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Association among serum ferritin, alanine aminotransferase levels, and metabolic syndrome in Korean postmenopausal women

K.M. Choi, K.W. Lee, H.Y. Kim, J.A. Seo, S.G. Kim, N.H. Kim, D.S. Choi, S.H. Baik*

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Guro Hospital, Seoul 152-050, Korea

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Abstract

We examined the relationships among serum ferritin, alanine aminotransferase (ALT) levels, and cardiovascular risk factors of metabolic syndrome in Korean postmenopausal women. We conducted a cross-sectional study of 959 postmenopausal women without an apparent cause of liver disease. 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. Serum ferritin and ALT levels were found to be correlated ($r = 0.374$, $P < .001$) and to be associated with the components of metabolic syndrome. Subjects with metabolic syndrome showed significantly higher serum ferritin (74.7 ± 2.0 vs 59.6 ± 2.0 ng/mL, $P < .001$) and ALT levels (21.3 ± 1.6 vs 18.7 ± 1.5 IU/L, $P < .001$). Moreover, the greater the number of metabolic syndrome components present, the higher were the serum ferritin and ALT levels ($P < .001$). Multiple regression analysis showed that serum ALT levels are significantly associated with serum ferritin levels, waist circumference, fasting blood glucose, age, and white blood cell count (adjusted $R^2 = 0.147$). Elevated iron stores were positively associated with serum ALT levels and metabolic syndrome in Korean postmenopausal women.
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1. Introduction

There is an increasing evidence that serum ferritin might be one of the components of metabolic syndrome [1]. Tuomainen et al [2] reported that serum ferritin concentrations are correlated with fasting serum glucose and insulin concentrations. Furthermore, higher iron stores are associated with an increased risk of type 2 diabetes in healthy women independently of the known diabetes risk factors [3]. Cross-sectional studies have found that elevated ferritin levels are associated with central obesity [4], hypertension [5], and dyslipidemia [6]. In addition, a recent study showed that elevated iron stores are positively associated with the prevalence of metabolic syndrome in Caucasians [7].

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are highly prevalent diseases that accompany the epidemic of obesity and metabolic syndrome [8]. An elevated serum alanine aminotransferase (ALT) level is the most common liver abnormality in NAFLD and NASH [9]. Nonalcoholic fatty liver disease is a common explanation for the asymptomatic elevation of aminotransferase levels in up to 90% of cases [10]. Recently, Jeong et al [11] suggested that ALT, even below the abnormal cutoff points, is a sensitive marker of hepatic dysfunction associated with metabolic syndrome. Oxidative stress appears to be a key factor in the pathogenesis of NASH. The "2-hit" theory suggests that the first "hit" involves accumulation of excess fat in the hepatic parenchyma [12]. This step has been linked to insulin resistance associated with metabolic syndrome. The second hit involves oxidative stress resulting from an imbalance between prooxidants and antioxidants in the liver [13]. Elevated iron stores may interfere with hepatic insulin extraction leading to peripheral hyperinsulinemia and insulin resistance [14]. It is known that liver-mediated insulin resistance is an early consequence of iron-dependent damage [15]. Moreover, iron catalyzes the formation of hydroxyl radicals, which are powerful prooxidants that attack cellular membrane lipids, proteins, and nucleic acids [16].

The purpose of the present study was to explore the relationship between serum ferritin and ALT levels, and the cardiovascular risk factors of metabolic syndrome in Korean postmenopausal women.

* Corresponding author. Tel.: +82 2 818 6646; fax: +82 2 866 1643.
E-mail address: medica7@korea.ac.kr (S.H. Baik).

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2. Subjects and methods

This study was conducted in 4 regional senior welfare centers of the Seoul metropolitan government by Korea University medical personnel. The subjects were included from 4 urban districts (Guro, Yangcheon, Gwanak, and Gangseo) located in the southwest area of Seoul. In this study, we included postmenopausal women more than 60 years old who did not take hormone replacement therapy. A total of 994 postmenopausal Korean women participated in this study. Informed consent was provided by all subjects before participating in the study, which was approved by the ethical committee of our institutions. We excluded individuals who had received treatment of anemia during the 6 months before the study, those with known current hepatitis B or C, and those who had donated blood within 6 months. Subjects with acute or chronic hepatic disease (serum ALT or aspartate aminotransferase [AST] levels greater than twice the upper limit of the laboratory reference range), malignant disease, acute inflammatory disease, a current smoking habit, and moderate alcohol intake (more than 10 g a day) were all excluded by clinical history taking or blood tests. After applying the exclusion criteria and excluding incomplete data, the final analytic sample consisted of 959 individuals.

Medical history, familial history, and lifestyle data were obtained by interview. Blood pressure was measured on the right arm in a sitting position, using a standard mercury manometer after at least 5 minutes of rest. The average of 2 readings measured 5 minutes apart was recorded. Height, weight, and waist circumference were measured with the participants wearing light clothing and no shoes. The body mass index (BMI) was calculated as weight per height squared (kilograms per meter squared). All subjects were required to fast overnight (for a minimum of 10 hours), and compliance was ascertained by personal interview. After history taking, a 75-g standard oral glucose tolerance test was performed. Blood samples were drawn after an overnight fast and immediately centrifuged. Blood chemistry was measured at the laboratory of Korea University Guro Hospital, Seoul, Korea. Plasma glucose was measured using the glucose oxidase method. Liver and renal function tests and lipid profiles (serum total cholesterol, triglycerides, and high-density lipoprotein [HDL] cholesterol) were analyzed enzymatically using a chemistry analyzer (Hitachi 747, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was calculated using the formula of Friedewald et al [17]. Complete blood and reticulocyte counts were obtained using a Coulter counter (Coulter Electronics, Hialeah, Fla). Serum levels of iron and total iron binding capacity (TIBC) were determined using an Integra 700 (Roche Diagnostics, Basel, Switzerland), and ferritin using an IMx apparatus (Abbott Laboratories, Abbott Park, Ill). Anemia was defined as a hemoglobin level of less than 12 g/dL and iron deficiency anemia by serum ferritin level, using a cutoff level of 10 ng/mL in accordance with the World Health Organization (WHO) criteria [18]. A participant was defined to have metabolic syndrome if she fulfilled 3 or more of the criteria listed below, according to the National Cholesterol Education Program criteria [19]. The WHO Asia-Pacific

Table 1
Baseline characteristics of study subjects

	Without metabolic syndrome (n = 537)	With metabolic syndrome (n = 422)
Age (y)	72 ± 7	72 ± 7
BMI (kg/m^2)	24.2 ± 3.2	25.9 ± 3.0*
Waist circumference (cm)	84.3 ± 9.8	90.3 ± 8.2*
Systolic blood pressure (mm Hg)	135 ± 21	146 ± 18*
Diastolic blood pressure (mm Hg)	83 ± 10	86 ± 10*
Total cholesterol (mg/dL)	203.7 ± 33.4	202.3 ± 34.8
HDL cholesterol (mg/dL)	63.4 ± 12.6	50.5 ± 11.3*
Triglyceride (mg/dL)[a]	106.6 ± 1.4	175.7 ± 1.5*
LDL cholesterol (mg/dL)	117.6 ± 30.8	114.4 ± 30.4
Fasting blood glucose (mg/dL)	95.6 ± 13.3	107.9 ± 25.7*
Postload 2 h glucose (mg/dL)	129.1 ± 34.4	151.8 ± 61.0*
WBC ($\times 10^9$/L)	5.8 ± 1.4	6.3 ± 1.3*
Hemoglobin (g/dL)	12.9 ± 1.0	13.1 ± 1.1*
Hematocrit (%)	38.5 ± 2.8	39.1 ± 3.1*
Platelet ($\times 10^9$/L)	243 ± 53	254 ± 55*
Iron (μg/dL)	102.4 ± 31.0	100.7 ± 29.9
TIBC (μg/dL)	338.2 ± 42.3	339.0 ± 43.6
Ferritin (ng/mL)[a]	59.6 ± 2.0	74.7 ± 2.0*
AST (IU/L)[a]	21.8 ± 1.3	22.3 ± 1.3
ALT (IU/L)[a]	18.7 ± 1.5	21.3 ± 1.6*
Alkaline phosphatase (IU/L)	72.3 ± 19.5	76.7 ± 22.0*
Total protein (g/dL)	7.2 ± 0.4	7.3 ± 0.4*
Albumin (g/dL)	4.6 ± 0.2	4.6 ± 0.2

[a] Geometric mean and SD are given.
* $P < .05$.

Table 2
Age-adjusted correlations for serum ferritin, ALT, and baseline characteristics

	Ferritin	ALT
BMI	0.106	0.210**
Waist circumference	0.077	0.208**
Systolic blood pressure	0.135*	0.038
Diastolic blood pressure	0.095	0.070
Total cholesterol	−0.049	0.006
HDL cholesterol	−0.060	0.051
Triglyceride	0.052	0.098
LDL cholesterol	−0.046	−0.053
Fasting blood glucose	0.164**	0.260**
Postload 2 h glucose	0.187**	0.338**
WBC	0.021	0.135*
Hemoglobin	0.338**	0.274**
Platelet	−0.159*	−0.082
Iron	0.305**	0.280**
TIBC	−0.392**	0.006
Ferritin	–	0.374**
ALT	0.374**	–
AST	0.330**	0.725**
Alkaline phosphatase	−0.084	−0.034

Correlation coefficients were calculated using partial correlation analysis.
* $P < .05$.
** $P < .01$.

obesity criteria were used to define abdominal obesity in this study [20].

1. Abdominal obesity: waist circumference 80 cm or more.
2. Hypertriglyceridemia: 150 mg/dL (1.695 mmol/L) or greater.
3. Low HDL cholesterol: less than 50 mg/dL (1.295 mmol/L).
4. High blood pressure: 130/85 mm Hg or greater.
5. High fasting glucose: 110 mg/dL (6.1 mmol/L) or greater.

Data were expressed as means ± SD. (Variables not normally distributed are presented as geometric mean and SD.) Age-adjusted partial correlation analysis was performed to determine the relationship among serum ferritin, ALT, and the risk factors of cardiovascular disease. Mean values of serum ferritin and ALT according to the existence of each of metabolic syndrome components were compared using the Student *t* test. To compare mean values of serum ferritin and ALT with respect to an addition of metabolic syndrome components, 1-way analysis of variance and Duncan test were performed. Multiple linear regression models using ALT as a dependent variable was conducted to determine the relative contributions of each variable to the outcome variable. Age, waist circumference, HDL cholesterol, triglyceride, fasting blood glucose, systolic blood pressure, serum ferritin levels, white blood cell (WBC) counts, and serum albumin levels were used as independent variables. Significant independent variables were chosen using a stepwise variable selection method. *P* values were based on 2-sided tests, and the cutoff point for statistical significance was 0.05. Data were analyzed using SPSS for Windows (version 10.0; SPSS Inc, Chicago, Ill).

3. Results

The characteristics and the descriptive statistics of the subjects included in the study are summarized in Table 1.

Table 3
Levels of ferritin and liver function test according to presence/absence of each metabolic syndrome components

		n (%)	Ferritin (ng/mL)	ALT (IU/L)
High blood pressure	Yes	730 (76.1)	66.3 ± 2.0	20.1 ± 1.5
	No	229 (23.9)	64.0 ± 2.0	18.8 ± 1.6
Abdominal obesity	Yes	734 (76.5)	67.9 ± 2.0	20.7 ± 1.5**
	No	225 (23.5)	59.5 ± 2.1	17.2 ± 1.5
High triglyceride	Yes	371 (38.7)	73.4 ± 2.0**	21.1 ± 1.5**
	No	588 (61.3)	61.4 ± 2.0	19.0 ± 1.5
Low HDL cholesterol	Yes	284 (29.6)	70.7 ± 2.1*	19.7 ± 1.6
	No	675 (70.4)	63.8 ± 2.0	19.8 ± 1.5
High fasting glucose	Yes	168 (17.5)	86.1 ± 2.0**	24.5 ± 1.6**
	No	791 (82.5)	62.0 ± 2.0	18.9 ± 1.5
Metabolic syndrome	Yes	422 (44.0)	74.7 ± 2.0**	21.3 ± 1.6**
	No	537 (56.0)	59.6 ± 2.0	18.7 ± 1.5

Geometric means and SDs are given.
* $P < .05$.
** $P < .01$.

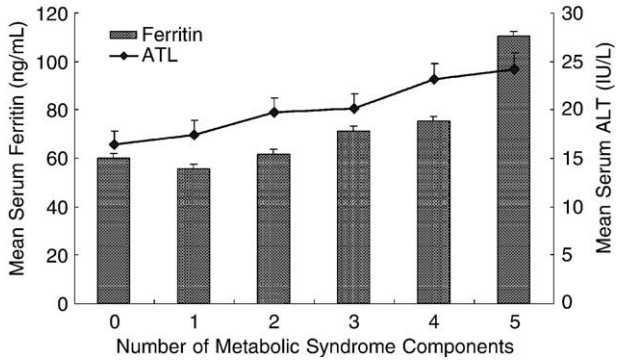

Fig. 1. Mean serum ferritin and ALT levels by the number of metabolic syndrome components. Geometric mean and SD are shown for ferritin (gray bar) and ALT (black line).

The mean age of our study subjects was 71.9 years (range, 61-89 years) and all were postmenopausal women. Age-adjusted partial correlation analysis showed that serum ferritin and ALT levels are associated with the variables of metabolic syndrome, especially with hyperglycemia and obesity (Table 2). Serum ferritin and ALT were found to be positively correlated ($r = 0.374$, $P < .001$).

The levels of serum ferritin and ALT according to the presence or the absence of each component of the metabolic syndrome are described in Table 3. In this study, the prevalence of metabolic syndrome was 44.0%, when WHO Asia-Pacific obesity criteria were used to define abdominal obesity. Among these components, subjects with a high triglyceride, low HDL cholesterol, and hyperglycemia showed significantly higher ferritin levels. Moreover, higher ALT levels were associated with abdominal obesity, high triglyceride, and hyperglycemia. Subjects with metabolic syndrome showed significantly higher serum ferritin (74.7 ± 2.0 vs 59.6 ± 2.0 ng/mL, $P < .001$) and ALT levels (21.3 ± 1.6 vs 18.7 ± 1.5 IU/L, $P < .001$).

Fig. 1 shows serum ferritin and ALT levels with respect to metabolic syndrome components. We found that the greater the number of metabolic syndrome components present, the higher were the serum ferritin ($P < .001$) and the ALT levels ($P < .001$).

Multiple regression analysis was performed using serum ALT level as a dependent variable. Serum ALT levels were significantly associated with serum ferritin levels, waist circumference, fasting blood glucose, age, and WBC count by multiple regression analysis (adjusted $R^2 = 0.147$).

4. Discussion

Serum ferritin is widely used as a marker of iron status in epidemiological studies [21] and accurately reflects differences in the levels of body iron stores by age and sex [22]. Iron overload may contribute to metabolic syndrome through a mechanism of insulin resistance related to both reduced extraction of insulin and impaired insulin secretion

[23]. Alternatively, hyperinsulinemia of metabolic syndrome may be directly responsible for the accumulation of iron in the liver, because insulin can stimulate cellular iron uptake by a mechanism of transferrin receptor externalization [24]. Another explanation of the relationship between iron stores and metabolic syndrome involves inflammation. Obesity in metabolic syndrome is associated with a chronic inflammatory response, characterized by abnormal cytokine production and increased acute phase reactants [25]. The activation of inflammatory cytokines increases the transcription of ferritin messenger RNA in macrophage, which may subsequently transfer ferritin to hepatocytes [26].

Recently, the prevalence of NAFLD is about 20%, and the prevalence of NASH is 2% to 3%, making NAFLD the most common form of liver disease in the United States [27]. Although the pathogenic mechanism of hepatic steatosis remains unclear, recent studies show that insulin resistance reduces the ability of insulin to suppress lipolysis [28] and increases the levels of free fatty acid and triglyceride in serum and hepatocytes [29]. Iron overload is also associated with liver injury, although the mechanisms involved are not clear. According to the 2-hit theory of steatohepatitis, the first hit includes obesity, hyperglycemia, and hyperlipidemia, whereas second hit involves reactive oxygen species and/or lipid peroxidation. It has been hypothesized that elevated iron stores may interfere with hepatic insulin extraction leading to insulin resistance [14], and that iron may catalyzed the formation of hydroxyl radicals [30]. The present study suggests that iron stores might affect serum ALT levels in metabolic syndrome.

In this study, including elderly Korean women, the prevalence of metabolic syndrome was relatively high even when compared with that of the United States [31]. The prevalence of metabolic syndrome of Korean women was 26.9% in previous study, which included younger subjects than our study [32]. The high prevalence rates of metabolic syndrome noted in elderly Korean women may herald an increased socioeconomic burden in the future.

Two other aspects of this study deserve to be mentioned. First, we included only postmenopausal women. Hyperferritinemia had a much lower prevalence in women before menopause because of iron losses by menstruation and pregnancy [33], and the cessation of regular bleeding contributes to higher ferritin levels and iron stores after menopause [33]. Moreover, the greater levels of stored iron in postmenopausal women may explain the higher incidence of heart disease in this group [34]. Second, alcoholism is a potential confounding factor in the present study, although most of our study subjects are nondrinkers (n = 907, 94.6%), and analysis performed to exclude drinkers showed similar results. Therefore, a drinking problem is not likely to be a confounder in our study.

However, this study has limitations, because it is a cross-sectional study without longitudinal follow-up. Therefore, we could not define a causal relationship between serum ferritin and ALT levels or the variables of metabolic syndrome.

In conclusion, we found that serum ferritin levels are related to serum ALT levels and to the components of metabolic syndrome in Korean postmenopausal woman. Further studies on the pathogenesis of metabolic syndrome and on the causal relationship between serum ferritin and elevated ALT levels in metabolic syndrome are warranted.

References

[1] Fernandez-Real JM, Ricart-Engel W, Arroyo E, et al. Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 1998; 21:62-8.

[2] Tuomainen TP, Nyyssonen K, Salonen R, et al. Body iron stores are associated with serum insulin and blood glucose concentrations. Population study in 1013 eastern Finnish men. Diabetes Care 1997; 20:426-8.

[3] Jiang R, Manson JE, Meigs JB, et al. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA 2004;291: 711-7.

[4] Gillum RF. Association of serum ferritin and indices of body fat distribution and obesity in Mexican American men—the Third National Health and Nutrition Examination Survey. Int J Obes Relat Metab Disord 2001;25:639-45.

[5] Piperno A, Trombini P, Gelosa M, et al. Increased serum ferritin is common in men with essential hypertension. J Hypertens 2002;20: 1513-8.

[6] Williams MJ, Poulton R, Williams S. Relationship of serum ferritin with cardiovascular risk factors and inflammation in young men and women. Atherosclerosis 2002;165:179-84.

[7] Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in US adults. Diabetes Care 2004;27:2422-8.

[8] Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003;37: 917-23.

[9] Falck-Ytter Y, Younossi ZM, Marchesini G, et al. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver Dis 2001;21:17-26.

[10] Daniel S, Ben-Menachem T, Vasudevan G, et al. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. Am J Gastroenterol 1999; 94:3010-4.

[11] Jeong SK, Nam HS, Rhee JA, et al. Metabolic syndrome and ALT: a community study in adult Koreans. Int J Obes Relat Metab Disord 2004;28:1033-8.

[12] Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology 1998;114:842-5.

[13] Mulhall BP, Ong JP, Younossi ZM. Non-alcoholic fatty liver disease: an overview. J Gastroenterol Hepatol 2002;17:1136-43.

[14] Ferrannini E. Insulin resistance, iron, and the liver. Lancet 2000; 355:2181-2.

[15] Niederau C, Berger M, Stremmel W, et al. Hyperinsulinaemia in non-cirrhotic haemochromatosis: impaired hepatic insulin degradation? Diabetologia 1984;26:441-4.

[16] Andrews NC. Disorders of iron metabolism. N Engl J Med 1999; 341:1986-95.

[17] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18: 499-502.

[18] DeMaeyer E, Adiels-Tegman M. The prevalence of anaemia in the world. World Health Stat Q 1985;38:302-16.

[19] NCEP. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486-97.

[20] World Health Organization. The Asian-pacific perspective: defining obesity and its treatment. IOTF; 2002.
[21] Witte DL, Crosby WH, Edwards CQ, et al. Practice guideline development task force of the College of American Pathologists. Hereditary hemochromatosis. Clin Chim Acta 1996;245:139-200.
[22] Zacharski LR, Ornstein DL, Woloshin S, et al. Association of age, sex, and race with body iron stores in adults: analysis of NHANES III data. Am Heart J 2000;140:98-104.
[23] Wilson JG, Lindquist JH, Grambow SC, et al. Potential role of increased iron stores in diabetes. Am J Med Sci 2003;325:332-9.
[24] Davis RJ, Corvera S, Czech MP. Insulin stimulates cellular iron uptake and causes the redistribution of intracellular transferrin receptors to the plasma membrane. J Biol Chem 1986;261:8708-11.
[25] Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest 2003;112:1785-8.
[26] Sibille JC, Kondo H, Aisen P. Interactions between isolated hepatocytes and Kupffer cells in iron metabolism: a possible role for ferritin as an iron carrier protein. Hepatology 1988;8:296-301.
[27] Younossi ZM, Diehl AM, Ong JP. Nonalcoholic fatty liver disease: an agenda for clinical research. Hepatology 2002;35:746-52.
[28] Walker M, Berrish TS, Stewart MW, et al. Metabolic heterogeneity in impaired glucose tolerance. Metabolism 1997;46:914-7.
[29] Lewis GF, Steiner G. Acute effects of insulin in the control of VLDL production in humans. Implications for the insulin-resistant state. Diabetes Care 1996;19:390-3.
[30] Wolff SP. Diabetes mellitus and free radicals. Free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. Br Med Bull 1993;49:642-52.
[31] Freiberg MS, Cabral HJ, Heeren TC, et al. Alcohol consumption and the prevalence of the metabolic syndrome in the US: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2954-9.
[32] Yoon YS, Oh SW, Baik HW, et al. Alcohol consumption and the metabolic syndrome in Korean adults: the 1998 Korean National Health and Nutrition Examination Survey. Am J Clin Nutr 2004;80:217-24.
[33] Milman N. Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy. Int J Hematol 1996; 63:103-35.
[34] Sullivan JL. Iron and the sex difference in heart disease risk. Lancet 1981;1:1293-4.