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Association of serum ferritin with metabolic syndrome and diabetes mellitus in the South Korean general population according to the Korean National Health and Nutrition Examination Survey 2008

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ABSTRACT

We examined the association of serum ferritin levels with metabolic syndrome (MS) and diabetes mellitus in a representative sample of the adult South Korean population using data from the 2008 Korean National Health and Nutrition Examination Survey. We conducted a cross-sectional study of 6311 adults older than 20 years who participated in the 2008 Korean National Health and Nutrition Examination Survey. *Metabolic syndrome* was defined as the presence of at least 3 of the following: elevated blood pressure, low high-density lipoprotein cholesterol, elevated serum triglycerides, elevated plasma glucose, and abdominal obesity. *Diabetes mellitus* was defined as fasting glucose of at least 126 mg/dL. Insulin resistance was determined using the homeostasis model assessment estimate of insulin resistance. In a representative sample of the adult Korean population, MS was more prevalent in the highest quartile compared with the lowest quartile of serum ferritin concentrations in women following adjustments for age, education, smoking, alcohol intake, body mass index, aspartate aminotransferase, and alanine aminotransferase. Diabetes mellitus was more prevalent in the highest quartile compared with the lowest quartile of serum ferritin concentrations in premenopausal women and men. The geometric means of fasting insulin and insulin resistance determined using the homeostasis model assessment of insulin resistance in the fourth serum ferritin quartiles of postmenopausal women and men were significantly higher compared with those in the first quartile of the respective groups. The present study demonstrates that elevated serum ferritin concentrations are associated with an increased risk of MS and diabetes mellitus in a representative sample of the adult South Korean population.

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1. Introduction

Following socioeconomic development and changes in nutrition between the late 1980s and 2005, the prevalence of diabetes mellitus (DM) in Korea increased from 3% to 7.3%, whereas the prevalence of metabolic syndrome (MS) was as high as 24.1% in 2005 [1].

Ferritin, a ubiquitous intracellular protein that is the key to the regulation of iron homeostasis, is a widely available clinical biomarker for the diagnosis of iron deficiency. However, increasing evidence indicates that moderately elevated body iron stores may be associated with adverse health outcomes. Elevated serum ferritin levels have been demonstrated to independently predict type 2 DM in prospective studies of healthy men and women [2,3]. In cross-sectional studies, elevated ferritin levels have been associated with hypertension [4], dyslipidemia [5-8], elevated fasting insulin and blood glucose levels [9-13], and central adiposity [14,15]. The association between elevated iron stores and MS, however, has been less well explored; and previous studies investigating this association have demonstrated conflicting results [16-19]. These discrepancies may be due to differences in the age distribution, sex, menopausal status, and ethnicity of the study participants. Therefore, a comprehensive study of a representative sample of the adult general population is required.

Here, we conducted a cross-sectional study of a representative sample of the adult South Korean population using data from the 2008 Korean National Health and Nutrition Examination Survey (KNHANES) [20] to test whether MS and DM are more common in those individuals with elevated serum ferritin levels.

2. Methods

2.1. Study design and data collection

This study was performed using data from KNHANES 2008, the second year of the ongoing KNHANES IV 2007-2009 survey. KNHANES IV was conducted for 3 years (2007-2009) using a rolling sampling design that involved a complex, stratified, multistage probability-cluster survey of a representative sample of the noninstitutionalized civilian population who were not in prisons, jails, mental institutions, hospitals, schools, etc, as nonmilitary people in South Korea.

The survey was performed by the Korean Ministry of Health and Welfare and possessed 3 main components: a health interview survey, a health examination survey, and a nutrition survey. The target population of the survey was all noninstitutionalized civilian Korean individuals 1 year or older. The survey used stratified multistage probability-sampling units based on geographical area, sex, and age, which were determined based on the household registries of the 2005 National Census Registry, the most recent 5-year national census in Korea. The survey sample pool ultimately consisted of 264 186 primary sampling units, each consisting of approximately 60 households.

For the KNHANES 2008, 200 sampling units were randomly selected from the 264 186 primary sampling units encompassing the target population in Korea, with 20 to 23 households selected from each primary sampling unit to yield 4600 households. The health interview and health examination surveys in the KNHANES 2008 were conducted by specially trained interviewers during 2008 at specially designed and equipped mobile centers at specific locations throughout the country, and at the households of the participants. These surveys were completed by 9308 participants (74.3% of the total target population of 12 528). Eighty-two percent (8641) of the total eligible target population of 10 539, who were selected from those households completing the health interview and health examination, participated in the nutrition survey. The interviewer was not provided with any prior information regarding the specific participants before performing the interview, and all participants provided written consent to participate in the study.

The present analysis was restricted to participants at least 20 years of age who completed the health examination survey (n = 7108). We excluded individuals who were pregnant, had received treatment of anemia within the last 3 months, had liver cirrhosis or chronic liver disease, or had chronic renal disease. Those participants whose serum ferritin levels were exceptionally high (>500 μg/L) or whose serum liver enzyme (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) activities were greater than 2 times the screening criteria (AST = 80 IU and ALT = 70 IU) were excluded from the study. Thus, the final sample consisted of 6311 participants.

Information regarding the age, education, smoking history, alcohol intake, and use of antihypertensive and diabetes medications was collected during the health interview. *Menopausal status* was defined as self-reported cessation of menstruation for more than 1 year or hysterectomy.

Height and weight measurements were performed with the participants wearing light clothing and their shoes removed. The body mass index (BMI) of the participants was calculated as the weight in kilograms divided by the square of the height in meters. The education level was categorized into 3 groups: below high school, high school, and college or higher education. Smoking status was divided into 3 categories: current smoker, past smoker, and nonsmoker. Alcohol consumption was assessed by asking the participants about their drinking behavior during the month before the interview. The participants were asked about their average frequency (days per month) of alcoholic beverage consumption and average amount (in milliliters) of alcoholic beverages consumed on any single occasion. The responses were converted to the amount of pure alcohol (in grams) consumed per day. Alcohol consumption status was categorized into 4 groups according to average daily alcohol consumption: nondrinker, light drinker (1-15 g), moderate drinker (16-30 g), and heavy drinker (>30 g).

Blood pressure was measured with subjects in the sitting position following a 5-minute rest period. Blood pressure was measured on 3 occasions with a mercury sphygmomanometer on the right arm and averaged for a final blood pressure reading. Waist circumference was measured midway between the costal margin and iliac crest at the end of a normal expiration.

Blood samples were obtained in the morning following an overnight fast. The serum concentrations of glucose, high-

density lipoprotein (HDL) cholesterol, and triglycerides were measured using a Hitachi automatic analyzer 7600 (Tokyo, Japan). Serum ferritin and insulin were measured by immunoradiometric assays using a 1470 Wizard gamma-counter (Perkin-Elmer, Turku, Finland). All clinical analyses were performed by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare.

In accordance with the 2005 revised National Cholesterol Education Program Adult Treatment Panel III criteria [21] and the Korean Society for the Study of Obesity criteria for waist circumference [22], MS was defined as the presence of 3 or more of the following: (1) elevated blood pressure (average systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg) or current blood pressure medication use, (2) low HDL cholesterol (<40 mg/dL in men and 50 mg/dL in women), (3) elevated serum triglycerides (≥150 mg/dL) or current antidyslipidemia medication use, (4) elevated fasting glucose levels (≥100 mg/dL) or current antidiabetic medication use, and (5) abdominal obesity (waist circumference ≥90 cm in men and ≥85 cm in women).

Diabetes mellitus was defined as a fasting glucose of at least 126 mg/dL or current use of antidiabetic medications. Insulin resistance was determined using the homeostasis model assessment estimate of insulin resistance (HOMA-IR = fasting insulin [in micro–international units per milliliter] × fasting glucose [millimoles per liter]/22.5) and fasting insulin levels [23].

2.2. Statistical analyses

Statistical analyses were performed using the SAS (Version 9.22; SAS Institute, Cary, NC) and SUDAAN (Release 10.0; Research Triangle Institute, Research Triangle Park, NC) software packages, which incorporate sample weights and adjust the analyses for the complex sample design of the survey. The survey sample weights, which were calculated taking into consideration the sampling rate, response rate, and age/sex proportion of the reference population (2005 National Census Registry), were used in all analyses to produce estimates representative of the noninstitutionalized civilian Korean population considering a complex, stratified, multistage probability-sampling design.

All analyses were performed separately for men, premenopausal women, and postmenopausal women and included the calculation of quartiles for the serum ferritin concentration. The prevalence and 95% confidence intervals (CIs) for MS and DM were calculated using cross-tabulation.

The mean values of various continuous variables were compared using Student *t* test. Differences in the proportion of participants who had MS were analyzed using the χ^2 test. The adjusted odds ratios (ORs) (95% CIs) for the prevalence of MS and its components and of DM were calculated for quartiles of serum ferritin using logistic regression. The covariates for the adjusted OR calculation were age, educational level, smoking, alcohol intake, BMI, AST, and ALT.

The geometric mean (GM) (95% CI) values of estimated insulin resistance by sex and menopausal-specific quartiles of serum ferritin were calculated. Tests for trends across the quartiles in the insulin resistance analysis were determined by a regression model using Satterthwaite-adjusted χ^2 statistics. The significance level was set at .05.

3. Results

When the mean levels of serum ferritin were analyzed, we observed significantly lower values in women (46.02 μg/L) compared with men (122.30 μg/L). Furthermore, premenopausal women showed a significantly lower mean level of serum ferritin compared with postmenopausal women. The prevalence of MS was 16.8% in women and 16.3% in men and was not significantly different; however, a significant difference in the prevalence of MS between premenopausal (9.5%) and postmenopausal women (31.5%) was evident (Table 1).

In all 3 groups, the highest prevalence of MS was observed in the highest quartile of serum ferritin concentration (Table 2). However, the lowest prevalence of MS was observed in the second or third quartile of serum ferritin concentration. The

Table 1 – General and clinical characteristics of study participants

	Women			Men		
	Premenopausal	Postmenopausal	*P* value	Total		*P* value
	n = 2120	n = 1507		n = 3627	n = 2684	
Age (y)	36.93 ± 0.33	62.57 ± 0.37	<.01	45.39 ± 0.43	43.32 ± 0.45	<.01
Serum ferritin (μg/L)	33.92 ± 1.14	70.58 ± 3.20	<.01	46.02 ± 1.43	122.30 ± 2.92	<.01
MS (%)	9.52	31.50	<.01	16.79	16.29	.61
Waist circumferences (cm)	76.08 ± 0.32	82.39 ± 0.36	<.01	78.16 ± 0.29	84.12 ± 0.24	<.01
Systolic BP (mm Hg)	106.70 ± 0.42	121.90 ± 0.57	<.01	111.70 ± 0.42	116.70 ± 0.39	<.01
Diastolic BP (mm Hg)	70.67 ± 0.33	75.56 ± 0.36	<.01	72.29 ± 0.29	77.69 ± 0.29	<.01
Serum triglyceride (mg/dL)	98.66 ± 2.14	138.50 ± 3.01	<.01	111.80 ± 2.06	158.20 ± 2.83	<.01
Serum HDL (mg/dL)	55.88 ± 0.44	51.31 ± 0.41	<.01	54.37 ± 0.37	48.54 ± 0.31	<.01
Serum glucose (mg/dL)	92.90 ± 0.50	103.10 ± 0.97	<.01	96.28 ± 0.50	98.24 ± 0.48	<.01
BMI (kg/m^2)	22.65 ± 0.09	24.01 ± 0.10	<.01	23.10 ± 0.08	24.00 ± 0.07	<.01
Serum insulin (μIU/L)	9.92 ± 0.23	10.21 ± 0.22	.29	10.02 ± 0.19	9.75 ± 0.14	.18
HOMA-IR	2.30 ± 0.05	2.73 ± 0.08	<.01	2.44 ± 0.05	2.41 ± 0.04	.62

Data are means ± SEs. The mean values of various continuous variables were compared using Student *t* test. Differences in the proportion of participants who had MS were analyzed using χ^2 test. BP indicates blood pressure.

Table 2 – Prevalence (95% CI) of the MS and its components by sex and menopausal-specific quartiles of serum ferritin

Premenopausal women (n = 2120)	Quartile of serum ferritin								Test for trend P value
	1st Q (≤12)		2nd Q (13-26)		3rd Q (27-45)		4th Q (>46)		
Median ferritin in quartile (μg/L)	6.93		18.72		34.08		63.26		
MS	7.07	(4.60-9.54)	9.15	(6.39-11.91)	5.54	(3.34-7.74)	16.26	(12.92-19.59)	<.001
Waist circumference ≥85 cm	18.83	(14.83-22.82)	14.97	(11.59-18.34)	12.66	(9.43-15.89)	22.93	(18.26-27.59)	.230
Serum triglyceride ≥150 mg/dL[c]	10.10	(7.199-13.00)	13.45	(10.58-16.31)	10.61	(7.728-13.49)	21.21	(17.74-24.67)	<.001
Serum HDL ≤50 mg/dL	31.72	(27.11-36.32)	30.29	(26.07-34.50)	28.45	(23.94-32.95)	40.67	(35.80-45.53)	.011
Blood pressure ≥130/85 mm Hg[a]	10.52	(7.78-13.32)	6.20	(3.97-8.43)	8.13	(5.33-10.93)	12.38	(9.26-15.49)	.256
Blood glucose ≥100 mg/dL[b]	14.09	(10.89-17.28)	13.50	(10.07-16.93)	13.69	(10.18-17.19)	19.22	(15.43-23.00)	.048
Postmenopausal women (n = 1507)	**Quartile of serum ferritin**								**Test for trend P value**
	1st Q (≤37)		2nd Q (38-54)		3rd Q (55-84)		4th Q (>85)		
Median ferritin in quartile (μg/L)	25.34		45.35		66.38		111.00		
MS	26.80	(21.97-31.62)	21.47	(16.23-26.70)	30.72	(25.33-36.11)	46.67	(40.82-52.51)	<.001
Waist circumference ≥85 cm	35.06	(28.84-41.27)	30.47	(24.70-36.23)	39.13	(33.36-44.89)	49.36	(43.00-55.71)	<.001
Serum triglyceride ≥150 mg/dL[c]	29.52	(23.99-35.04)	22.97	(17.61-28.32)	30.77	(25.30-36.23)	40.87	(34.93-46.80)	<.001
Serum HDL ≤50 mg/dL	45.17	(39.76-50.57)	43.69	(37.47-49.90)	47.08	(41.06-53.09)	57.87	(51.51-64.22)	.003
Blood pressure ≥130/85 mm Hg[a]	41.77	(36.67-46.86)	32.53	(25.80-39.25)	44.01	(38.63-49.38)	43.09	(37.24-48.93)	.267
Blood glucose ≥100 mg/dL[b]	32.93	(27.40-38.45)	36.66	(31.42-41.89)	38.28	(32.43-44.12)	47.53	(41.74-53.31)	<.001
Male (n = 2684)	**Quartile of serum ferritin**								**Test for trend P value**
	1st Q (≤62)		2nd Q (63-96)		3rd Q (97-149)		4th Q (>150)		
Median ferritin in quartile (μg/L)	43.94		78.58		116.99		196.67		
MS	12.96	(10.13-15.78)	10.94	(8.49-13.39)	17.58	(14.15-21.01)	23.73	(20.49-26.96)	<.001
Waist circumference ≥90 cm	18.04	(15.02-21.05)	20.33	(16.56-24.09)	27.14	(23.57-30.70)	34.56	(30.30-38.81)	<.001
Serum triglyceride ≥150 mg/dL[c]	31.49	(27.57-35.41)	29.28	(25.20-33.35)	38.00	(34.17-41.82)	52.03	(47.81-56.24)	<.001
Serum HDL ≤40 mg/dL	18.95	(15.32-22.57)	17.59	(14.23-20.94)	21.91	(18.20-25.61)	27.82	(23.88-31.75)	<.001
Blood pressure ≥130/85 mm Hg[a]	19.08	(15.57-22.58)	19.77	(15.92-23.61)	18.90	(15.66-22.13)	23.46	(20.12-26.79)	.147
Blood glucose ≥100 mg/dL[b]	23.29	(19.68-26.89)	26.34	(22.51-30.16)	28.95	(25.03-32.87)	39.72	(35.60-43.83)	<.001

Data are prevalence (95% CI). Tests for trends across the quartiles in MS and its components were determined by Cochran-Mantel-Haenszel χ^2 test. Q indicates quartile.

[a] Includes individuals who reported current use of antihypertensive medications regardless of blood pressure values.

[b] Includes individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values.

[c] Includes individuals who reported current use of oral antidyslipidemic medication regardless of lipid profile values.

prevalence of elevated serum triglycerides, decreased serum HDL, and increased blood glucose increased significantly with increasing serum ferritin in all 3 groups. Abdominal obesity increased significantly according to the increasing serum ferritin quartiles in postmenopausal women and men. In contrast, the prevalence of elevated blood pressure did not increase with increasing serum ferritin in all 3 groups.

The prevalence of DM was significantly higher in the fourth quartile of all 3 groups compared with the other 3 quartiles (Table 3).

Following adjustments for age, educational level, smoking, alcohol intake, BMI, AST, and ALT, MS was more prevalent in the highest compared with the lowest serum ferritin quartile among premenopausal women (OR, 2.06;

Table 3 – Prevalence (95% CI) of the diabetes by sex and menopausal-specific quartiles of serum ferritin

	Quartile of serum ferritin (μg/L)								Test for trend P value
	1st Q		2nd Q		3rd Q		4th Q		
Premenopausal women (n = 2120)[a]	1.95	(0.95-2.95)	3.10	(1.85-4.35)	5.46	(4.23-6.69)	7.34	(6.28-8.40)	<.001
Postmenopausal women (n = 1507)[a]	8.68	(5.01-12.34)	8.42	(4.97-11.86)	8.03	(4.85-11.20)	15.97	(10.91-21.02)	<.001
Men (n = 2684)[a]	1.42	(0.40-2.439)	0.94	(0.27-1.61)	1.69	(0.32-3.06)	5.27	(3.13-7.41)	<.001

Data are prevalence (95% CI). Tests for trends across the quartiles in diabetes were determined by Cochran-Mantel-Haenszel χ^2 test.

[a] Includes individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values. Serum ferritin level is as follows: for premenopausal women—1st Q (≤12), 2nd Q (13-26), 3rd Q (27-45), 4th Q (>46); for postmenopausal women—1st Q (≤37), 2nd Q (38-54), 3rd Q (55-84), 4th Q (>85); for men—1st Q (≤62), 2nd Q (63-96), 3rd Q (97-149), 4th Q (>150), respectively.

Table 4 – Adjusted [a] ORs (95% CI) of the MS and its components by sex and menopausal-specific quartiles of serum ferritin

Premenopausal women (n = 2120)	Quartile of serum ferritin				Test for trend P value
	1st Q (≤12)	2nd Q (13-26)	3rd Q (27-45)	4th Q (>46)	
Median ferritin in quartile (μg/L)	6.93	18.72	34.08	63.26	
MS	1.00	1.75 (0.97-3.14)	0.72 (0.36-1.45)	2.06 (1.12-3.78)	.002
Waist circumference ≥85 cm	1.00	0.70 (0.42-1.19)	0.44 (0.23-0.84)	1.20 (0.71-2.03)	.008
Serum triglyceride ≥150 mg/dL [d]	1.00	1.51 (0.96-2.40)	1.13 (0.70-1.83)	2.06 (1.31-3.23)	.003
Serum HDL ≤50 mg/dL	1.00	0.96 (0.72-1.29)	0.91 (0.66-1.26)	1.38 (1.02-1.86)	.037
Blood pressure ≥130/85 mm Hg [b]	1.00	0.55 (0.33-0.93)	0.66 (0.39-1.09)	0.58 (0.35-0.95)	.088
Blood glucose ≥100 mg/dL [c]	1.00	1.03 (0.68-1.55)	1.05 (0.67-1.62)	1.21 (0.81-1.80)	.823
Postmenopausal women (n = 1507)	**Quartile of serum ferritin**				**Test for trend P value**
	1st Q (≤37)	2nd Q (38-54)	3rd Q (55-84)	4th Q (>85)	
Median ferritin in quartile (μg/L)	25.34	45.35	66.38	111	
MS	1.00	0.67 (0.43-1.04)	1.09 (0.71-1.67)	1.82 (1.24-2.67)	.006
Waist circumference ≥85 cm	1.00	0.61 (0.34-1.09)	1.12 (0.66-1.90)	1.18 (0.68-2.04)	.069
Serum triglyceride ≥150 mg/dL [d]	1.00	0.67 (0.44-1.02)	0.97 (0.64-1.48)	1.34 (0.92-1.94)	.011
Serum HDL ≤50 mg/dL	1.00	0.96 (0.70-1.32)	1.06 (0.75-1.50)	1.55 (1.08-2.22)	.035
Blood pressure ≥130/85 mm Hg [b]	1.00	0.59 (0.39-0.91)	1.04 (0.74-1.47)	0.73 (0.52-1.04)	.013
Blood glucose ≥100 mg/dL [c]	1.00	1.12 (0.80-1.56)	1.14 (0.80-1.61)	1.50 (1.09-2.05)	.104
Men (n = 2684)	**Quartile of serum ferritin**				**Test for trend P value**
	1st Q (≤62)	2nd Q (63-96)	3rd Q (97-149)	4th Q (>150)	
Median ferritin in quartile (μg/L)	43.94	78.58	116.99	196.67	
MS	1.00	0.73 (0.49-1.09)	0.98 (0.65-1.45)	1.24 (0.82-1.88)	.064
Waist circumference ≥90 cm	1.00	0.98 (0.63-1.51)	0.97 (0.63-1.51)	1.47 (0.94-2.29)	.110
Serum triglyceride ≥150 mg/dL [d]	1.00	0.77 (0.58-1.02)	0.92 (0.73-1.16)	1.33 (0.98-1.81)	.001
Serum HDL ≤40 mg/dL	1.00	0.94 (0.67-1.31)	1.14 (0.81-1.60)	1.34 (0.95-1.89)	.131
Blood pressure ≥130/85 mm Hg [b]	1.00	1.11 (0.75-1.64)	0.84 (0.58-1.21)	1.08 (0.73-1.59)	.417
Blood glucose ≥100 mg/dL [c]	1.00	1.19 (0.90-1.59)	1.14 (0.83-1.55)	1.58 (1.18-2.10)	.019

Data are OR (95% CI). The adjusted ORs were calculated using logistic regression.

[a] Adjusted for age, educational level, smoking, alcohol intake, BMI, AST, and ALT. The referent group is adults whose ferritin level is within the first quartile.

[b] Includes individuals who reported current use of antihypertensive medications regardless of blood pressure values.

[c] Includes individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values.

[d] Includes individuals who reported current use of oral antidyslipidemic medication regardless of lipid profile values.

95% CI, 1.12-3.78) and postmenopausal women (1.82; 1.24-2.671) (Table 4). Serum ferritin was significantly associated with an increased level of serum triglycerides and a decrease in serum HDL in the fourth serum ferritin quartile in women; and the fourth quartile serum ferritin level was significantly associated with increased blood glucose in men, but not in women.

Following adjustment for the covariates, the fourth quartile serum ferritin levels were associated with DM in premenopausal women and men (Table 5).

Table 5 – Adjusted [a] ORs (95% CI) of the diabetes [b] by sex and menopausal-specific quartiles of serum ferritin

	Quartile of serum ferritin (μg/L)				Test for trend P value
	1st Q	2nd Q	3rd Q	4th Q	
Premenopausal women (n = 2120)	1.00	0.70 (0.23-2.15)	1.30 (0.38-4.48)	3.57 (1.38-9.21)	.008
Postmenopausal women (n = 1507)	1.00	1.02 (0.51-2.03)	0.88 (0.49-1.60)	1.54 (0.90-2.65)	.225
Men (n = 2684)	1.00	1.04 (0.61-1.77)	1.08 (0.63-1.84)	1.80 (1.09-2.97)	.031

Data are OR (95% CI). The adjusted ORs were calculated using logistic regression.

bIncludes individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values. Serum ferritin level is as follows: for premenopausal women—1st Q (≤12), 2nd Q (13-26), 3rd Q (27-45), 4th Q (>46); for postmenopausal women—1st Q (≤37), 2nd Q (38-54), 3rd Q (55-84), 4th Q (>85); for men—1st Q (≤62), 2nd Q (63-96), 3rd Q (97-149), 4th Q (>150), respectively.

[a] Adjusted for age, educational level, smoking, alcohol intake, BMI, AST, and ALT. The referent group is adults whose ferritin level is within the first quartile.

Table 6 – Geometric mean (95% CI) values of estimated insulin resistance by sex and menopausal-specific quartiles of serum ferritin

Premenopausal women (n = 2120)	Quartile of serum ferritin								Test for trend *P* value
	1st Q (≤12)[b]		2nd Q (13-26)		3rd Q (27-45)		4th Q (>46)		
Median ferritin in quartile (μg/L)	6.93		18.72		34.08		63.26		
	Crude	Adjusted[a]	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	
Fasting insulin (mIU/L)	9.21 (8.74-9.69)	10.30 (9.58-11.0)	8.91 (8.53-9.29)	9.68 (9.20-10.10)	8.91 (8.50-9.32)	10.00 (8.99-11.10)	8.98 (8.57-9.39)	9.68 (8.89-10.40)	.541
HOMA-IR	2.08 (1.96-2.19)	2.38 (2.20-2.56)	1.98 (1.89-2.07)	2.21 (2.09-2.33)	2.00 (1.90-2.10)	2.33 (2.04-2.62)	2.09 (1.98-2.20)	2.28 (2.09-2.47)	.602
Postmenopausal women (n = 1507)	**Quartile of serum ferritin**								**Test for trend *P* value**
	1st Q (≤37)[b]		2nd Q (38-54)		3rd Q (55-84)		4th Q (>85)		
Median ferritin in quartile	25.34		45.35		66.38		111.00		
	Crude	Adjusted[a]	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	
Fasting insulin (mIU/L)	8.57 (8.04-9.10)	9.80 (9.01-10.60)	8.49 (8.00-8.98)	9.65 (8.97-10.30)	9.11 (8.62-9.59)	10.20 (9.44-11.10)	10.20 (9.58-10.80)	11.00 (10.30-11.70)[*]	.042
HOMA-IR	2.07 (1.92-2.22)	2.53 (2.29-2.78)	2.05 (1.91-2.18)	2.55 (2.27-2.82)	2.24 (2.09-2.38)	2.72 (2.38-3.07)	2.67 (2.45-2.88)	3.08 (2.76-3.40)[*]	.032
Men (n = 2684)	**Quartile of serum ferritin**								**Test for trend *P* value**
	1st Q (≤ 62)[b]		2nd Q (63-96)		3rd Q (97-149)		4th Q (>150)		
Median ferritin in quartile	43.94		78.58		116.99		196.67		
	Crude	Adjusted[a]	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	
Fasting insulin (mIU/L)	8.42 (8.11-8.72)	9.41 (8.95-9.87)	8.52 (8.20-8.85)	9.51 (9.06-9.96)	8.82 (8.50-9.15)	9.66 (9.25-10.00)	9.50 (9.09-9.91)[*]	10.40 (9.79-11.00)[*]	.022
HOMA-IR	1.96 (1.88-2.03)	2.28 (2.13-2.43)	2.00 (1.92-2.08)	2.32 (2.18-2.47)	2.09 (2.00-2.17)	2.37 (2.24-2.50)	2.35 (2.24-2.47)[*]	2.65 (2.47-2.83)[*]	.003

Data are GMs (95% CI). Tests for trends across the quartiles in insulin resistance were determined by a regression model using Satterthwaite-adjusted χ^2 statistics.

[a] Adjusted for age, educational level, smoking, alcohol intake, BMI, AST, and ALT using analysis of covariance calculated by the Proc Regress function.

[b] The referent group is adults whose ferritin level is within the first quartile.

[*] $P < .01$.

The GM values (95% CI) of estimated insulin resistance were calculated by the quartile of serum ferritin (Table 6). The GMs of fasting insulin and HOMA-IR in the fourth quartile among postmenopausal women and men were significantly higher compared with those in the first quartile in the respective groups, but no differences were observed between fasting insulin and HOMA-IR among the 4 quartiles in premenopausal women.

4. Discussion

In this study, we observed a positive association between elevated iron stores (measured by serum ferritin levels) and the prevalence of MS and DM after adjustment for age, sex, educational level, smoking, alcohol intake, BMI, AST, and ALT.

Previous studies investigating this association have reported conflicting results among study participants who varied according to age, sex, and ethnic group distribution. One such study examining the association of DM with serum ferritin concentrations in 6 racial/ethnic groups found that the serum ferritin concentration was significantly higher in women with DM compared with women without DM in all racial/ethnic groups; however, the recorded serum ferritin concentrations were significantly lower in Asian men with DM than in those without [24]. The relationships among serum ferritin concentration, insulin resistance [25], and the risk of DM [26] have been reported in Chinese women, but not men. Other Chinese studies [27] found that the 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. Salonen et al [2] reported that elevated serum ferritin concentrations were associated with higher ORs for type 2 DM in Finnish men. However, Sun et al [19] showed a strong positive association between elevated serum ferritin concentrations and the risk of type 2 DM, impaired fasting glucose (IFG), and MS in both men and women aged 50 to 70 years. This discrepancy is most likely due to differences in age distribution, sex, menopausal status, and ethnicity of the study participants. Recently, Kim et al [18] reported that increased serum concentrations of ferritin were independently associated with type 2 DM, IFG, and MS in men, but only with IFG in women. Contrasting results in the Korean study [18] could be explained by discrepancies between the data collection methods; Kim et al [18] did not collect data for research purposes, meaning their participants (who visited the hospital for regular health checkups) did not represent the general Korean population. Thus, a selection bias in participants during the data collection process compared with the KNHANES study may account for the observed differences.

Most evidence linking iron metabolism to disorders of glucose metabolism have been performed in men, postmenopausal women, or women without information on their menopausal status [18,19,24-28]. In agreement with previous studies, the present study showed an association even in premenopausal women [17,29]. In a representative sample of the adult US population, Jehn et al [17] demonstrated that MS was more common in the highest compared with the lowest quartile of serum ferritin in pre- and postmenopausal women and in men. Taken together, these data suggest that elevated iron stores are persistently associated with the prevalence of MS and DM.

The HOMA-IR has been widely applied as a reasonable surrogate measure of insulin resistance in epidemiologic studies [23]. We observed a trend toward increasing insulin resistance (HOMA-IR and fasting insulin) with increasing serum ferritin levels in both postmenopausal women and men.

Regarding the directionality of the association between iron overload and altered glucose metabolism, several lines of evidence suggest that elevated iron stores contribute to the pathogenesis of altered glucose metabolic states. Results from prospective studies showed that iron overload preceded the development of abnormal glucose metabolism [2,3,30,31]. Decreased iron stores resulting from blood donation or phlebotomy have been associated with increased insulin sensitivity [28,32,33], supporting the notion that stored iron negatively impacts the activity of insulin. In addition, iron is a transition metal capable of causing oxidative tissue damage by catalyzing the formation of free radicals [34,35]. Free radicals can attack cell membrane lipids, proteins, and DNA, leading to cellular stress and subsequent tissue damage [35-37]. Merkel et al [38] showed that iron deposition in the muscle decreases glucose uptake due to such muscle damage. Data obtained from oral glucose tolerance tests in patients with hemochromatosis have suggested that hepatic iron overload results in impaired insulin extraction [39]. It has additionally been suggested that iron deposition in pancreatic β-cells impairs insulin secretion in more advanced states of iron overload [40]. Excess iron contributes to the initial phase of insulin resistance with increased insulin and subsequently to decreased insulin secretion [40].

However, it is possible that glucose metabolism also influences the body's iron stores. Insulin, through the activation of hypoxia-inducible factor–1α, may decrease the synthesis of hepcidin, the key hepatic enzyme regulating iron balance, thus increasing the efficiency of intestinal iron absorption [41-44]. Previous studies have suggested a link between serum ferritin, insulin resistance, and nonalcoholic fatty liver disease [45,46] and that the association between serum ferritin and MS is mediated by undiagnosed nonalcoholic fatty liver disease [47].

The present study has several important strengths. First, the study was performed using a representative sample of the general South Korean population. Second, rigorous quality controls were applied to the study procedures in KNHANES. Third, a significant association between elevated iron stores and MS/DM was identified in premenopausal women. The present findings show that moderately elevated iron levels as in the highest quartile of premenopausal women (the median ferritin level, 63.26 μg/L) were also associated with an increased prevalence of MS/DM. The associations may be of considerable public health importance considering that modest levels of iron storage may occur in otherwise healthy individuals probably attributable to changes in dietary habits along with iron supplementation [48-50].

Serum ferritin is a widely used marker of iron status in epidemiological studies [51] and accurately reflects differences in body iron stores by age and sex [52]. However, serum ferritin

is an acute-phase reactant and may be artificially elevated in the presence of inflammation [53]. We attempted to minimize this potential confounding factor by excluding those individuals with renal disease or liver disease in our sensitivity analyses; however, we cannot rule out residual confounding effects due to a failure to adjust for C-reactive protein. Similarly, we cannot rule out any residual confounding factor caused by other inflammatory conditions. In addition, ferritin was measured only once in KNHANES, despite the fact that repeated measurements on 2 different days are recommended. Alcohol consumption was assessed during the month before interview, which is probably not representative of participants' alcohol habits. We did not exclude participants with diseases potentially related to insulin resistance such as hemochromatosis [24,39], thalassemia [38], polycystic ovaries [54,55], and nonalcoholic fatty liver disease [45-47], or those on medications potentially related to insulin resistance including statins, β-blockers, and insulin sensitizers. A further limitation of this study is the cross-sectional design, which prevented us from making inferences regarding the directionality of the associations. Prospective studies are required to confirm whether elevated serum ferritin predicts insulin resistance and its associated conditions, or whether it is merely a secondary marker of metabolic abnormalities.

In conclusion, elevated circulating ferritin concentrations were associated with an increased risk of MS and DM in a representative sample of the general South Korean population. Prospective studies are needed to determine whether elevated iron stores precede the development of MS/DM and whether a threshold exists above which ferritin levels are associated with increased risk.

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