nature publishing group

Increased Serum Ferritin Predicts the Development of Hypertension Among Middle-Aged Men

Mee Kyoung Kim[1], Ki Hyun Baek[1], Ki-Ho Song[1], Moo Il Kang[1], Ji Hoon Choi[2], Ji Cheol Bae[2], Cheol Young Park[2], Won Young Lee[2] and Ki Won Oh[2]

BACKGROUND
We aimed to examine the relationship between iron status and hypertension as few studies have addressed this.

METHODS
We analyzed the association between ferritin/total iron-binding capacity (TIBC) and the subsequent development of hypertension. A total of 8,580 men who visited the Health Promotion Center for a medical checkup in 2005 were followed-up after 4 years.

RESULTS
Of the 8,580 men who were not hypertensive at baseline, 818 were found to be hypertensive at the 4-year follow-up. Compared with those who remained normotensive, these hypertensive subjects had higher levels of ferritin and TIBC at baseline, but had no significant difference in iron levels. After adjustment for age and body mass index (BMI), the odds ratios (OR) was substantially higher for new hypertension (OR 1.54, 95% confidence intervals (CIs) 1.26–1.88; *P* for trend <0.001) in subjects with the highest ferritin quartiles compared with those in the lowest quartiles. The association of serum ferritin levels with the incidence of hypertension was unchanged after adjustment for baseline blood pressure (BP). Adjustment for insulin resistance as measured by the homeostasis model assessment and the presence of a fatty liver reduced the magnitude of the OR for hypertension (first quartile reference, fourth quartiles OR 1.24, 95% CI 1.01–1.53, *P* for trend = 0.012), but did not affect their statistical significance.

CONCLUSION
Serum ferritin, but not iron level, was a significant predictor of hypertension in middle-aged Korean men. Fatty liver disease and insulin resistance may be mediators of this high ferritin–hypertension association.

Keywords: *blood pressure; ferritin; hypertension; total iron-binding capacity*

American Journal of Hypertension, advance online publication 26 January 2012; doi:10.1038/ajh.2011.241

Iron plays an important role in maintaining physiological homeostasis in the body; however, excess iron can lead to free radical damage, resulting in tissue damage.[1] Ferritin, one of the key proteins regulating iron homeostasis, is a widely available clinical biomarker to evaluate iron status and is especially important for detecting iron deficiency.[2] Several studies have reported an association between serum ferritin concentration and insulin resistance or type 2 diabetes[3–6] and it has been suggested that disturbances of iron metabolism are part of the metabolic syndrome,[7] which associates insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia[8] and central obesity.[9]

The relationship between body iron store and blood pressure (BP) status has not been well established. Heme iron intake, which is exclusively provided by red meat, poultry, and fish, is positively associated with increased BP.[10] On the other hand, low nonheme iron intake, abundant in fruits, vegetables, and cereal products, is associated with a greater risk of hypertension.[10] Dietary heme iron represents 2/3 of all absorbed iron, while nonheme iron provides only 1/3, because its absorption is influenced by various foods and nutrients.[11] It was recently reported that erythropoietin—closely associated with iron or ferritin metabolism—can increase oxidative stress and lead to the accentuation of hypertension.[12,13] Correcting anemia with erythropoietin administration in patients with chronic renal failure might lead to the accentuation of existing hypertension or the development of de novo hypertension.[12] A cross-sectional study using serum ferritin as an indicator of iron stores showed that serum ferritin levels and the prevalence of hyperferritinemia were increased in men with hypertension compared with normotensive healthy individuals.[14] However, Pilar *et al.* found that baseline hemoglobin and ferritin concentrations were not associated with changes in BP or incidental hypertension after 5.4 years of follow-up.[10] Therefore, further studies are needed to confirm the relationship between iron status and hypertension.

In Korea, hypertension is the most important cause of cardiovascular disease.[15] The Korean population differs importantly in cardiovascular disease patterns compared with Caucasians.[16] The major causes of death in Western countries are atherosclerotic coronary diseases. In contrast, in Korea,

[1]Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea; [2]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. Correspondence: Ki Won Oh (okwendo@yahoo.co.kr)

Received 11 August 2011; first decision 18 September 2011; accepted 11 November 2011.

hypertensive heart disease and stroke are more common. Moreover, BP factors are not linked closely with other components of metabolic syndrome in the Korean population.[15]

The purpose of this study was to test the hypothesis that higher circulating iron levels are associated with an increased risk of hypertension. We analyzed the association between ferritin/total iron-binding capacity (TIBC) and the development of hypertension over a 4-year period using patients in a follow-up cohort selected from a health checkup program in a single health promotion center in Korea.

METHODS

Subjects. Among subjects who underwent a health checkup at the Health Promotion Center at Kangbuk Samsung Hospital, Seoul, South Korea, in 2005, 11,384 men were included in this study at the baseline. The participants were employees of the company, or their family members, whose health checkup was performed in the health promotion center. At baseline, 2,804 men were excluded from the enrollment: those who had hypertension at baseline (n = 2,182; see below for definition); those with missing data for serum ferritin (n = 387); those with exceptionally high ferritin concentrations (>800 ng/ml; n = 5); those who had renal failure (creatinine >1.3 mg/dl; n = 199) or those with a history of malignancy (n = 31). A total of 8,580 participants were enrolled and they repeated their health checkup in 2009 (**Figure 1**). No specific informed consent was obtained. The institutional review board waived the requirement for informed consent at the time the study was in its planning phase, because researchers only accessed the database and did not require identifying personal information. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Measurements. All participants were required to fast for 12 h before a physical examination by trained staff and physicians using standard protocols. Body weight and height were measured with the subject barefoot and wearing light clothing and used to calculate the body mass index (BMI). Waist circumference was measured at the midpoint between the lower limit of the ribcage and the iliac crest. BP was measured two times in seated subjects after a 5-min rest using a mercury sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol. The mean of these measurements was used in analyses. A subject was classified hypertensive if his systolic BP was ≥140 mm Hg, or his diastolic BP was ≥90 mm Hg, or if he had been diagnosed with hypertension previously and was taking antihypertensive medications. The presence of a fatty liver was defined as abnormal hepatic features seen by ultrasonography (Logic Q700 MR; GE, Milwaukee, WI) suggestive of fatty infiltration using standardized criteria.[17]

Serum ferritin levels were measured by an immunoradiometric assay (IRMA-mat Ferritin; DiaSorin, Stillwater, MN). Serum iron and TIBC were measured by a colorimetric method (Advia 1800; Siemens, Berlin, Germany). Interassay coefficients of variation were 8.0% for ferritin, 1.4% for iron, and 3.1% for TIBC assays. The reference range was 15–332 ng/ml for ferritin, 65–175 μg/dl for iron and 250–450 μg/dl for TIBC assays. Serum insulin concentration was measured using an immunoradiometric assay (INS-IRMA; Biosource, Nivelles, Belgium). The homeostasis model assessment estimate of insulin resistance was calculated using the formula: fasting plasma glucose (mmol/l) × fasting insulin (mIU/l)/22.5.[18]

Statistical analysis. All data were analyzed using the SPSS statistical package (SPSS, Chicago, IL). Data are presented as the mean ± s.d. unless otherwise stated. If necessary, logarithmic transformation was performed to achieve a normal distribution. Participants were classified into four groups according to serum ferritin concentration quartiles. χ^2-tests and analysis of variance were used to compare proportions and means, respectively, according to serum ferritin concentration quartiles. Participant characteristics were compared according to their hypertension status using independent sample Student's t-tests for continuous measures and χ^2-tests for categorical measures. Subjects were divided into four groups by the quartiles of baseline ferritin and TIBC concentrations. The relationships between the 4-year development of hypertension with ferritin levels and TIBC after adjustment for confounding factors were analyzed by logistic regression analyses. $P < 0.05$ was accepted as statistically significant.

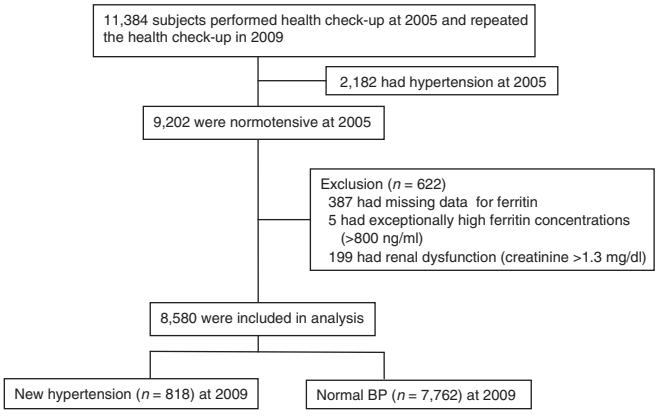

Figure 1 | Study populations for analysis of serum ferritin and incidence of hypertension. BP, blood pressure.

RESULTS

Baseline characteristics of participants according to serum ferritin level

The mean age of the study participants was 41.9 years. Across the ferritin concentration quartiles (Q), subjects in the higher quartiles were more likely to have higher concentrations of C-reactive protein (CRP), white blood cell counts, serum alanine aminotransferase and γ-glutamyl transferase and to have higher waist circumference. Fasting blood glucose, total cholesterol, and triglyceride levels increased linearly in subjects with the lowest to the highest serum ferritin quartiles (Q1–Q4; all $P < 0.001$). High-density lipoprotein cholesterol levels decreased linearly in subjects in parallel with the lowest to the highest serum ferritin quartiles ($P < 0.001$, **Table 1**).

Table 1 | Baseline characteristics of study subjects according to quartiles of serum ferritin in men

	Quartiles of ferritin (ng/ml)				
	Q1 (≤68.6)	Q2 (68.6–100.1)	Q3 (100.1–145.5)	Q4 (≥145.6)	*P* for trend*
n	2,144	2,145	2,146	2,145	
Median ferritin in quartile (ng/ml)	51.2 (39.6–60.5)	85.0 (77.3–92.6)	120.7 (110.5–131.9)	186.6 (163.8–234.8)	—
Age (years)	42.0 ± 6.7	41.8 ± 6.8	41.7 ± 6.9	41.6 ± 6.9	0.32
BMI (kg/m^2)	23.6 ± 2.6	23.9 ± 2.6	24.1 ± 2.6	24.7 ± 2.8	<0.001
Waist circumference (cm)	81.8 ± 7.5	83.0 ± 7.1	83.4 ± 7.4	85.2 ± 7.6	<0.001
Iron (μg/dl)	121.0 (89.0–155.0)	126.0 (94.0–155.0)	126.0 (96.8–155.3)	130.0 (98.0–160.8)	<0.001
TIBC (μg/dl)	315.0 (291.0–340.0)	304.0 (282.0–328.0)	301.0 (277.0–328.0)	297.5 (275.0–322.0)	<0.001
Systolic BP (mm Hg)	110.0 (100.0–120.0)	110.0 (100.0–120.0)	110.0 (100.0–120.0)	110.0 (100.0–120.0)	0.57
Diastolic BP (mm Hg)	74.0 (70.0–80.0)	76.0 (70.0–80.0)	76.0 (70.0–80.0)	78.0 (70.0–80.0)	<0.001
CRP (mg/l)	0.05 (0.02–0.09)	0.05 (0.03–0.11)	0.06 (0.03–0.11)	0.06 (0.03–0.12)	<0.001
WBC (10^3/μl)	5.9 (5.1–6.9)	6.0 (5.1–7.0)	6.1 (5.2–7.0)	6.2 (5.3–7.2)	<0.001
Glucose (mg/dl)	94.0 (89.0–100.0)	95.0 (90.0–100.0)	95.0 (90.0–101.0)	96.0 (90.0–102.0)	<0.001
$HOMA_{IR}$	1.8 (1.4–2.3)	1.9 (1.5–2.5)	1.9 (1.5–2.6)	2.2 (1.6–2.9)	<0.001
ALT (IU/l)	22.0 (17.0–29.0)	24.0 (18.0–32.0)	26.0 (19.0–36.0)	30.0 (22.0–44.0)	<0.001
GGT (IU/l)	23.0 (16.0–36.0)	27.0 (19.0–42.0)	31.0 (20.0–48.0)	37.0 (24.0–62.0)	<0.001
Fatty liver (%)	22.8	26.5	29.4	40.8	<0.001
Total cholesterol (mg/dl)	190.0 (170.0–211.0)	191.0 (170.0–213.0)	194.0 (173.0–215.0)	196.0 (175.0–219.0)	<0.001
Triglycerides (mg/dl)	111.0 (80.0–155.0)	117.0 (84.0–163.5)	125.0 (88.0–173.0)	137.0 (97.0–193.0)	<0.001
HDL-cholesterol (mg/dl)	50.1 (44.0–57.9)	49.6 (44.0–57.0)	50.0 (43.0–57.0)	48.0 (43.0–56.0)	<0.001

Data are presented as the mean ± s.d. or median (interquartile range).
ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; GGT. γ-glutamyl transferase; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostasis model assessment-insulin resistance; Q, quartile; TIBC, total iron-binding capacity; WBC, white blood cell counts.
**P* values refer to *P* for trend.

Diastolic BP increased linearly in subjects from the lowest to the highest serum ferritin quartiles (Table 1).

Serum ferritin, TIBC, and 4-year incidence of hypertension

Of the 8,580 men who were normotensive at baseline, 818 were found to be hypertensive at the 4-year follow-up. Compared with those who remained normotensive, these subjects had higher median levels of ferritin (100.4 vs. 109.1 ng/ml, $P < 0.001$) and TIBC (303.0 vs. 313.0 μg/dl, $P < 0.001$) at baseline, but had no significant difference in iron levels (126.0 vs. 122.0 μg/dl, $P = 0.329$) (Table 2). The subjects with hypertension were further classified into those newly diagnosed through BP readings (incident hypertension; $n = 494$) and those diagnosed because of use of hypertensive medications (self-reported hypertension; $n = 324$). Compared with those who remained normotensive, both incident and self-reported hypertensive subjects had higher median levels of ferritin and TIBC at baseline (see **Supplementary Table S1** online). However, there was no significant difference in baseline ferritin and TIBC between these two hypertensive groups. The subjects with self-reported hypertension were older and had a higher baseline systolic BP and greater insulin resistance than those newly diagnosed through BP readings.

Participants were divided into quartiles (Q1–4) based on their baseline ferritin and TIBC levels. Multiple logistic

Table 2 | Baseline characteristics of men according to the subsequent development of hypertension

	Hypertension (–)	Hypertension (+)	*P* value
n	7,762	818	
Age (years)	41.4 ± 6.9	44.5 ± 8.1	<0.001
BMI (kg/m^2)	23.9 ± 2.6	25.1 ± 2.6	<0.001
Ferritin (ng/ml)	100.4 (69.4–146.2)	109.1 (72.3–166.7)	<0.001
Iron (μg/dl)	126.0 (95.0–158.0)	122.0 (92.5–152.0)	0.33
TIBC (μg/dl)	303.0 (280.0–328.0)	313.0 (288.0–340.0)	<0.001
Systolic BP (mm Hg)	110.0 (100.0–116.0)	118.0 (110.0–124.0)	<0.001
Diastolic BP (mm Hg)	76.0 (70.0–80.0)	80.0 (76.0–86.0)	<0.001
CRP (mg/l)	0.05 (0.03–0.11)	0.07 (0.04–0.14)	0.38
Glucose (mg/dl)	95.0 (90.0–100.0)	98.0 (92.0–105.0)	<0.001
$HOMA_{IR}$	1.9 (1.5–2.5)	2.3 (1.7–3.0)	<0.001
ALT (IU/l)	25.0 (19.0–34.0)	28.0 (21.0–41.0)	<0.001
GGT (IU/l)	28.0 (19.0–45.0)	37.0 (23.0–62.0)	<0.001
Fatty liver (%)	28.2	43.2	<0.001

Data are presented as the mean ± s.d. or median (interquartile range).
ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; GGT, γ-glutamyl transferase; $HOMA_{IR}$, homeostasis model assessment-insulin resistance; TIBC, total iron-binding capacity.

regression analyses revealed a significant association of ferritin with the incidence of hypertension (Q1 reference; Q4 odds ratios (OR) 1.54; 95% confidence intervals (CIs) 1.26–1.88, *P* for trend < 0.001; model 1, **Table 3**). Further adjustment for baseline BP, CRP, homeostasis model assessment estimate of insulin resistance and the presence of a fatty liver (model 5) reduced the magnitude of the ORs for hypertension, but did not affect their statistical significance (OR 1.24; 95% CI 1.01–1.53, *P* for trend = 0.012). After adjustment for TIBC levels (model 6), the ORs were unchanged or slightly increased (OR 1.34; 95% CI 1.04–1.73, *P* for trend = 0.006). Little change in the magnitude and direction of associations was observed when waist circumference instead of BMI, or alanine aminotransferase concentration instead of the presence of fatty liver, was adjusted respectively (data not shown).

Multiple logistic regression analyses revealed a significantly positive association of TIBC with the incidence of hypertension (Q1 reference; Q4 OR 1.49; 95% CI 1.15–1.92, *P* for trend = 0.009; model 5, **Table 3**). The association of serum TIBC levels with the incidence of hypertension was unchanged after adjustment for ferritin levels (OR 1.57; 95% CI 1.20–2.06, *P* for trend = 0.003).

DISCUSSION

Serum ferritin, but not the iron level, was a significant predictor of hypertension in these middle-aged men and this association was significant even after adjustment for age, BMI and baseline BP. Further adjustment for insulin resistance and the presence of a fatty liver reduced the magnitude of the OR for hypertension, suggesting that fatty liver disease and insulin resistance might be mediators of this strong ferritin–hypertension association. Both ferritin and TIBC values were positively associated with the development of hypertension over a 4-year period, although the two were negatively correlated with each other. Our data suggest that dysregulation of iron metabolism is an important independent risk factor for the onset of hypertension in middle-aged men.

Our study linked increased serum ferritin levels in nonpathologic conditions, reflecting subclinical iron overload, to an increased risk of hypertension. There are three possible mechanisms to explain this association. First, insulin resistance could be the main mechanism involved, as numerous studies support a link between insulin resistance and hypertension. According to the DESIR study, ferritin levels were associated with insulin resistance and the development of type 2 diabetes.[5] Second, this association can be mediated by the presence of fatty liver disease.[19,20] This is associated with a progressive increase in BP over time and with incident hypertension.[21] Iron overload might play a role in the pathogenesis of fatty liver disease by increasing insulin resistance and oxidative stress.[19] In our study, we found that after adjustment for homeostasis model assessment estimate of insulin resistance and the presence of a fatty liver, the ORs for development of hypertension were attenuated. However, baseline ferritin remained

Table 3 | Odds ratio (95% CI) of incident hypertension by quartiles of ferritin and TIBC at baseline in men

	Quartiles of ferritin (ng/ml)				
	Q1 (≤68.6)	Q2 (68.6–100.1)	Q3 (100.1–145.5)	Q4 (≥145.6)	*P* for trend
Median ferritin in quartile (ng/ml)	51.2	85.0	120.7	186.6	
Hypertension unadjusted	8.8%	8.9%	8.7%	12.4%	<0.001
Model 1	1 (ref.)	1.05 (0.85, 1.29)	1.01 (0.82,1.25)	1.54 (1.26,1.88)	<0.001
Model 2	1 (ref.)	1.00 (0.81, 1.24)	0.95 (0.76,1.18)	1.41 (1.15,1.73)	<0.001
Model 3	1 (ref.)	1.02 (0.79, 1.33)	0.84 (0.64,1.10)	1.32 (1.03,1.68)	0.005
Model 4	1 (ref.)	0.98 (0.79, 1.22)	0.90 (0.73,1.13)	1.28 (1.04,1.58)	0.005
Model 5	1 (ref.)	0.98 (0.78, 1.21)	0.89 (0.72,1.11)	1.24 (1.01,1.53)	0.012
Model 6	1 (ref.)	1.05 (0.80, 1.36)	0.84 (0.64,1.11)	1.34 (1.04,1.73)	0.004
	Quartiles of TIBC (μg/dl)				
	Q1 (≤280)	Q2 (281–303)	Q3 (304–329)	Q4 (≥330)	
Median TIBC in quartile (μg/dl)	264	293	316	347	
Unadjusted	7.5%	8.5%	10.4%	13.2%	<0.001
Model 1	1 (ref.)	1.16 (0.88, 1.51)	1.48 (1.14,1.92)	1.95 (1.52,2.50)	<0.001
Model 2	1 (ref.)	1.10 (0.84, 1.44)	1.29 (0.99,1.67)	1.60 (1.25,2.07)	0.001
Model 3	1 (ref.)	1.10 (0.84, 1.44)	1.29 (0.99,1.67)	1.61 (1.25,2.07)	0.001
Model 4	1 (ref.)	1.08 (0.83, 1.42)	1.23 (0.94,1.60)	1.52 (1.18,1.96)	0.005
Model 5	1 (ref.)	1.08 (0.82, 1.41)	1.21 (0.93,1.58)	1.49 (1.15,1.92)	0.009
Model 6	1 (ref.)	1.06 (0.80, 1.41)	1.27 (0.96,1.67)	1.57 (1.20,2.06)	0.003

Data represent %. Model 1, adjusted for baseline age, BMI. Model 2, adjusted for baseline age, BMI, blood pressure. Model 3, adjusted for baseline age, BMI, blood pressure, CRP. Model 4, adjusted for baseline age, BMI, blood pressure, $HOMA_{IR}$. Model 5, adjusted for baseline age, BMI, blood pressure, $HOMA_{IR}$, the presence of fatty liver. Model 6, adjusted for age, BMI, blood pressure, $HOMA_{IR}$, the presence of fatty liver, TIBC (or ferritin).
BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; $HOMA_{IR}$, homeostasis model assessment-insulin resistance; TIBC, total iron-binding capacity.

an independent predictor for the development of hypertension, suggesting that iron status itself may be involved. Third, oxidative stress increased by excessive iron plays a role in the development of hypertension. Iron accumulation promotes increased free radicals and oxidative stress, which eventually lead to cell and tissue damage.[1] It has been hypothesized that the formation of free radicals catalyzed by iron contributes initially to endothelial damage and subsequently to the development of hypertension. Experimental studies have confirmed that hypertension is related to oxidative stress, which could contribute to endothelial dysfunction, leading to elevated BP.[22] Further studies are needed to evaluate the mechanism of this association.

Inflammation is closely associated with prevalent and/or incident hypertension and is also associated with the ferritin level itself. In the highest quartile of ferritin levels, subjects had higher BMI, waist circumference, CRP levels and elevated peripheral blood white blood cell counts indicating the presence of inflammation. Increased ferritin levels, which are also known as a positive inflammatory marker, may reflect another underlying mechanism for the development of hypertension. We attempted to minimize this potential confounding factor by excluding those individuals with renal disease or a history of malignancy. We also included CRP levels in the multivariate analysis. The association of serum ferritin levels with the incidences of hypertension was unchanged after adjustment for CRP levels.

A high iron load is reflected in high ferritin levels, but by a decreased TIBC. Although negatively correlated, both ferritin and TIBC were positively associated with the development of hypertension in this longitudinal study. Moreover, these associations were independent of each other. After adjustment for TIBC or ferritin, the ORs were unchanged or slightly increased, respectively. Dietary iron restriction has protective effects on high salt-induced hypertension and cardiovascular remodeling by reducing oxidative stress in the aorta.[1] In general, high iron conditions downregulate expression of the transferrin receptor 1 and upregulate ferritin expression. However, both transferrin receptor 1 and ferritin expression were upregulated in the aorta of high-salt diet Dahl salt-sensitive rats, suggesting that dysregulation of cellular iron transport proteins occurred in the aorta.[1] Upregulated aortic transferrin receptor 1 might have increased iron uptake into the cell and participated in vascular remodeling in the high-salt group. It has also been found that the expression of transferrin receptor 1 in atherosclerotic lesions is significantly associated with ferritin accumulation and macrophage infiltration, which contribute to the development and rupture of human carotid atheromas, thus suggesting a relevant role of intralesional iron metabolism in atherogenesis.[23] Transferrin itself might be involved in the pathogenesis of insulin resistance [24] or as a major determinant of the lipolytic activity of human serum in adipocytes.[25]

Increased TIBC values are likely to be found in most subjects with iron deficiency. Therefore, it might suggest that iron deficiency is more likely to cause hypertension than iron overload. Iron deficiency is associated with idiopathic pulmonary hypertension.[26] A report in iron-deficient patients with chronic kidney disease showed that correction of anemia was effective in reducing oxidative stress and the consequent cardiovascular risk.[27] Iron appears to be a "double-edged sword" for living systems. Both iron deficiency and iron overload might contribute to the production of reactive oxygen species, increasing oxidative stress, and inflammation and could have deleterious effect on endothelial function, which could result in BP increasing.[10] Our data suggest that dysregulation of iron metabolism is an important independent risk factor for the onset of hypertension. Further assessment of hepatic iron overload by liver biopsy or magnetic resonance imaging or the levels of other indicators such as transferrin, hepcidin, the transferrin receptor, and the soluble transferrin receptor are needed to provide some insight into the pathophysiology of iron overload.

To our knowledge, this is the first study investigating the association of serum ferritin levels with the development of hypertension. Our analyses took into account many potential covariates that might confound the observed associations. Thus, the presence of a fatty liver was not assessed in previous studies.[4,5] We found that baseline ferritin levels were associated with the development of hypertension, independently of the presence of a fatty liver.

Our longitudinal study had some limitations. First, we did not have data about iron intake and supplements. Second, most (88%) of our participants were younger than 50 years and all of the participants were volunteers or employees required to undertake a comprehensive health examination. Our study subjects were middle-aged Korean men. Therefore, these results cannot be extrapolated to women or to other ethnic groups. Third, we did not have data regarding a family history of hypertension, alcohol consumption, serum creatinine and uric acid. We could not adjust for all relevant confounding variables, and this could have affected our results. Fourth, we diagnosed hypertension based on the average of two BP readings at one visit, instead of two or more properly measured readings at each of two or more visits.

In conclusion, our data suggest a putative role for iron metabolism as an independent risk factor for hypertension in middle-aged Korean men. Our data support the idea that disturbances in iron status are associated with metabolic diseases—especially hypertension—in such men. Therefore, iron supplementation could be problematic for male subjects who are not anemic.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ajh

Acknowledgment: This work was supported by the Samsung Biomedical Research Institute grant, #SBRI C-B0-226-1, C-B0-226-2.

Disclosure: The authors declared no conflict of interest.

1. Naito Y, Hirotani S, Sawada H, Akahori H, Tsujino T, Masuyama T. Dietary iron restriction prevents hypertensive cardiovascular remodeling in Dahl salt-sensitive rats. *Hypertension* 2011; 57:497–504.
2. Sun L, Franco OH, Hu FB, Cai L, Yu Z, Li H, Ye X, Qi Q, Wang J, Pan A, Liu Y, Lin X. Ferritin concentrations, metabolic syndrome, and type 2 diabetes in middle-aged and elderly chinese. *J Clin Endocrinol Metab* 2008; 93:4690–4696.
3. Fernández-Real JM, López-Bermejo A, Ricart W. Cross-talk between iron metabolism and diabetes. *Diabetes* 2002; 51:2348–2354.

4. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. *Diabetes Care* 2004; 27:2422–2428.
5. Fumeron F, Péan F, Driss F, Balkau B, Tichet J, Marre M, Grandchamp B; Insulin Resistance Syndrome (DESIR) Study Group. Ferritin and transferrin are both predictive of the onset of hyperglycemia in men and women over 3 years: the data from an epidemiological study on the Insulin Resistance Syndrome (DESIR) study. *Diabetes Care* 2006; 29:2090–2094.
6. 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; 291:711–717.
7. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. *Diabetes Care* 2004;27:2422–2428.
8. Williams MJ, Poulton R, Williams S. Relationship of serum ferritin with cardiovascular risk factors and inflammation in young men and women. *Atherosclerosis* 2002; 165:179–184.
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; 25:639–645.
10. Galan P, Vergnaud AC, Tzoulaki I, Buyck JF, Blacher J, Czernichow S, Hercberg S. Low total and nonheme iron intakes are associated with a greater risk of hypertension. *J Nutr* 2010; 140:75–80.
11. Conrad ME, Umbreit JN. Iron absorption: relative importance of iron transport pathways. *Am J Hematol* 2001; 67:215.
12. Rancourt ME, Rodrigue ME, Agharazii M, Larivière R, Lebel M. Role of oxidative stress in erythropoietin-induced hypertension in uremic rats. *Am J Hypertens* 2010; 23:314–320.
13. Vaziri ND. Role of oxidative stress in the pathogenesis of erythropoietin-induced hypertension. *Am J Hypertens* 2010; 23:226–227.
14. Piperno A, Trombini P, Gelosa M, Mauri V, Pecci V, Vergani A, Salvioni A, Mariani R, Mancia G. Increased serum ferritin is common in men with essential hypertension. *J Hypertens* 2002; 20:1513–1518.
15. Choi KM, Lee J, Kim KB, Kim DR, Kim SK, Shin DH, Kim NH, Park IB, Choi DS, Baik SH; South-west Seoul Study. Factor analysis of the metabolic syndrome among elderly Koreans–the South-west Seoul Study. *Diabet Med* 2003; 20: 99–104.
16. Stellman SD. Proportional mortality ratios among Korean immigrants to New York City, 1986-1990. *Yonsei Med J* 1996; 37:31–37.
17. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *Br Med J (Clin Res Ed)* 1986; 292:13–15.
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28:412–419.
19. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R. NAFLD and hyperinsulinemia are major determinants of serum ferritin levels. *J Hepatol* 2007; 46:700–707.
20. Mascitelli L, Pezzetta F, Goldstein MR. Iron, metabolic syndrome, nonalcoholic fatty liver disease and carotid atherosclerosis. *Atherosclerosis* 2009; 205:39–40.
21. Lau K, Lorbeer R, Haring R, Schmidt CO, Wallaschofski H, Nauck M, John U, Baumeister SE, Völzke H. The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study. *J Hypertens* 2010; 28:1829–1835.
22. Wang H, Li H, Hou Z, Pan L, Shen X, Li G. Role of oxidative stress in elevated blood pressure induced by high free fatty acids. *Hypertens Res* 2009; 32:152–158.
23. Li W, Xu LH, Forssell C, Sullivan JL, Yuan XM. Overexpression of transferrin receptor and ferritin related to clinical symptoms and destabilization of human carotid plaques. *Exp Biol Med (Maywood)* 2008; 233:818–826.
24. Rumberger JM, Peters T Jr, Burrington C, Green A. Transferrin and iron contribute to the lipolytic effect of serum in isolated adipocytes. *Diabetes* 2004; 53:2535– 2541.
25. Vargas L, Kawada ME, Bazaes S, Karplus PA, Faerman CH. Insulin antagonism: a novel role for human serum transferrin. *Horm Metab Res* 1998; 30:113–117.
26. Ruiter G, Lankhorst S, Boonstra A, Postmus PE, Zweegman S, Westerhof N, van der Laarse WJ, Vonk-Noordegraaf A. Iron deficiency is common in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2011; 37:1386–1391.
27. Garneata L. Intravenous iron, inflammation, and oxidative stress: is iron a friend or an enemy of uremic patients? *J Ren Nutr* 2008; 18:40–45.