.31)	1.14 (0.97-1.34)	1.31 (1.11-1.55)	.017
Women					
Model 1	1.00	1.10 (0.92-1.32)	1.34 (1.11-1.61)	1.68 (1.40-2.02)	<.001
Model 2	1.00	1.07 (0.88-1.29)	1.26 (1.04-1.53)	1.53 (1.25-1.87)	<.001
Model 3	1.00	1.06 (0.88-1.28)	1.24 (1.02-1.50)	1.45 (1.19-1.78)	.001

Model 1: adjusted for age. Model 2: adjusted for age, BMI, waist circumference, systolic and diastolic blood pressure, triglyceride, HDL cholesterol, hsCRP, smoking, alcohol use, and menopause status in women. Model 3: adjusted for the factors in model 2 as well as AST, ALT, and GGT.

resistance and glucose regulation. Specifically, increased serum concentrations of ferritin were associated with insulin resistance, metabolic syndrome, IFG, and type 2 DM in men, but only with IFG in women.

Previous reports have suggested that ferritin plays different roles in insulin resistance in the two sexes. Our data show that, in men, increased serum levels of ferritin were associated with insulin resistance, and the ORs for type 2 DM, IFG, and metabolic syndrome were higher. However, an increased OR was noted only for IFG in women. These results suggest that iron overload is associated with insulin resistance in men, but not in women. Our findings in men correspond well with previous studies, which found that elevated serum ferritin concentrations were associated with higher ORs for type 2 DM in Finnish men [12] and US adults [13]. In contrast, studies of the Chinese population have shown that serum ferritin concentrations are associated with insulin resistance [16] and risk of diabetes [19] in women, but not in men. The reasons for these discrepancies remain unclear. The proportion of postmenopausal women was greater in our study (52%) than in the Chinese report [16] (37%). However, our results were not notably different when results from pre- and postmenopausal women were analyzed separately (online supplementary Tables S1-S3). Another possibility may be that fewer male subjects were included in the Chinese study, which may have reduced the statistical power of analysis. A study by Shi and associates [19] may also have had limited statistical power because of the small number of diabetic subjects, and the cited authors did not adjust for potential confounding effects of inflammation or infection on serum ferritin concentrations. Chinese studies that combined data from men and women after adjusting for sex reported that an elevated circulating ferritin concentration was associated with a higher risk of type 2 DM [20,23]. Genetic and lifestyle factors, including dietary habits in different populations and regions, may influence the relationship between ferritin concentration and insulin resistance.

Consistent with previous studies, we found that mean serum ferritin concentrations were markedly lower in women than in men. This is likely attributable to menstrual iron loss in women [24]. Reduced ferritin concentrations may also contribute to the lower prevalence of type 2 DM or IFG in women compared with men and may also explain why no relationship between ferritin and insulin resistance or diabetes was observed in women in this study. The mean serum ferritin concentration in our study subjects was lower than that in a study performed on Taiwanese subjects (167 vs 224 ng/mL in men; 65 vs 108 ng/mL in women) [16]. In contrast, the mean serum ferritin concentration in our study was somewhat higher than that observed in men (132 ng/mL) but similar to that observed in women (71 ng/mL) in eastern China [19]. Dietary iron

Table 6
Odds ratios (95% CI) for metabolic syndrome according to quartile of serum ferritin concentration in subjects with NFG

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend
Men					
Model 1	1.00	1.57 (1.08-2.27)	1.72 (1.19-2.49)	2.85 (1.99-4.07)	<.001
Model 2	1.00	1.39 (0.88-2.21)	1.54 (0.96-2.46)	1.67 (1.05-2.66)	.010
Model 3	1.00	1.27 (0.85-1.89)	1.39 (0.94-2.07)	1.58 (1.06-2.37)	.024
Women					
Model 1	1.00	1.01 (0.69-1.48)	1.09 (0.74-1.61)	1.21 (0.82-1.79)	.726
Model 2	1.00	0.98 (0.67-1.44)	1.06 (0.72-1.56)	1.10 (0.74-1.64)	.676
Model 3	1.00	0.97 (0.66-1.44)	1.03 (0.69-1.53)	1.07 (0.71-1.63)	.742

Model 1: adjusted for age. Model 2: adjusted for age, BMI, hsCRP, smoking, alcohol use, and menopause status in women. Model 3: adjusted for the factors in model 2 as well as AST, ALT, and GGT.

intake and genetic factors may account for differences in serum ferritin concentrations.

If serum ferritin is causally related to glucose metabolism and insulin sensitivity, it is unclear why highest serum ferritin concentrations increase the OR of having IFG, but not diabetes, in women. One possible explanation is that mean serum ferritin concentration was markedly lower in women than in men, so it might not be enough to lead to development of diabetes. Another reason could be that development of diabetes is influenced by many other factors, in addition to insulin resistance associated with high serum ferritin. We also could not exclude the possibility that the relatively small number of type 2 DM subjects in women may have limited the statistical power in logistic regression analysis.

The exact mechanism by which elevated ferritin promotes the development of insulin resistance or type 2 DM is unknown. Elevated serum ferritin concentration may reflect systemic inflammation as well as elevated iron stores [25]. Inflammation is thought to be involved in the pathophysiologic mechanisms underlying insulin resistance and diabetes [26]. However, we excluded subjects with possible inflammation by examining historical and laboratory data; and the association between elevated serum ferritin and insulin resistance or type 2 DM persisted after further adjustment for hsCRP level. This is consistent with a report by Sun and colleagues [20], who found that the associations between elevated circulating ferritin concentration and the risk of type 2 DM and metabolic syndrome remained significant after robust adjustment for inflammatory markers, such as CRP, interleukin-6, and tumor necrosis factor–α receptor 2. It may be argued that elevated serum ferritin concentration is secondary to hyperglycemia or type 2 DM. However, ferritin concentration is already significantly increased in subjects with IFG/impaired glucose tolerance or in normal glucose–tolerant first-degree relatives of type 2 DM patients when compared with healthy control subjects, implying that hyperferritinemia occurs before elevation of plasma glucose concentration [17,27]. The IFG subjects in our study also had significantly increased serum ferritin concentrations, consistent with previous studies. It should be noted, however, that we cannot exclude the possibility that the elevation is secondary to impaired insulin sensitivity or glucose metabolism because early impairment could elevate serum ferritin concentration before the development of IFG/impaired glucose tolerance or diabetes. It has been suggested that abnormalities in ferritin metabolism might be a primary cause of type 2 DM [28,29]. In addition, decreased iron stores resulting from blood donation or phlebotomy have been associated with increased insulin sensitivity [30-32], supporting the notion that stored iron negatively impacts insulin action even in people not associated with classic pathologic conditions of iron overload, such as hemochromatosis or hemosiderosis. Some investigators have suggested a link between serum ferritin, insulin resistance, and nonalcoholic fatty liver disease [33,34]; and the association between serum ferritin and metabolic syndrome is mediated by undiagnosed nonalcoholic fatty liver disease [35]. Prospective studies are needed to confirm whether elevated serum ferritin predicts insulin resistance and its associated conditions, or is merely a secondary marker of metabolic abnormalities.

Our study had several limitations. First, it was cross-sectional in design; and the possibility of reverse causation, that is, that insulin resistance or type 2 DM causes increase of serum ferritin concentration, cannot be excluded completely. Second, the data were not collected for the purpose of research; and therefore, there may be more error in the data collection process than prospectively planned studies, particularly in measurements of blood pressure, waist circumference, BMI, etc. Third, we could get only limited semiquantitative information about smoking, alcohol consumption, and physical exercise. In addition, aspirin use data were not available. Therefore, we were not able to adjust for all relevant confounding variables; and the residual confounding could have affected our results. Another limitation is that the standard measurement of insulin resistance (ie, the euglycemic clamp method) was not used in our study. However, HOMA-IR has been widely used as a reasonable surrogate measure in epidemiologic studies.

In conclusion, an increased serum concentration of ferritin was independently associated with type 2 DM, IFG, and metabolic syndrome in men, but only with IFG in women. Further studies are needed to investigate the pathophysiologic mechanisms by which increased serum ferritin concentrations are associated with metabolic disorders in men and women.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2010.03.007.

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