Serum ferritin and high sensitivity C-reactive protein are associated with metabolic syndrome in Japanese men and women

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ABSTRACT

Objective Ferritin is involved in the occurrence of oxidative stress and regulation of adiponectin, both of which can modulate metabolic syndrome (MetS). To investigate the association of ferritin with MetS in Japanese, a cross-sectional study was conducted involving 324 men and 340 women who underwent anti-aging health checks at Tokai University Tokyo Hospital.

Methods The MetS criteria of the Japanese Society of Internal Medicine was used and the levels of serum ferritin and high sensitivity C-reactive protein (hsCRP) were compared with or without MetS-related abnormalities (abdominal obesity, waist circumference ≥ 85 cm in men and ≥ 90 cm in women; hypertension, systolic BP ≥ 130 and/or diastolic BP ≥ 85 mmHg; hyperglycemia, fasting glucose ≥ 110 mg/dL; and dyslipidemia, triglycerides ≥ 150 mg/dL and/or HDL-C < 40 mg/dL).

Results Ferritin levels were significantly higher in the subjects with hyperglycemia and dyslipidemia in both men and women, and in those with abdominal obesity in women. HsCRP levels were significantly higher in the subjects with abdominal obesity in both sexes, and in those with hypertension in men. Serum ferritin increased in proportion to the number of MetS components and was significantly higher in MetS subjects than in non-MetS counterparts in both men and women, although these results were not obtained regarding hsCRP.

Conclusion Ferritin is not considered inferior compared with the well-known marker hsCRP with respect to the association with MetS. High serum ferritin concentrations could potentially be used as a biomarker for MetS as well as hsCRP. (HEP. 2016; 43: 511-517.)

Key words Ferritin, high sensitivity C-reactive protein (hsCRP), metabolic syndrome (MetS), anti-aging health checkup system

INTRODUCTION

Ferritin is a protein commonly used as a biomarker of body iron stores, and is also induced by inflammation. Increasing evidence has suggested that elevated serum ferritin levels are associated with increased risk of type 2 diabetes¹⁻⁵, hypertension⁶, dyslipidemia^{7,8} and central adiposity⁹. Not only single cardiovascular risk factors, but also a positive relationship between high ferritin levels and MetS has been demonstrated by a meta-analysis¹⁰. According to Abril-Ulloa *et al.*, the pooled odds ratio for MetS comparing the highest and the lowest category of ferritin levels was 1.73 (95% CI: 1.54, 1.95). However, this study did not include Japanese people and the criteria used for MetS diagnosis were mainly those of the National Cholesterol Education Program's Adults Treatment Panel III (NCEP ATP III)¹¹.

The mechanisms of the effect of elevated ferritin on metabolic

disorders are not fully understood. Chronic inflammation in adipose tissue plays an important part in the pathophysiology of metabolic syndrome (MetS)¹², and increased ferritin may reflect the inflammatory component of MetS. It was recently reported that iron excess decreases adiponectin levels¹³, causing insulin resistance and glucose intolerance, which can well modulate the MetS condition.

To investigate the association of ferritin with MetS in Japanese, we carried out a cross-sectional study involving 324 men and 340 women who underwent anti-aging health checks at Tokai University Tokyo Hospital. The MetS criteria of the Japanese Society of Internal Medicine were used and the levels of serum ferritin and high sensitivity C-reactive protein (hsCRP), which is well known as a useful marker for predicting cardiovascular events in MetS, were compared with or without MetS-related abnormalities.

SUBJECTS AND METHODS

1. Subjects

664 subjects (324 men and 340 women) aged between 26 and 86 years who first underwent anti-aging health checks at Tokai University Tokyo Hospital were enrolled. The surveillance period

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was from June 2006 to December 2013. All subjects gave written informed consent to the use of their health records for analysis. This study was approved by the Ethics Committee of Tokai University, and was conducted in accordance with the Declaration of Helsinki.

2. Measurements

Anthropometric measurements were performed and blood samples were obtained after overnight fasting. Of the measurements included in the anti-aging health check examinations¹⁵⁾, the following parameters were used for analysis: body mass index (BMI), waist circumference (WC), systolic and diastolic blood pressure (BP), fasting glucose, HDL-C, triglycerides, serum ferritin and hsCRP. Height and weight were measured in the standing position, and BMI was calculated as weight/height² (kg/m²). WC was assessed at the end of expiration by measuring the minimum circumference at the level of the umbilicus. BP was measured in the sitting position. The value for HDL-C and triglycerides were determined enzymatically. Serum level of ferritin was measured by the latex agglutination method. HsCRP concentration was measured by turbidimetric immunoassay.

3. Statistical analysis

Data is expressed as mean $\pm$ standard deviation (SD). SPSS Statistics (Version 22.0; SPSS Inc.) was used for the statistical analyses. Pearson's correlation coefficient was calculated as a measure of association between serum ferritin and the clinical parameters. The levels of serum ferritin and hsCRP were compared with or without MetS-related abnormalities (MetS components). MetS components were defined as follows: abdominal obesity, WC $\geq$ 85 cm in men and $\geq$ 90 cm in women; hypertension, systolic BP $\geq$ 130 and/or diastolic BP $\geq$ 85 mmHg; hyperglycemia, fasting glucose $\geq$ 110 mg/dL; and dyslipidemia, triglycerides $\geq$ 150 mg/dL and/or HDL-C $<$ 40 mg/dL. MetS was diagnosed if subjects had abdominal obesity plus at least two of the following MetS components: hypertension, hyperglycemia and dyslipidemia according to the definition by the Japanese Society of Internal Medicine¹⁴⁾. Student's *t*-test was used for comparisons between the two groups. Statistical significance for comparisons of ferritin and hsCRP values among the groups with different numbers of components was determined using analysis of variance (ANOVA) followed by Dunnett's multiple comparison

test by comparison with a zero-component group. A value of $p < 0.05$ was considered significant.

RESULTS

The clinical characteristics of the subjects are shown in **Table 1**. The study subjects consisted of 324 men and 340 women. The mean age was 62.9 ± 11.0 for men and 61.2 ± 11.0 for women. The average serum ferritin level was higher in men (179.9 ± 118.4 ng/mL) than in women (82.4 ± 63.8 ng/mL). The subjects were not obese on average (BMI 23.6 ± 4.3 kg/m² for men and 21.7 ± 4.6 kg/m² for women), and the mean BP, fasting glucose, HDL-C, triglycerides and hsCRP values were within the normal ranges.

The correlations between serum ferritin and MetS-related parameters are shown in **Table 2**. Serum ferritin was significantly positively correlated with TG and hsCRP, and negatively correlated with HDL-C in men. In women, age, BMI, WC, systolic and diastolic BP, glucose and TG showed a significantly positive correlation, and HDL-C showed a significantly negative correlation with ferritin.

Next, serum ferritin and hsCRP levels were compared with or

Table 1 Background characteristics of the study subjects

	Men	Women
No. of subjects	324	340
Age (years)	62.9 ± 11.0	61.2 ± 11.0
Ferritin (ng/mL)	179.9 ± 118.4	82.4 ± 63.8
BMI (kg/m ²)	23.6 ± 4.3	21.7 ± 4.6
Waist circumference (cm)	84.9 ± 9.9	78.5 ± 11.1
Systolic BP (mmHg)	127.9 ± 17.0	120.9 ± 18.5
Diastolic BP (mmHg)	76.3 ± 10.6	68.9 ± 10.4
Fasting glucose (mg/dL)	103.0 ± 17.0	95.8 ± 16.3
HDL-C (mg/dL)	57.8 ± 13.9	71.5 ± 15.3
Triglyceride (mg/dL)	119.4 ± 72.5	93.9 ± 49.2
hsCRP (ng/mL)	0.129 ± 0.431	0.059 ± 0.126

Data are mean $\pm$ SD.

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein

Table 2 Correlations between ferritin and MetS-related parameters

	Men		Women	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age	-0.056	0.315	0.202	<0.001
BMI	0.027	0.627	0.133	0.015
Waist circumference	0.122	0.029	0.244	<0.001
Systolic BP	-0.040	0.474	0.151	0.006
Diastolic BP	0.060	0.285	0.141	0.010
Fasting glucose	0.082	0.140	0.183	0.001
Triglyceride	0.170	0.002	0.170	0.002
HDL-C	-0.147	0.008	-0.155	0.004
hsCRP	0.135	0.015	0.048	0.380

without MetS-related abnormalities. Compared with the normal group, the group with abdominal obesity showed significantly higher ferritin levels in women, and significantly higher hsCRP levels in both sexes (**Figure 1**). The male hypertensive group showed significantly higher hsCRP levels than the normotensive counterparts (**Figure 2**). The hyperglycemic group showed sig-

nificantly higher ferritin levels compared with the normoglycemic group in both men and women, while there was no significant difference in hsCRP levels between those two groups (**Figure 3**). The group with dyslipidemia also showed significantly higher ferritin levels, but not hsCRP, than those of the group without dyslipidemia in both sexes (**Figure 4**).

Fig. 1 Comparison of ferritin and hSCPR levels by with or without abdominal obesity.

Abdominal obesity: Waist circumference men ≥ 85 cm, women ≥ 90 cm, *: $p < 0.05$, **: $p < 0.01$ (t -test)

Fig. 2 Comparison of ferritin and hSCPR levels by with or without hypertension.

Hypertension: Systolic BP ≥ 130 and/or diastolic BP ≥ 85 mmHg, *: $p < 0.05$ (t -test)

Fig. 3 Comparison of ferritin and hsCRP levels by with or without hyperglycemia.
Hyperglycemia: Fasting glucose ≥ 110 mg/dL, *: $p < 0.05$ (*t*-test)

Fig. 4 Comparison of ferritin and hsCRP levels by with or without dyslipidemia.
Dyslipidemia: TG ≥ 150 mg/dL and/or HDL-C < 40 mg/dL, *: $p < 0.05$, **: $p < 0.01$ (*t*-test)

To investigate whether serum ferritin increased in proportion to the severity of MetS, ferritin levels were compared stratified by the numbers of the four MetS components (abdominal obesity, hypertension, hyperglycemia and dyslipidemia). In men, serum ferritin levels increased with increasing number of components, and there was a significant difference between the zero-compo-

nent group and the four-component group (Figure 5). Although there were no women with four components, statistical differences were observed in the one-, two- and three-component groups compared with the zero-component group (Figure 5). HsCRP seemed to increase with increasing number of components, though it failed to reach statistical significance in both men

Fig. 5 Comparison of ferritin and hsCRP levels stratified by the number of MetS components.

*: $p < 0.05$, **: $p < 0.01$ (ANOVA with Dunnett's multiple comparison test)

Fig. 6 Comparison of ferritin and hsCRP levels by with or without MetS.

*: $p < 0.05$, **: $p < 0.01$ (*t*-test)

and women (**Figure 5**). We further compared serum ferritin and hsCRP levels with or without MetS (**Figure 6**). The prevalence of MetS was 19.7% in men and 3.9% in women. It was found that ferritin, but not hsCRP, was significantly higher in MetS subjects (average ferritin values, 172.2 ± 112.7 ng/mL for men and $80.9 \pm$

62.2 ng/mL for women) than in non-MetS counterparts (average ferritin values, 213.8 ± 137.6 ng/mL for men and 126.3 ± 88.4 ng/mL for women) in both men and women.

DISCUSSION

In the present study, the association between serum ferritin and MetS-related abnormalities was examined in 324 men and 340 women, and compared with that of between hsCRP and MetS. We identified that ferritin levels were significantly higher in the subjects with hyperglycemia and dyslipidemia in both men and women, and in those with abdominal obesity in women. On the other hand, hsCRP levels were significantly higher in the subjects with abdominal obesity in both sexes, and in those with hypertension in men. Serum ferritin increased in proportion to the number of MetS components and was significantly higher in MetS subjects than in non-MetS counterparts in both men and women, though these results were not obtained regarding hsCRP.

The first diagnostic criteria for MetS were proposed by the World Health Organization (WHO) in 1998¹⁶⁾. Since then, several MetS definitions have been established^{11, 14, 17, 18)}. The prevalence of MetS differs according to the criteria used for diagnosis^{19, 20)}. The MetS criteria by the Japanese Society of Internal Medicine stands at variance with others in the following respect: (i) increased WC is a prerequisite for MetS diagnosis, and (ii) TG and HDL-C are used in combination to define dyslipidemia, whereas TG and HDL-C are used separately in the other criteria. WC is measured according to population- and country-specific criteria, therefore, it is not surprising that different diagnostic rates are obtained in different racial groups even when using the same MetS definition. Although the positive relationship between high ferritin levels and MetS has been demonstrated by a meta-analysis¹⁰⁾, this study did not include Japanese people and the criteria used for MetS diagnosis were mainly those of NCEP ATP III¹¹⁾. Therefore, the main strength of our study is that we demonstrated the association between elevated ferritin levels and MetS in Japanese men and women using the MetS criteria established specifically for Japanese people. Although we did not necessarily obtain statistically significant results in serum ferritin levels for all of the MetS components, ferritin is not considered inferior compared with the well-known marker hsCRP with respect to the association with MetS.

The normal ranges of serum ferritin used in the present study were 21.0–282.0 ng/mL for men, and 5.0–157.0 ng/mL for women. These normal ranges are probably established based on the 2.5th and 97.5th percentiles using reference individuals, and the upper limit does not mean the cutoff value is considered as a risk factor of MetS. WHO defines levels of ferritin that indicate severe iron overload as > 200 ng/mL for men and > 150 ng/mL for women²¹⁾. There are several studies which compared the lowest and the highest quartiles of ferritin levels, and the highest quartile values lay between 194–423 for men and 94–231 for women^{22–29)}. In our subjects with MetS, average ferritin values were 213.8 ± 137.6 ng/mL for men and 126.3 ± 88.4 ng/mL for women, which is in accord with previously published data. Our study as well as most of the other studies did not distinguish premenopausal women from postmenopausal women. In only one study²²⁾, premenopausal and postmenopausal women were analyzed separately, and it was reported that the values of ferritin that

were associated with metabolic syndrome were 89 ng/mL in premenopausal and 212 ng/mL in postmenopausal women because of iron losses by menstruation in premenopausal women. The positive correlation between ferritin and age observed in our female subjects may be for this reason. However, because we do not have information about menstruation, we could not distinguish premenopausal women from postmenopausal women, which is one of the limitations of this study.

The mechanisms of the effect of elevated ferritin on metabolic disorders are not fully understood. Chronic inflammation in adipose tissue plays an important part in the pathophysiology of MetS¹²⁾, and increased ferritin may reflect the inflammatory component of MetS. Iron may catalyze the formation of free radicals and cause oxidative stress²⁹⁾. HsCRP is also a marker of inflammation, and is widely used for predicting cardiovascular risks in MetS. Therefore, we examined the association of ferritin and MetS in comparison with that of hsCRP and MetS in this study. In addition to inflammation, it was recently reported that iron regulates adiponectin and insulin sensitivity, which can well modulate the MetS condition. Gabrielsen *et al.* found that mice fed a high-iron diet and cultured adipocytes treated with iron exhibited decreased adiponectin mRNA and protein, iron negatively regulated adiponectin transcription via FOXO1-mediated repression using 3T3-L1 cells, and loss of the adipocyte iron export channel, ferroportin, in mice resulted in adipocyte iron loading, decreased adiponectin, and insulin resistance¹³⁾. They also demonstrated in humans that ferritin was increased and adiponectin was decreased in type 2 diabetic and in obese diabetic subjects compared with those in equally obese individuals without metabolic syndrome¹³⁾. More interestingly, they found that phlebotomy of humans with impaired glucose tolerance and ferritin values in the highest quartile of normal increased adiponectin and improved glucose tolerance¹³⁾. These findings demonstrate a causal role for iron as a risk factor for metabolic syndrome and a role for adipocytes in modulating metabolism through adiponectin in response to iron stores.

There were some limitations in the present study. First, the interpretation of ferritin values may become difficult in the presence of malnutrition causing iron deficiency, infection, inflammation or liver diseases. Our subjects who undergo anti-aging health checks at Tokai University Tokyo Hospital are considered to be more wealthy and health-conscious than ordinary people, and there is little likelihood that they are in such severe condition. Second, we could not distinguish people on medication for hypertension, dyslipidemia, or diabetes from those without treatment. Third, because of the cross-sectional nature of the study, the cause-effect relationship of our findings is uncertain. Finally, we simply carried out univariate analysis between ferritin and the clinical parameters. Further investigations are necessary to examine the interrelations and also to elucidate the causal relationships among these factors.

In conclusion, the present study shows that serum ferritin increased in proportion to the number of MetS components and was significantly higher in MetS subjects than in non-MetS counterparts in Japanese men and women. Ferritin is involved in the

occurrence of oxidative stress and regulation of adiponectin, both of which can modulate the MetS condition. High serum ferritin concentrations could potentially be used as a biomarker for MetS as well as hsCRP.

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The authors state that they have no Conflict of Interest (COI).

REFERENCES

- 1) Fernández-Real JM, López-Bermejo A, Ricart W. Cross-talk between iron metabolism and diabetes. *Diabetes* 2002; 51: 2348-54.
- 2) Ford ES, Cogswell ME. Diabetes and serum ferritin concentration among U.S. adults. *Diabetes Care* 1999; 22: 1978-83.
- 3) Forouhi NG, Harding AH, Allison M, Sandhu MS, Welch A, Luben R, et al. Elevated serum ferritin levels predict new-onset type 2 diabetes: results from the EPIC-Norfolk prospective study. *Diabetologia* 2007; 50: 949-56.
- 4) Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 2004; 291: 711-7.
- 5) Mojiminiyi OA, Marouf R, Abdella NA. Body iron stores in relation to the metabolic syndrome, glycemic control and complications in female patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis* 2008; 18: 559-66.
- 6) Piperno A, Trombini P, Gelosa M, Mauri V, Pecci V, Vergani A, et al. Increased serum ferritin is common in men with essential hypertension. *J Hypertens* 2002; 20: 1513-8.
- 7) Halle M, König D, Berg A, Keul J, Baumstark MW. Relationship of serum ferritin concentrations with metabolic cardiovascular risk factors in men without evidence for coronary artery disease. *Atherosclerosis* 1997; 128: 235-40.
- 8) 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.
- 9) 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.
- 10) Abril-Ulloa V, Flores-Mateo G, Solà-Alberich R, Manuel-y-Keenoy B, Arija V. Ferritin levels and risk of metabolic syndrome: meta-analysis of observational studies. *BMC Public Health* 2014; 14: 483. doi: 10.1186/1471-2458-14-483. (Accessed February 2, 2016, at <http://bmcpubhealth.biomedcentral.com/articles/10.1186/1471-2458-14-483>).
- 11) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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.
- 12) Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 14 2006; 444: 860-7.
- 13) Gabrielsen JS, Gao Y, Simcox JA, Huang J, Thorup D, Jones D, et al. Adipocyte iron regulates adiponectin and insulin sensitivity. *J Clin Invest* 2012; 122: 3529-40.
- 14) Committee for Japanese Definition of Metabolic Syndrome. Definition and criteria of metabolic syndrome. *J Jpn Soc Int Med* 2005; 94: 794-809 (in Japanese).
- 15) Nishizaki Y, Kubo A, Kuwahira I, et al. Anti-aging health check-up system – For the prevention of potentially progress aging related disadvantageous changes in elderly. *Health Evaluation and Promotion* 2012; 39: 549-57.
- 16) Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539-53.
- 17) Alberti KG, Zimmet P, Shaw J. Metabolic syndrome: a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469-80.
- 18) Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JJ, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640-5.
- 19) Kahn R, Buse J, Ferrannini E, Stern M. American Diabetes Association; European Association for the Study of Diabetes. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; 28: 2289-304.
- 20) Oda E, Abe M, Veeraveedu PT, Watanabe K. Considerable disagreement among definitions of metabolic syndrome for Japanese. *Circ J* 2007; 71: 1239-43.
- 21) WHO. Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.2). (Accessed January 7, 2016, at http://www.who.int/vmnis/indicators/serum_ferritin.pdf).
- 22) Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. *Diabetes Care* 2004; 27: 2422-8.
- 23) Shi Z, Hu X, Yuan B, Hu G, Pan X, Holmboe-Ottesen G. Coexistence of anaemia and the metabolic syndrome in adults in Jiangsu, China. *Asia Pac J Clin Nutr* 2008; 17: 505-13.
- 24) Sun L, Franco OH, Hu FB, Cai L, Yu Z, Li H, et al. Ferritin concentrations, metabolic syndrome, and type 2 diabetes in middle-aged and elderly Chinese. *J Clin Endocrinol Metab* 2008; 93: 4690-6.
- 25) Ryu SY, Kim KS, Park J, Kang MG, Han MA. Serum ferritin and risk of the metabolic syndrome in some Korean rural residents. *J Prev Med Public Health* 2008; 41: 115-20.
- 26) Kang HT, Linton JA, Shim JY. Serum ferritin level is associated with the prevalence of metabolic syndrome in Korean adults: the 2007–2008 Korean National Health and Nutrition Examination Survey. *Clin Chim Acta* 2012; 413: 636-41.
- 27) Hamalainen P, Saltevo J, Kautiainen H, Mantyselka P, Vanhala M. Erythropoietin, ferritin, haptoglobin, hemoglobin and transferrin receptor in metabolic syndrome: a case control study. *Cardiovasc Diabetol*; 11:116. doi: 10.1186/1475-2840-11-116, 2012. (Accessed February 2, 2016, at <http://cardiab.biomedcentral.com/articles/10.1186/1475-2840-11-116>).
- 28) Li J, Wang R, Luo D, Li S, Xiao C. Association between serum ferritin levels and risk of the metabolic syndrome in Chinese adults: a population study. *PLoS One* 2013; 8: e74168.
- 29) Reif DW. Ferritin as a source of iron for oxidative damage. *Free Radic Biol Med* 1992; 12: 417-27.