Serum Ferritin Is Associated With Visceral Fat Area and Subcutaneous Fat Area

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OBJECTIVE — Until now, few clinical studies have reported on the association between the indexes of body fat distribution and serum ferritin, an indicator of body iron stores and a putative risk factor for insulin resistance. We investigated the association between serum ferritin concentrations and the indexes of distribution of adipose tissues in the body, such as the visceral fat area (VFA), the subcutaneous fat area (SFA), and the hepatic fat content in Japanese subjects.

RESEARCH DESIGN AND METHODS — A total of 248 Japanese subjects (127 men and 121 postmenopausal women aged 57.8 ± 13.9 years, BMI 25.7 ± 4.6 kg/m^2; 140 subjects with type 2 diabetes and 108 nondiabetic subjects) were evaluated. Subjects with a history of alcohol intake were excluded from the study. We measured body height, body weight, and serum ferritin, as well as fasting plasma glucose and plasma insulin concentrations. We estimated insulin resistance by homeostasis model assessment. The fat distribution was evaluated by measuring the VFA and SFA by abdominal computed tomography at the umbilical level. To assess the hepatic fat content, the ratio of the computed tomography attenuation value of the liver to that of the spleen was calculated.

RESULTS — Serum ferritin was significantly correlated with the various indexes of adiposity examined, such as the hepatic fat content ($r = -0.280$, $P < 0.0001$), VFA ($r = 0.254$, $P < 0.0001$), SFA ($r = 0.231$, $P = 0.0005$), and homeostasis model assessment ($r = 0.286$, $P = 0.0008$).

CONCLUSIONS — This is the first report to directly demonstrate an association between serum ferritin and VFA and SFA. The results of this study suggest that the serum ferritin concentration may be a useful indicator of systemic fat content and degree of insulin resistance.

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Previous studies (1,2) have investigated the relationship between radiologically measured abdominal fat accumulation, hepatic fat content, and metabolic risk factors. It has been reported that both the visceral fat area (VFA) and the hepatic fat content are correlated with plasma triglyceride levels and glucose disposal (1,2). Elevation of serum ferritin concentrations has been suggested to be one of the components of the insulin resistance syndrome (3–5). In a population study of 1,013 eastern Finnish men (3), the serum ferritin concentrations were shown to be well correlated with the fasting plasma glucose and insulin concentrations. A subsequent study also revealed that circulating ferritin levels were related to the degree of insulin resistance (4). However, only a few studies have reported on the relationship between the serum ferritin concentrations and various indexes of adiposity. A study of Spanish subjects demonstrated no association between serum ferritin concentrations and the waist-to-hip ratio (4). On the other hand, a study of Norwegian men demonstrated independent associations between serum ferritin concentrations and the waist-to-thigh ratio and BMI (6). Gillum et al. also reported that the serum ferritin concentrations were correlated with the waist-to-hip ratio (7). It is well established by now that body circumference measures and skin fold measures representing body fat distribution and adiposity are associated with insulin sensitivity, non–insulin-dependent diabetes, and other cardiovascular risk factors constituting the insulin resistance syndrome (8). These reports prompted us to hypothesize that body fat distribution may be significantly associated with body iron stores as reflected by serum ferritin concentrations. Therefore, we investigated the association between serum ferritin concentrations and sex, age, various clinical parameters (HbA1c [A1C], plasma glucose, and insulin), and indexes of body fat distribution, namely the hepatic fat content, the visceral fat area (VFA), and the subcutaneous fat area (SFA).

RESEARCH DESIGN AND METHODS

— We evaluated the clinical indicators in patients who were admitted to the Yokohama City University Hospital between 2003 and 2005. The protocol was reviewed and approved by the institutional ethical review committee. Informed consent was obtained from all subjects before the examinations. The study was carried out in 248 subjects admitted to our hospital for evaluation of elevated transaminase levels, fatty liver, or stringent control of blood glucose levels. A total of 140 of these were diabetic patients, and 108 were nondiabetic patients. The study was restricted to men and postmenopausal women to eliminate the influence of pregnancy and female hormone replacement therapy and to reduce possible confounding by iron deficiency/

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Abbreviations: CT, computed tomography; HOMA-IR, homeostasis model assessment of insulin resistance; L/S ratio, ratio of the CT attenuation value of the liver to that of the spleen; SFA, subcutaneous fat area; VFA, visceral fat area.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

iron supplementation. The study was also restricted to persons >20 years of age to reduce the possible confounding effect of growth and development. A total of 248 Japanese (127 men and 121 postmenopausal women aged 57.8 ± 13.9 years, BMI 25.7 ± 4.6 kg/m^2, 140 with type 2 diabetes, and 108 without diabetes) subjects were evaluated. Persons with a history of alcohol intake of ≥20 g/day were excluded from the study. Serum ferritin is an acute-phase reactant and does not accurately reflect the body's iron stores in the presence of inflammation. We therefore measured the serum C-reactive protein in this study to exclude patients with obvious inflammation. The proportion of subjects with history of smoking was 26% in the diabetic group and 13% in the nondiabetic group.

Table 1 —*Clinical characteristics of all subjects*

	Diabetic	Nondiabetic
n	140	108
Age (years)	61.1 ± 10.2	54.1 ± 14.6*
Sex (male/female)	75/65	52/56
BMI (kg/m^2)	25.1 ± 0.4	26.1 ± 0.57
L/S ratio	1.090 ± 0.020	1.006 ± 0.028†
VFA (cm^2)	124 ± 6.23	117 ± 5.87
SFA (cm^2)	178 ± 8.58	192 ± 10.1
Ferritin (ng/ml)	167.3 ± 13.6	188.9 ± 18.2
Glucose (mg/dl)	148.5 ± 4.87	105.2 ± 1.43*
Insulin (μU/ml)	8.93 ± 0.745	9.34 ± 0.746
HOMA-IR	3.10 ± 0.225	2.10 ± 0.113†
A1C (%)	7.51 ± 0.122	5.09 ± 0.39*
C-reactive protein (mg/dl)	0.097 ± 0.009	0.101 ± 0.011
AST (IU/l)	27.4 ± 1.47	23.6 ± 2.41*
ALT (IU/l)	34.3 ± 2.41	51.9 ± 4.59*
Smoking (%)	26.4	12.6

Data are means ± SE. *$P < 0.01$ diabetic vs. nondiabetic; †$P < 0.05$. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Blood sampling and biochemical assay

Blood samples were obtained before breakfast on the 2nd day of hospitalization for measurements of the plasma glucose and insulin levels. The insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula: [fasting serum insulin (μU/ml) × fasting plasma glucose (mg/dl)/405]. However, the HOMA-IR and measurement of serum ferritin was performed in only 128 subjects for whom the fasting plasma glucose was <170 mg/dl because HOMA-IR has been reported to be a suitable method for evaluating the presence of insulin resistance in patients with type 2 diabetes only when the fasting glucose levels are <170 mg/dl (9). Ono et al. reported that the results of HOMA-IR were not significantly correlated with the insulin resistance in subjects with fasting glucose levels >200 mg/dl (9).

Determination of the visceral and subcutaneous fat areas

The abdominal fat distribution in the subjects was determined by computed tomography (CT) with the subjects in the supine position, in accordance with a previously described procedure (10). The SFA and intra-abdominal VFA were measured at the level of the umbilicus using a standardized method in terms of the CT number. In brief, a region of interest was defined in the subcutaneous fat layer by tracing its contour on each scan, and the attenuation range for fat tissue was measured in terms of the CT number (in Hounsfield units).

Assessment of hepatic fat content

The degree of liver steatosis was measured by CT. Previous studies have shown a strong correlation between the CT attenuation values of the liver and the extent of fatty infiltration as measured by biopsy (11,12). The ratio of the CT attenuation value of the liver to that of the spleen (L/S ratio) was used for quantitative estimation of the hepatic fat content, with an L/S ratio of <1 being considered to represent fatty liver (11).

Data analysis

All the data were expressed as means ± SD. The relationship between any two variables was analyzed by standard correlation analysis conducted using the StatView version 5.0 software (SAS, Cary, NC). ANOVA was applied for group comparisons, followed by Student's *t* test for confirmation of the statistical associations. The relationship between the L/S ratio, VFA, or SFA and other relevant covariates was examined by multiple regression analysis and determination of the standardized correlation coefficients. Sta-

Table 2 —*Clinical characteristics of the 64 diabetic patients with fasting plasma glucose levels <170 mg/dl and the same number of nondiabetic patients*

	Diabetic	Nondiabetic
n	64	64
Age (years)	59.8 ± 10.6	54.1 ± 10.8*
Sex (male/female)	35/32	31/30
BMI (kg/m^2)	24.8 ± 0.6	26.2 ± 0.77
L/S ratio	1.063 ± 0.034	1.039 ± 0.036
VFA (cm^2)	117 ± 11.7	114 ± 7.59
SFA (cm^2)	180 ± 12.9	180 ± 10.9
Ferritin (ng/ml)	167.1 ± 17.5	183.9 ± 24.6
Glucose (mg/dl)	129.2 ± 2.86	105.2 ± 1.43†
Insulin (μU/ml)	9.10 ± 0.861	9.34 ± 0.746
HOMA-IR	2.893 ± 0.233	2.100 ± 0.113†
A1C (%)	6.87 ± 0.128	5.09 ± 0.39†
C-reactive protein (mg/dl)	0.099 ± 0.014	0.103 ± 0.014
AST (IU/l)	30.5 ± 3.08	31.6 ± 2.37
ALT (IU/l)	37.4 ± 5.09	45.6 ± 5.40
Smoking (%)	20.7	12.8

Data are means ± SE. *$P < 0.05$; †$P < 0.01$ diabetic vs. nondiabetic.

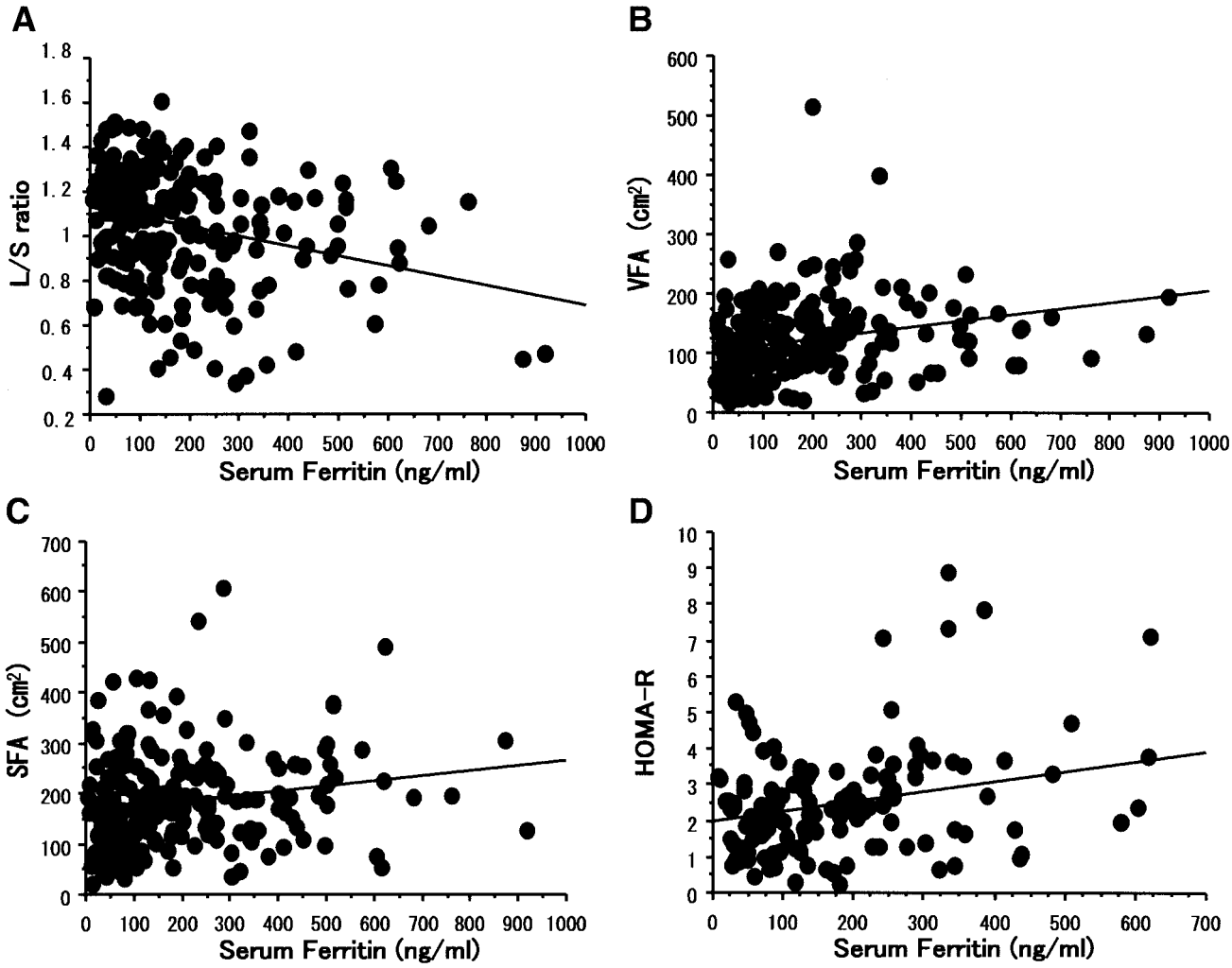

Figure 1—A: *Relationship between the serum ferritin concentration and the L/S ratio; there is a significant correlation* (r = −*0.280,* P < *0.0001).* B: *Relationship between the serum ferritin concentration and VFA; there is a significant correlation* (r = *0.254,* P < *0.0001).* C: *Relationship between the serum ferritin concentration and the SFA; there is a significant correlation* (r = *0.231,* P = *0.0005).* D: *Relationship between the serum ferritin concentration and the degree of insulin resistance as assessed by HOMA-IR; there is a significant correlation* (r = *0.286,* P = *0.0008). Analysis of these relationships was performed in 126 subjects with fasting plasma glucose levels <170 mg/dl.*

tistical significance was assumed when the *P* value was <0.05.

RESULTS

Relationship between the serum ferritin concentration and clinical parameters

The baseline characteristics of the 140 patients with type 2 diabetes and 108 nondiabetic patients are shown in Table 1. There were no significant differences in the serum ferritin concentrations, VFA, or SFA between the two groups (type 2 diabetic patients and nondiabetic patients). The baseline characteristics of the 64 diabetic patients for whom the fasting plasma glucose levels were <170 mg/dl and the same number of nondiabetic patients are shown in Table 2. The relationships between the serum ferritin concentrations and the other factors examined in this study are illustrated in Fig. 1. The serum ferritin concentration was inversely correlated with the L/S ratio ($r = -0.280$, $P < 0.0001$; Fig. 1*A*), that is, they were positively correlated with the degree of liver steatosis. The serum fer-

Table 3 —*Correlation* of the serum ferritin concentrations with theVFA and SFA in patients aged 20–79 years*

	Age (years)					
	≤29	30–39	40–49	50–59	60–69	70–79
n	9	23	30	54	75	57
VFA	—	—	0.344	0.214	0.308	0.299
SFA	—	0.256	0.220	—	0.243	0.271
VFA + SFA	—	0.178	0.332	—	0.315	0.323

*Pearson's correlation coefficients <0.10 not shown.

Table 4 —*Multiple regression analysis of the relationship between L/S ratio and other associated variables for the entire group*

Risk factors	Regression coefficient	SE	Standardized regression coefficient	*P*
Age (years)	0.012	0.001	0.646	<0.0001
Sex	0.073	0.035	0.151	0.0394
Ferritin (ng/ml)	−0.0001897	−0.0001129	−0.121	0.0944
A1C	0.47	0.009	0.308	<0.0001
Smoking	0.067	0.043	0.114	0.1172

The dependent variable is the L/S ratio. The independent variables are age, sex, serum ferritin, serum A1C, and smoking status. R^2 for entire model = 0.975.

ritin concentration was also significantly correlated with the VFA ($r = 0.254$, $P < 0.0001$; Fig. 1*B*) and SFA ($r = 0.231$, $P = 0.0005$; Fig. 1*C*). In the 64 nondiabetic patients and the 64 patients with type 2 diabetes for whom the fasting plasma glucose levels were <170 mg/dl, the serum ferritin concentration was significantly correlated with the insulin resistance as measured by HOMA-IR ($r = 0.286$, $P = 0.0008$; Fig. 1*D*).

Chronic metabolic and inflammatory diseases may confound the present assessment in diabetic patients. In this study, we excluded subjects with a serum C-reactive protein level of >0.5 mg/dl because serum ferritin is an acute-phase reactant and does not accurately reflect the body iron stores in the presence of inflammation. We also examined the relationship between the serum ferritin concentrations and other factors in the diabetic patients or nondiabetic subjects. The serum ferritin concentration was significantly correlated with the L/S ratio, VFA, SFA, and the degree of insulin resistance in both the diabetic and nondiabetic groups (data not shown). Although Gillum et al. found that the association between the waist-to-hip ratio and the serum ferritin concentration became weaker with increasing age (13), our study revealed no such weakening of the association between the serum ferritin concentrations and the VFA, SFA, and VFA + SFA with age (Table 3).

Multiple regression analysis

Multiple regression analysis was conducted to quantify the impact of the measured variables (age, sex, serum ferritin concentration, A1C, and smoking status) on the L/S ratio, VFA, and SFA. The results shown in Table 4 indicate that the age, sex, and serum A1C, but not the serum ferritin concentration, were significantly related to the L/S ratio in all of the study subjects. We then carried out multiple regression analysis separately in the diabetic group and the nondiabetic group. Interestingly, the serum ferritin concentration was found to be significantly correlated with the L/S ratio in the diabetic patients (Table 5), but not in the nondiabetic patients (Table 6). The results shown in Table 7 indicate that the age, sex, serum ferritin concentration, and serum A1C were also significantly correlated with the VFA. The results shown in Table 8 indicate that the sex, serum ferritin concentration, and serum A1C were also significantly correlated with the SFA. The results shown in Table 9 indicate that the serum ferritin and serum A1C were significantly correlated with the HOMA-IR. Smoking status was not an independent variable. Thus, after adjustment for these five variables, the serum ferritin concentration was still found to be correlated significantly with the VFA, SFA, and HOMA-IR, but not the L/S ratio.

CONCLUSIONS

— In this study, we investigated the association between the serum ferritin concentrations and the hepatic fat content, VFA, SFA, and degree of insulin resistance. We demonstrated that the serum ferritin concentration was significantly associated with the CT-estimated VFA and SFA (Fig. 1*B* and *C*). We were also able to reproduce the previously reported association between the serum ferritin concentration and the hepatic fat content and the degree of insulin resistance (4,14) (Fig. 1*A* and *D*, Table 4). We also independently analyzed the association between the serum ferritin concentrations and the indexes of distribution of adipose tissues in diabetic patients and nondiabetic subjects. Serum ferritin concentrations were significantly correlated with VFA, SFA, and HOMA-IR in both the diabetic patients and nondiabetic patients

Table 5 —*Multiple regression analysis of the relationship between L/S ratio and other associated variables for the diabetic group*

Risk factors	Regression coefficient	SE	Standardized regression coefficient	*P*
Age (years)	0.010	0.001	0.535	<0.0001
Sex	0.101	0.043	0.219	0.0196
Ferritin (ng/ml)	−0.0002740	−0.0001362	−0.188	0.0465
A1C	0.057	0.010	0.342	<0.0001
Smoking	0.047	0.047	0.092	0.3168

The dependent variable is the L/S ratio. The independent variables are age, sex, serum ferritin, serum A1C, and smoking status. R^2 for entire model = 0.954.

Table 6 —*Multiple regression analysis of the relationship between L/S ratio and other associated variables for the nondiabetic group*

Risk factors	Regression coefficient	SE	Standardized regression coefficient	*P*
Age (years)	0.008	0.002	0.437	0.0003
Sex	−0.021	0.062	−0.042	0.7309
Ferritin (ng/ml)	−0.0002384	−0.0001921	−0.141	0.2184
A1C	0.115	0.028	0.167	<0.0001
Smoking	0.114	0.084	0.152	0.1773

The dependent variable is the L/S ratio. The independent variables are age, sex, serum ferritin, serum A1C, and smoking status. R^2 for entire model = 0.949.

(data not shown). Interestingly, there was a significant relationship between serum ferritin concentrations and the L/S ratio in the diabetic patients, but not in the nondiabetic patients (Tables 5 and 6). A previous study on Spanish subjects assessed the associations between obesity and central or abdominal fat distribution and the serum ferritin concentrations (4); they did not find a significant relationship between the serum ferritin and measures of adiposity. Our results, however, were not consistent with these results. This discrepancy may be explained, at least in part, by the reported finding that the waist-to-hip ratio is greater in the Spanish population than in other Caucasian populations (15) and that the ratio is lower in the Japanese population than in western populations.

Gillum et al. reported that the serum ferritin concentration was associated with the waist-to-hip ratio (6). Increased waist-to-hip ratio may suggest an excess VFA in each subject. However, anthropometric measures such as the waist-to-hip ratio do not always distinguish visceral obesity from subcutaneous obesity. To investigate the relationship between the serum ferritin concentration, VFA, and SFA more directly, we elected to use CT in this study and confirmed the relationship between serum ferritin concentrations, VFA, and SFA. After adjustment for age, sex, and serum A1C, serum ferritin concentrations were still significantly correlated with VFA, SFA, and HOMA-IR (Tables 7–9). This is the first report to demonstrate a direct association between the serum ferritin concentrations and VFA and SFA.

Increased iron stores in the liver are postulated to induce liver-mediated insulin resistance, with a reduced ability of insulin to suppress hepatic glucose production (4). Serum ferritin levels have been reported previously to be associated with decreased insulin sensitivity and increased fasting plasma insulin and glucose levels (3,4). These abnormalities might lead to increased adiposity. Several studies have demonstrated correlations between serum ferritin concentrations and other components of the insulin resistance syndrome (3,4,16). It has been reported that the chelation of iron is highly resistant to oxidant-mediated injury (13) and is associated with reduced iron-induced lipid peroxidation (17). It is possible to consider that overexpression of ferritin plays a role as an iron cytoprotective agent by limiting the reactivity of intracellular iron with lipids at the site of their biosynthesis within adipocytes. Thus, ferritin overexpression probably represents adaptive adipocyte response to iron-induced oxidative stress, resulting in a positive association between the serum ferritin concentration and the amount of fat tissue in the body.

Although the hepatic fat content, VFA, and SFA can be evaluated by CT, measurement of the serum ferritin level is a nonradiological and inexpensive test. Therefore, the serum ferritin concentration may be a very useful and cost-effective marker of not only the fat distribution in various organs (hepatic fat content, VFA, and SFA), but also of insulin resistance. Estimation of the serum ferritin concentration may thus be more valuable than CT for evaluation of the fat distribution in subjects with the metabolic syndrome. That is, monitoring of the serum ferritin concentration would be more feasible than serial CT for the follow-up of subjects with the metabolic syndrome. We are now investigating whether changes in the serum ferritin levels after treatment would also be correlated with the changes in the hepatic fat content, VFA, and SFA, as evaluated by CT.

In conclusion, a direct correlation

Table 7 —*Multiple regression analysis of the relationship between the VFA and other associated variables for the entire group*

Risk factors	Regression coefficient	SE	Standardized regression coefficient	*P*
Age (years)	0.505	0.249	0.101	0.0444
Sex	31.505	9.232	0.240	0.0008
Ferritin (ng/ml)	0.121	0.030	0.282	<0.0001
A1C	8.670	2.397	0.214	0.0004
Smoking	−16.172	11.190	−0.102	0.1499

The dependent variable is the VFA. The independent variables are age, sex, serum ferritin, serum A1C, and smoking status. R^2 for entire model = 0.792.

Table 8 —*Multiple regression analysis of the relationship between the SFA and other associated variables for the entire group*

Risk factors	Regression coefficient	SE	Standardized regression coefficient	*P*
Age (years)	0.619	0.319	0.102	0.0538
Sex	−28.925	11.816	−0.181	0.0152
Ferritin (ng/ml)	0.195	0.038	0.373	<0.0001
A1C	17.822	3.068	0.360	<0.0001
Smoking	−27.733	14.322	−0.143	0.0542

The dependent variable is the SFA. The independent variables are age, sex, serum ferritin, serum A1C, and smoking status. R^2 for entire model = 0.816.

Table 9 —*Multiple regression analysis of the relationship between the degree of insulin resistance as assessed by HOMA-IR and other associated variables for the entire group*

Risk factors	Regression coefficient	SE	Standardized regression coefficient	*P*
Age (years)	0.005	0.006	0.005	0.9423
Sex	0.019	0.218	0.008	0.9311
Ferritin (ng/ml)	0.003	0.001	0.373	0.0001
A1C	0.281	0.064	0.303	<0.0001
Smoking	−0.258	0.278	−0.083	0.3547

The dependent variable is insulin resistance assessed by HOMA-IR. The independent variables are age, sex, serum ferritin, serum A1C, and smoking status. R^2 for entire model = 0.817.

was demonstrated between the serum ferritin concentrations and the VFA and SFA as estimated by CT. Therefore, measurement of the serum ferritin concentration may be a highly useful noninvasive and cost-effective test for the assessment of the fat distribution and degree of insulin resistance.

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