Original Article

Serum ferritin and risk of the metabolic syndrome: a population-based study

Jung-Su Chang PhD[1], Shiue-Ming Lin MSc[2], Tzu-chieh Huang MSc[1], Jane C-J Chao PhD[1], Yi-Chun Chen PhD[1], Wen-Harn Pan PhD[3,4], Chyi-Huey Bai PhD[2]

[1]*School of Nutrition and Health Sciences, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan. ROC*
[2]*Department of Public Health, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC*
[3]*Institute of Biomedical Science, Academia Sinica, Taipei, Taiwan, ROC*
[4]*Institute of Population Health Sciences, National Health Research Institutes, Taiwan, ROC*

Ferritin concentrations in circulation reflect iron stores in healthy individuals. However, elevated serum ferritin (SF) concentrations have recently been implicated in the pathogenesis of the metabolic syndrome (MetS). We aim to investigate factors associated with elevated SF and to evaluate the association between SF and risk of MetS in Taiwanese adults. Data was collected from 2654 healthy individuals aged ≥19 years old, who participated in the Nutrition and Health Survey in Taiwan (NAHSIT Adults 2005-2008). Mean concentrations of SF were 173±282 ng/mL (men 229±349 ng/mL and women 119±180 ng/mL). Prevalence proportion of MetS was 34.6% (men 43.1% and women 26.5%). Prevalence proportion of iron overload was 18.6% (men 21.5% and women 15.8%) and iron deficiency anemia was 5.2% (2.0% for men and 8.3% for women). Individuals with the highest SF tertile (T3) were more likely to consume higher amount of animal protein (p=0.001), betel nuts (p=0.004), and lower amounts of carbohydrates (p<0.0001), compared with the lowest SF group (T1). After adjustments, individuals with the highest SF tertile were associated with risk of MetS compared with those with the lowest (OR=1.724, 95% CI: 1.21-2.45). Serum ferritin concentrations showed a gradient relationship with individual components of MetS (all p<0.0001). Individuals with the highest SF tertile were significantly associated with fasting serum glucose (OR=2.16, 95% CI: 1.75-2.65) and serum triglyceride (OR=2.58, 95% CI: 1.07-3.22) than those with the lowest. In conclusions, our results highlight the crucial role of serum ferritin in the pathogenesis of the MetS in healthy Taiwanese adults.

Key Words: metabolic syndrome, serum ferritin, National Nutrition and Health Survey in Taiwan, dietary iron intake, obesity

INTRODUCTION

The amount of ferritin in circulation normally reflects the amount of iron stored in the body in healthy individuals. However, elevated serum ferritin (SF) concentrations have recently been implicated in the pathogenesis of many chronic inflammatory diseases including the metabolic syndrome (MetS).[1-4] The first evidence linking iron to MetS was the observation that patients with hereditary hemochromatosis were at higher risk of developing type II diabetes.[5-7] Hemochromatosis is an inherited disorder commonly associated with European ancestry. Patients with type 2 diabetes have a high frequency of the C282Y mutation of the hemochromatosis gene.[8] The prevalence of diabetes (23%) and impaired glucose tolerance (IGT) (30%) increased in hemochromatosis compared with matched control subjects (0% diabetes and 14% IGT).[7] Serum ferritin >1000 μg/L at diagnosis is associated with increased risk for cirrhosis in patients with hemochromatosis C282Y homozygosity in many studies.[9] Blood letting, resulting in reduced body iron stores (refers to SF levels), is commonly used in the treatment of hemochromatosis. Secondly, increased body iron stores predicted the development of MetS and diabetes in epidemiologic studies in healthy individuals of European ancestry[10,11] and recently in healthy East Asians.[3,12] Asians and Pacific islanders have higher circulating SF compared with Caucasians but clinical significances are unclear.[13,14] Decreased SF levels through regular blood donation is associated with decreased risk of type 2 diabetes and cardiovascular disease.[10] Regular blood letting decreased blood HbA1c levels and improved insulin sensitivity and β-cell function in type II diabetic patients with high SF levels.[2] This finding is especially of importance given the fact that Asians have higher crude and adjusted mean SF than their Caucasians counterparts.[13,14] Thirdly, the link be-

Corresponding Author: Dr Chyi-Huey Bai, Department of Public Health, College of Medicine, Taipei Medical University, Taipei, Taiwan R.O.C.
Tel:+886-(2)27361661#6510; Fax:+886-(2) 2738-4831
Email: baich@tmu.edu.tw
Manuscript received 14 January 2013. Initial review completed 1 February 2013. Revision accepted 13 April 2013.
doi: 10.6133/apjcn.2013.22.3.07

tween hepatic iron overload and insulin-resistance syndrome is commonly observed in patients with nonalcoholic fatty liver disease.[15,16]

Unlike the role of hepatic ferritin as iron storage protein, the physiological function of ferritin in circulation is unclear. The underlying mechanisms lead to the production, secretion and uptake of secreted ferritin in the peripheral remains less understood.[17] In conditions of chronic inflammatory diseases, at least three sources may contribute to elevated ferritin in circulation: 1) tissue ferritin secreted by the Kupffer cells or macrophages;[18] 2) tissue ferritin released from damaged hepatocytes;[19] and 3) serum ferritin induced by inflammatory-related mechanisms such as IL6 and TNF.[17,20] In conditions of chronic hepatic iron overload, tissue ferritin released from damaged hepatocytes, kupffer cells or macrophages may contribute to the elevated ferritin concentrations in the local tissue or in the peripheral. Circulating ferritin levels may rise independently of iron overload in conditions of inflammation, infection, alcohol abuse, liver diseases, neurodegenerative diseases, cancer and MetS.

The aim of this study was to evaluate whether SF concentrations are independently associated with risk of MetS in healthy adults by the use of Nutrition and Health Survey in Taiwan. The objectives of this study were as follows: 1) to identify the possible factors associated with elevated SF levels; 2) to assess the association between SF and MetS; and 3) to examine the association between SF concentrations and individual components of MetS.

MATERIALS AND METHODS

Study design

The Third National Nutrition and Health Survey in Taiwan (NAHSIT 2005-2008, Adults) was funded by the Department of Health to provide continued assessment of health and nutrition of the people in Taiwan. The survey was conducted using a multi-staged, stratified and clustered sampling scheme which includes a wide range of age groups across the whole of Taiwan. The present study only analyzed data on adults, aged ≥19 years old. The survey divided 358 townships and city districts of Taiwan into five sampling strata based on geographical location and population density. Theses strata included the first northern stratum, the second northern stratum, the central stratum, the southern stratum and the Eastern stratum. The five strata were selected for inference to the whole of Taiwan. This study was approved by the Research Ethics Committee of Taipei Medical University (201203029) and Academia Sinica (AS-IRB01-07020). Written informed consent was obtained from all participants.

Sample inclusion and exclusion

A total of 2,808 participants, 1365 male and 1443 female, were recruited to this study. Exclusion criteria were as followed: 1) individuals with missing data for clinical biochemistry, anthropometry and 24 hours dietary recall (n=20); 2) total calorie intake ≥5,000 kcal/day or ≤500 kcal/day (n=19); and 3) Individuals with abnormal serum ferritin levels (>500 ng/mL) (n=115). As such, a total of 2,654 participants, 1,260 men and 1,394 women, were selected for analysis.

Data collection

Information on social-demographic variables, family health history and 24 hours dietary recall were obtained using a standardized questionnaire. Smoking status was divided into 3 categories: current smoker, past smoker and non-smoker. Questions about alcohol intake included the frequency of alcohol consumption on a weekly basis and the amount of alcohol consumed was categorized into 4 groups: non-drinker, light drinker (1-20 g/day), moderate drinker (≥21-40 g/day) and heavy drinker (≥41 g/day). Measurements of body weight and height, waist circumference and blood pressure were described elsewhere.[21] Waist circumference measurements were taken at the midpoint between the lower edge of the rib cage and the top of the iliac crest.[21] Dietary intake was estimated by the 24 hour dietary recall which includes measurement of household recipes, the individual dietary recall and validation of individual dietary recall by food models. Dietary data on total calorie intake, total iron intake, type of iron (heme iron and non-heme iron) consumed, intakes of carbohydrates, protein, fats and oils were obtained from 24-hour dietary recall. All nutrient intakes were energy adjusted by the residual method.[22] Details of the data collection and data analysis had been described elsewhere.[23]

Laboratory measurements

Biochemistry data were obtained from 8 hours fasting blood samples. Heparinized whole blood was collected for on-site measurement of hemoglobin. Peripheral venous blood samples were collected in tubes containing EDTA, centrifuged at 4℃ and stored serum at -80℃ until analysis. Clinical biochemistry included: serum cholesterol (including total cholesterol, LDL-C and HDL-C), triglycerides, blood glucose, uric acid, C-reactive protein (CRP), creatinine, homocysteine, liver function tests (GOT,GPT), amylase, BUN, alkaline phosphatase and iron parameters (serum iron, ferritin, TIBC).

Definitions of iron deficiency anemia (IDA) and iron overload

Iron status was evaluated by serum iron, transferring saturation and serum ferritin concentrations.[24] Serum ferritin was measured using a commercially available electrochemiluminescence immunoassay and was quantitated by the Roche Modular P800. Hemoglobin was measured by the cyanomethemoglobin method (Merckotest, Merck) using a portable filter photometer calibrated with hemoglobin cyanide standard solution (Merck). Serum iron and TIBC were measured by ferrozine-based colorimetric method. Percentage transferrin saturation (TS) was calculated by serum iron/TIBC × 100%. Iron deficiency was considered if ≥2 abnormal values of 3 indicators of iron status: SF <12 ng/mL, TS <15% and hemoglobin <13 mg/dL in men and <12 mg/dL in women. Hemoglobin cut-off point (men <13 mg/dL and women <12 mg/dL) was used to define anemia. Iron overload was defined as serum ferritin >300 ng/mL for men and >200 ng/mL for women.[3]

Definition of obesity and the metabolic syndromes

Obesity and overweight were defined based on definitions used by the Department of Health in Taiwan.[25,26] This

definition is in accordance with the World Health Organization (WHO)-Asian's criteria which define overweight as BMI ≥24 kg/m^2 and obese as BMI ≥27 kg/m^2. [27] Central obesity was defined as a waist circumference of ≥90 cm in men and ≥80 cm in women. Waist circumference measurements were taken at the midpoint between the lower edge of the rib cage and the top of the iliac crest.[21] Diabetes was defined as a fasting blood sugar of ≥126 mg/dL or the use of blood sugar lowering medications. Hypercholesterolemia was defined as a cholesterol level ≥240 mg/dL and hypertriglyceridemia was defined as a triglyceride level ≥200 mg/dL. Hypertension diagnosis was defined according to JNC VII criteria: the blood pressure (BP) recommendation has been set at ≥140/90 mmHg or current use of antihypertensive drugs.[28]

The Metabolic syndrome as a dependent variable

The metabolic syndrome was defined based on the modified National Cholesterol Education Program Adult Treatment Panel III criteria for Asia Pacific.[25,29] Individuals with the presence of ≥3 criteria listed below were classified with MetS:[26] 1) overweight as BMI ≥24 kg/m^2 and obese as BMI ≥27 kg/m^2; 2) waist circumference of ≥90 cm in men and ≥80 cm in women; 3) TG ≥150 mg/dL; 4) HDL <40 mg/dL for men and <50 mg/dL for women; 5) systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or current use of antihypertensive drugs; and (6) fasting blood glucose ≥100 mg/dL or current use of antihyperglycemic drugs.

Statistical analyses

Statistical analyses were performed using the Statistical Analysis Systems software (SAS version 9.22; SAS Institute, Inc). Categorical data presented as number (percentage) and continuous data presented as mean (SD). Logarithmic transformation of the data (transferring saturation and CRP) was used to achieve a normal distribution and to allow the use of parametric tests. Serum ferritin concentrations were divided into tertiles according to sex. Sex-specific SF cutoffs for tertiles were: 122.5 ng/mL and 230.2 ng/mL for men and 46.7 ng/ml and 122.6 ng/mL for women. The one-way analysis of variance and chi-square test were used to compare the differences among tertile groups of serum ferritin. Multivariable logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval (CI) for MetS and it's individual components. P<0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The mean age of study participants was 54.3±17.8 yrs old. Mean BMI was 24.5±4.0 kg/m^2. The prevalence proportion of obesity was 40.3 % (men 41.2 % and women 39.3%) and MetS was 34.6% (men 43.1% and women 26.5%). The prevalence proportion of iron overload was 18.6% (men 21.5% and women 15.8%), and IDA was 5.2% (2.0% for men and 8.3% for women). Mean concentrations of SF and TS were 173±282 ng/mL (men 229±349 ng/mL and women 119±180 ng/mL) and 34±14.1% (men 37.7±14.3% and women 30.5±12.9%), respectively. Dietary iron consumption was 14.9±15.6 mg/day (men 16.1±18.6 mg/day and women 13.6±11.7 mg/day). Men consumed higher amount of heme iron than females (men 4.9±15.6 mg/day and women 3.1±3.9 mg/day).

Association between SF concentrations and potential confounding variables

The clinical characteristics of the study subjects in relation to tertile groups of SF are shown in Table 1. The possible variables which may, directly or indirectly, modulate the distribution of SF levels were included in our analysis. These include: 1) dietary variables; 2) life style factors; 3) self-reported family health history; 4) inflammatory markers; 5) iron parameters; and 6) components of MetS.

Subjects with the highest SF tertile were older with higher prevalence of self-reported family health history of chronic diseases than the lowest (all p<0.001, except cirrhosis and hepatitis). With respect to iron parameters, individuals with the highest SF tertile had higher values of serum TIBC, % TS, hemoglobin and the lowest prevalence rate of IDA (all p<0.001). Regarding life-style factors, individuals with highest SF tertile were more likely to consume higher amount of animal protein (p=0.001), betel nuts (p=0.004), and lower amounts of carbohydrates (p<0.0001). With respect to metabolic parameters, individuals with the highest SF tertile had higher values of BMI, waist circumferences, waist to hip ratio, BP (systolic and diastolic), fasting glucose, total cholesterol, LDL, triglyceride, BUN, UA, ALK, GOT, GPT, CRP and decreased level of HDL (all p<0.001) (Table 1).

Association between serum ferritin concentrations and MetS

After adjusting for the age, sex, BMI, inflammation (GOT, GTP, ALK, amylase, BUN, UA, creatinine, homocysteine), lifestyle factors (past smoker, drinking habits and betel nut consumption), iron status (hemoglobin, IDA) and self-reported family health history of chronic diseases (hyperlipidemia, fatty liver disease, hypertension, diabetes mellitus); the adjusted OR and 95% confidence interval (CI) for MetS for individuals with the highest SF tertile compared with those with the lowest was 1.72 (1.21-2.45) (Table 2). The multivariable model showed a significantly graded relationship between SF concentrations and individual components of MetS (Table 3). Individuals with the intermediate SF tertile (T2) had increased risk for abnormal fasting glucose levels (OR=1.3, 95% CI: 1.06-1.58) and serum triglyceride (OR=1.57, 95% CI: 1.25-1.97) than those with the lowest SF tertile. The risk for individual components of MetS increased with increasing tertile groups of SF (p for trend <0.0001). Components such as fasting glucose concentrations (OR=2.16, 95% CI: 1.57-2.66), serum triglyceride (OR=2.58, 95% CI: 2.07-3.22), serum HDL-cholesterol (OR=1.68, 95% CI: 1.35-2.08) and waist circumference (OR=1.68, 95% CI: 1.34-2.12) were most affected by a sharp rise in SF levels (Table 3).

DISCUSSION

To our knowledge, this cross-sectional, population-based study is the first to clarify the association between body

Table 1. Baseline characteristics of participants aged ≥19 years presented by tertile groups of serum ferritin level (n=2654)

	Serum Ferritin, Tertile					Serum Ferritin, Tertile			
	T1 (n=881)	T2 (n=885)	T3 (n=888)	*p* for trend		T1 (n=881)	T2 (n=885)	T3 (n=888)	*p* for trend
Waist, cm	81.0±11.1	83.0±11.3	86.0±9.9	<0.001	CREA, mg/dL	0.86±0.42	0.85±0.36	0.87±0.47	0.764
W/H ratio	0.87±0.09	0.88±0.08	0.91±0.08	<0.001	Homocysteine, μmol/L	13.2±8.1	12.4±6.0	12.9±6.5	0.33
Iron status assessment					ALK, mg/dL	67.4±21.2	71.9±22.4	77.2±26.9	<0.001
TIBC, μg/dL	344 ±53.9	310±39.4	304±43.4	<0.001	GOT, IU/L	21.8±13.9	22.4±9.4	29.7±26.7	<0.001
Ferritin, ng/mL	46.2±34.7	126 ±51.9	347±431.3	<0.001	GPT, IU/L	18.3±14.2	21.0±16.2	29.4±29.7	<0.001
Log Transferrin saturation,	28.7±14.0	34.8±12.1	38.2±14.3	<0.001	Nutritional Intake (24 hours dietary recall)				
Hemoglobin, ug/dL	13.2±1.8	13.7±1.4	13.9±1.6	<0.001	Vit B-1, mg/day	1.22±0.02	1.18±0.02	1.19±0.02	0.462
Iron deficiency (n, %)	47(5.37)	6(0.68)	5(0.56)		Vit B-2, mg/day	1.36±0.03	1.37±0.03	1.33±0.03	0.549
Iron deficiency anemia (n, %)	81(9.26)	0	0	<0.001	Vit B-6, mg/day	1.80±0.03	1.82±0.03	1.82±0.03	0.652
Family health history					Vit B-12, mg/day	5.9±0.5	6.9±0.5	6.6±0.5	0.34
Hypertension (n, %)	244(27.7)	266(30.1)	354(39.9)	<0.001	Vit C, mg/day	173±5	170±5	175±5	0.793
Hyperlipidemia (n, %)	38(4.8)	70(8.91)	118(14.84)	<0.001	Vit D, ug/day	7.3±0.4	8.3±0.4	8.0±0.4	0.208
Diabetes mellitus (n, %)	214(24.3)	269(30.40)	375(42.23)	<0.001	Total iron, mg/day	14.9±0.5	15.4±0.5	14.6±0.5	0.604
Hepatitis (n, %)	52(6.21)	56(6.67)	75(8.77)	0.021	Plant iron mg/day ,	11.1±0.3	10.4±0.3	10.3±0.3	0.077
Fatty liver (n, %)	31(3.91)	49(6.19)	81(10.14)	<0.001	Animal iron mg/day	3.5±0.4	4.6±0.4	4.0±0.4	0.389
Cirrhosis (n, %)	5(0.63)	1(0.13)	4(0.51)	0.353	Plant/animal iron	10.5±1.6	9.5±1.7	14.0±1.6	0.131
Biochemistry serum value					Total protein, g/day	75±0.9	77±0.9	78±0.9	0.055
Sytolic BP, mmHg	115 ±19.6	117±18.4	123±18.1	<0.001	Plant protein g/day	35±0.6	35±0.6	32±0.6	0.445
Diastolic BP, mmHg	70.3±11.8	71.0±11.2	73.1±11.6	<0.001	Animal protein g/day	37±1.0	38±1.0	41±1.0	0.001
Total cholesterol, mg/dL	186 ±37.3	193 ±35.0	201±42.0	<0.001	Protein/calorie, g/Kcal	0.041±0.000	0.042±0.000	0.042±0.000	0.017
LDL cholesterol, mg/dL	117 ±33.6	123 ±33.4	127±39.8	<0.0001	Fat, mg/day	64±0.9	63±0.9	63±0.9	0.558
Triglyceride, mg/dL	109 ±75.8	125 ±81.0	157±116	<0.001	Fiber, g/day	17±0.4	17±0.4	16±0.4	0.052
HDL cholesterol, mg/dL	55.6±15.6	53.8±15.1	51.0±14.5	<0.001	Carbohydrate, g/day	244±2	240±2	231±2	<0.001
Fasting glucose, mg/dL	106 ±32.7	108±31.4	120±43.5	<0.001	Life style factors				
Amylase, mg/dL	68.0±24.8	68.6±25.5	69.1±37.5	0.427	Betel nuts use (n, %)	69 (8.4)	69 (8.2)	102 (12.3)	0.004
BUN, mg/dL	14.5±5.6	15.2±6.7	16.1±5.8	<0.001	Alcohol use (n, %)	307(37.2)	298 (35.6)	319 (38.3)	0.323
UA, mg/dL	5.8±1.7	6.0±1.7	6.4±1.8	<0.001	Past smoker (n, %)	119 (14.4)	99 (11.8)	98 (11.8)	
Log CRP, ng/mL	-0.90±0.35	-0.86±0.37	-0.78±0.39	<0.001	Current smoker (n, %)	148 (6.0)	148 (17.7)	170 (20.4)	0.06

[†]Categorical data presented as number (%); continuous data presented as mean ± SD; transferring saturation and CRP were log transformed due to the skewed nature of data
The *p* for trend by analysis of variance test for continuous variables and chi-square for categorical variables.
[‡]Serum ferritin tertile by gender: men:: 121.5 ng/mL and 230.2 ng/mL; women: 46.7 ng/mL and 122.6 ng/mL

Table 2. Odds ratio and 95% confidence intervals for MetS according to tertile groups of serum ferritin level

	Serum Ferritin, Tertile			*p* for trend
	T1	T2	T3	
Model I	Ref	1.35 (1.08-1.68)	2.36 (1.91-2.93)	<0.0001
Model II	Ref	1.34 (1.03-1.75)	1.92 (1.47-2.49)	<0.0001
Model III	Ref	1.28 (0.98-1.68)	1.89 (1.44-2.47)	<0.0001
Model IV	Ref	1.27 (0.94-1.72)	2.01 (1.47-2.75)	<0.0001
Model V	Ref	1.20 (0.85-1.68)	1.72 (1.21-2.45)	0.0049

†Serum ferritin tertile by gender: Male: 121.5ng/ml/230.2 ng/ml; Female: 46.7 ng/ml & 122.6 ng/ml
‡Model I: adjusted for age and sex
*Model II: adjusted for Model I and family history of chronic disease (4 covariates: hyperlipidemia, fatty liver disease, hypertension, diabetes mellitus)
#Model III: adjusted for Model II and lifestyle factors (3 covariates: past smoker, drinking habits, betel nut consumption)
※Model IV: adjusted for Model III and iron status (2 covariates: hemoglobin, iron deficiency anemia)
○Model V: adjusted for Model IV and inflammation (9 covariates: GOT, GPT, ALK, Amylase, BUN, UA, Creatinine, CRP, homocysteine)

Table 3. Adjusted odds ratio and 95% confidence intervals for the individual components of MetS by serum ferritin level

Components of the metabolic syndrome	Serum Ferritin, Tertile			*p* for trend
	T1	T2	T3	
Blood pressure ≥135/85 mmHg	Ref	0.94 (0.75-1.18)	1.33 (1.06-1.66)	0.003
Fasting serum glucose ≥110 mg/dL	Ref	1.30 (1.06-1.58)	2.16 (1.75-2.66)	<0.001
Triglyceride ≥150 mg/dL	Ref	1.57 (1.25-1.97)	2.58 (2.07-3.22)	<0.001
HDL, men: <40 mg/dL, women: <50 mg/dL	Ref	1.19 (0.96-1.49)	1.68 (1.35-2.08)	<0.001
Waist circumference, men: ≥ 90 cm, women: ≥80 cm	Ref	1.18 (0.94-1.49)	1.68 (1.34-2.12)	<0.001

†Adjusting for age and sex

iron store and risk of MetS in healthy Taiwanese adults. Our results confirm that high SF concentrations are strongly associated with MetS. This association was independent of age, sex, BMI, inflammation, lifestyle factors, iron status and family history of chronic diseases. Our data also indicate a strong relationship between SF and fasting glucose concentrations. We found individuals with intermediate SF tertile (T2) had 1.3 times (95% CI: 1.06-1.58) higher risk for developing high blood glucose and this risk increased to 2.16 times (95% CI: 1.57-2.66) for individuals with SF at T3. Our studies are in agreement with studies of individuals of European ancestry,[10,11] middle-aged and elderly Chinese[3] and South Koreans.[3,12] Ryoo and colleagues[3,12] also found a significantly graded relationship between fasting glucose and quartile groups of SF in healthy middle-aged Korean men. Sun *et al* reported 3.26 times (95% CI: 2.36-4.51) higher risk for developing type 2 diabetes and 2.8 (95% CI: 2.24-3.49) times higher risk for developing MetS for individuals with the highest SF quartile compared with those with the lowest.[3]

Currently, molecular mechanisms underlying elevated SF to type 2 diabetes are unclear. It has been suggested that formation of hydroxyl radicals catalyzed by iron may be involved in the etiology of diabetes because iron-mediated free radical can attack cell membrane and increased lipid peroxidation, contributing to DNA fragmentation and tissue damage.[30] Recently, the role of SF on adipose tissue has attracted a lot of attention. A study in the Chinese population showed that SF predicts trunk fat mass.[31] Another study found that SF inversely correlated with adiponectin.[32] Adiponectin is insulin-sensitizing adipokine which is decreased in people with obesity.[33] Mice fed with iron rich diet had altered body composition and decreased adiponectin synthesis by adipocyte.[34] Taken together, iron is essential for all living organisms; however, no physiologic mechanism of iron excretion in human exists. Therefore, excessive iron deposits throughout the body may have complex and multiple effects on organs or cells.

Dietary iron intake and disease risk

In our study, the amount of dietary iron consumed (total iron or heme iron) did not associate with SF tertile. However, a positive correlation between dietary iron intake (total iron or heme iron) and individual components of MetS was found (data not shown). Iron absorption must be closely regulated to maintain iron balance because humans cannot excrete surplus iron other than by hemorrhaging.[35] Because dietary intake of iron is an important determinant of body iron stores, higher intake of iron may be associated with an elevated risk of MetS. Heme iron intake, but not total iron or non-heme iron, was associated with risk of type 2 diabetes in healthy women in a 20 years follow-up study.[36] Women who consumed iron ≥2.25 mg/day had 1.5 fold increased risks for type 2 diabetes than those who consumed ≤0.75 mg/day (RR=1.52, 95% CI: 1.22-1.88). Human obtained dietary iron in two forms: non-heme and heme iron. It is now well understood that the absorption of heme iron is relatively unaffected by other dietary factors compared with the absorption of non-heme iron. Dietary components such as heme iron, supplementary iron, dietary vitamin C, animal protein, copper and alcohol were positively associated with iron stores,[37] whereas coffee, phytic acid, oxalic acid, zinc, calcium had negative association.[38] Negative association is mainly due to the inhibition of non-heme iron absorption.

SF concentrations and inflammation

A sharp rise in SF levels in middle-aged adults and elderly could be due to the high prevalence of inflammatory diseases. SF concentration normally reflects body iron stores in healthy individuals. However, SF is also an acute-phase protein and abnormal SF levels are commonly associated with chronic inflammation. As a result, abnormal SF might reflect systemic inflammation rather than body iron stores. Because SF levels are frequently cluster with well-established risk factors for MetS, we included most of the potential confounding factors that are known to associate with elevated SF in our study. Our result indicates that association between SF levels and MetS in Taiwanese adults is independent of obesity (BMI), inflammation, life style factors and family health history. However, we cannot rule out residual confounding effects due to failure to adjust other inflammatory conditions.

Limitation of the study

Our study is limited by the small sample size and confined by the nature of cross-sectional study. In order to understand the casual relationship between SF concentrations and MetS, longitudinal studies are necessary in order to understand if changes in iron store over time predict disease susceptibility in a healthy population. Due to the restricted sample size, we decided not to exclude individuals with self-reported healthy histories for fatty liver, cirrhosis, hepatitis, hypertension, hyperlipidemia and diabetes mellitus, all of which are known to cause hyperferritinemia. Instead, we used SF ≥500 ng/ml as cut-off point to exclude individuals with abnormal SF and adjust health history as potential confounding factor in the model. In addition, the use of the 24-hours dietary record may not be of sufficient length to obtain reliable data on iron intakes. A 12-days dietary record is considered the shortest time in which iron intake can be assessed to within 10% of the actual iron intake compared with food weights measurements.[39] Due to a wide variation in geographical location and limitation in workforce, our NAHSIT were unable to conduct longer dietary survey other than 24 hours. Finally, although not measured, the adiposity-related factors (e.g., leptin, adipokines), erythropoiesis (e.g., growth hormones and erythropoietin) and the iron regulatory element may play a role in iron metabolism through the action of hepcidin. Hepcidin is the master iron regulator which controls the iron uptake in the duodenum, iron release from macrophage and liver, and erythropoiesis process. Accumulation of iron in the liver may cause oxidative tissue damage by catalyzing the formation of free radicals. Oxidative stress and inflammation are known to activate ferritin at mRNA and protein levels,[20] and therefore, contribute to hyperferritinemia and disease risk.

In conclusion, our study confirms that SF is associated with an increased risk of MetS in healthy Taiwanese adults independent of obesity, inflammation and life-style factors.

ACKNOWLEDGMENTS

We express our sincere appreciation to the study participants. We also wish to thank staff from the Research Center for Humanities and Social Sciences, Center for Survey Research, Academia Sinica and directors of Dr Wen-Han Pan and Dr Su-Hao Tu.

Funding

Data analyzed in this paper were collected by the research project "The Third Nutrition and Health Survey in Taiwan (NAHSIT 2005-08, Adults)" sponsored by the Department of Health in Taiwan (DOH94-FS-6-4). Dr Jung-Su Chang was supported by grant TMU100-AE1-B09.

AUTHOR DISCLOSURES

The authors have declared that no competing interest exists.

REFERENCES

1. Bentley DP, Williams P. Serum ferritin concentration as an index of storage iron in rheumatoid arthritis. J Clin Pathol. 1974;27:786-8. doi: 10.1136/jcp.27.10.786
2. Fernandez-Real JM, Penarroja G, Castro A, Garcia-Bragado F, Hernandez-Aguado I, Ricart W. Blood letting in high-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function. Diabetes. 2002;51:1000-4. doi: 10.2337/diabetes.51.4.1000
3. 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. doi: 10.1210/jc.2008-1159
4. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao C et al. Plasma adiponectin levels in overweight and obese Asians. Obes Res. 2002;10: 1104-10. doi: 10.1038/oby.2002.150
5. Phelps G, Chapman I, Hall P, Braund W, Mackinnon M. Prevalence of genetic haemochromatosis among diabetic patients. Lancet. 1989;2:233-4. doi: 10.1016/S0140-6736(89)90426-1
6. Conte D, Manachino D, Colli A, Guala A, Aimo G, Andreoletti M et al. Prevalence of genetic hemochromatosis in a cohort of Italian patients with diabetes mellitus. Ann Intern Med. 1998;128:370-3.
7. McClain DA, Abraham D, Rogers J, Brady R, Gault P, Ajioka R et al. High prevalence of abnormal glucose homeostasis secondary to decreased insulin secretion in individuals with hereditary haemochromatosis. Diabetologia. 2006;49:1661-9. doi: 10. 1007/s00125-006-0200-0
8. Kwan T, Leber B, Ahuja S, Carter R, Gerstein HC. Patients with type 2 diabetes have a high frequency of the C282Y mutation of the hemochromatosis gene. Clin Invest Med. 1998;21:251-7.
9. Barton JC, Acton RT, So J, Chan S, Adams PC. Increased risk of death from iron overload among 422 treated probands with HFE hemochromatosis and serum levels of ferritin greater than 1000 mug/L at diagnosis. Clin Gastroenterol Hepatol. 2012;10:412-6. doi: 10.1016/j.cgh. 2011.11.032
10. Fernandez-Real JM, Lopez-Bermejo A, Ricart W. Iron stores, blood donation, and insulin sensitivity and secretion. Clin Chem. 2005;51:1201-5. doi: 10.1373/clinchem.2004.046847
11. Ford ES, Cogswell ME. Diabetes and serum ferritin concentration among U.S. adults. Diabetes Care. 1999;22:1978-83. doi: 10.2337/diacare.22.12.1978
12. Ryoo JH, Kim MG, Lee DW, Shin JY. The relationship between serum ferritin and metabolic syndrome in healthy Korean men. Diabetes Metab Res Rev. 2011;27:597-603. doi: 10.1002/dmrr.1211
13. Harris EL, McLaren CE, Reboussin DM, Gordeuk VR, BartonJ C, Acton RT et al. Serum ferritin and transferrin saturation in Asians and Pacific Islanders. Arch Intern Med. 2007;167:722-6. doi: 10.1001/ archinte.167.7.722

14. Zacharski LR, Ornstein DL, Woloshin S, Schwartz LM. Association of age, sex, and race with body iron stores in adults: analysis of NHANES III data. Am Heart J. 2000; 140:98-104. doi: 10.1067/mhj.2000.106646
15. Mendler MH, Turlin B, Moirand R, Jouanolle A M, Sapey T, Guyader D et al. Insulin resistance-associated hepatic iron overload. Gastroenterology. 1999; 117:1155-63. doi: 10.10 16/S0016-5085(99)70401-4
16. Aigner E, Theurl I, Theurl M, Lederer D, Haufe H, Dietze O et al. Pathways underlying iron accumulation in human nonalcoholic fatty liver disease. Am J Clin Nutr. 2008;87: 1374-83.
17. Tran TN, Eubanks SK, Schaffer KJ, Zhou CY, Linder MC. Secretion of ferritin by rat hepatoma cells and its regulation by inflammatory cytokines and iron. Blood. 1997;90:4979-86.
18. Cohen LA, Gutierrez L, Weiss A, Leichtmann-Bardoogo Y, Zhang DL, Crooks DR et al. Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. Blood. 2010;116:1574-84. doi: 10.1182/ blood-2009-11-253815
19. Orino K, Watanabe K. Molecular, physiological and clinical aspects of the iron storage protein ferritin. Vet J. 2008;178: 191-201. doi: 10.1016/j.tvjl.2007.07.006
20. Torti FM, Torti SV. Regulation of ferritin genes and protein. Blood. 2002;99:3505-16. doi: 10.1182/blood.V99.10.3505
21. Pan WH, Lee MS, Chuang SY, Lin YC, Fu ML. Obesity pandemic, correlated factors and guidelines to define, screen and manage obesity in Taiwan. Obes Rev. 2008;9(Suppl 1):22-31. doi: 10.1111/j.1467-789X.2007.00434.x
22. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 1986;124:17-27.
23. Wu SJ, Chang YH, Wei IL, Kao MD, Lin YC, Pan WH. Intake levels and major food sources of energy and nutrients in the Taiwanese elderly. Asia Pac J Clin Nutr. 2005;14:211-20.
24. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. JAMA. 1997;277:973-6. doi: 10.1001/jama.1997.03540360 041028
25. Exceutive 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. doi: 10.1001/jama.285.19.2486
26. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care. 2004;27:1182-6. doi: 10.2337/diacare.27.5. 1182
27. World Hhealth Organization. Thw Asia-Pacific persepective: redefining obesity and its treatment. Geneva: WHO; 2000.
28. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green L A, Izzo JL et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42:1206-52. doi: 10.1161/01.HYP.0000 107251.49515. c2
29. World Health Organization. The Asia-Pacific persepective: redefining obesity and its treatment. Geneva: WHO; 2000.
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. Wu H, Qi Q, Yu Z, Sun L, Li H, Lin X. Opposite associations of trunk and leg fat depots with plasma ferritin levels in middle-aged and older Chinese men and women. PLoS One. 2010;5:e13316. doi: 10.1371/journal.pone.0013 316
32. Ku BJ, Kim SY, Lee TY, Park KS. Serum ferritin is inversely correlated with serum adiponectin level: population-based cross-sectional study. Dis Markers. 2009; 27:303-10.
33. Fargnoli JL, Fung TT, Olenczuk DM, Chamberland JP, Hu FB, Mantzoros CS. Adherence to healthy eating patterns is associated with higher circulating total and high-molecular-weight adiponectin and lower resistin concentrations in women from the Nurses' Health Study. Am J Clin Nutr. 2008;88:1213-24.
34. 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. doi: 10.1172/JCI44421
35. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. Annu Rev Nutr. 2006;26:323-42. doi: 10.1146/ annurev.nutr.26.061505.111303
36. Rajpathak S, Ma J, Manson J, Willett WC, Hu FB. Iron intake and the risk of type 2 diabetes in women: a prospective cohort study. Diabetes Care. 2006;29:1370-6. doi: 10.2337/dc06-0119
37. Fleming DJ, Jacques PF, Dallal GE, Tucker KL, Wilson PW, Wood RJ. Dietary determinants of iron stores in a free-living elderly population: The Framingham Heart Study. Am J Clin Nutr. 1998;67:722-33.
38. Menzie CM, Yanoff LB, Denkinger BI, McHugh T, Sebring NG, Calis KA et al. Obesity-related hypoferremia is not explained by differences in reported intake of heme and nonheme iron or intake of dietary factors that can affect iron absorption. J Am Diet Assoc. 2008;108:145-8. doi: 10.1016 /j.jada.2007.10.034
39. Bingham S. The dietary assessment of individuals; methods, accuracy, new techniques and recommendations . Nutr Abstr Rev. 1987;7:706-42.

Original Article

Serum ferritin and risk of the metabolic syndrome: a population-based study

Jung-Su Chang PhD[1], Shiue-Ming Lin MSc[2], Tzu-chieh Huang MSc[1], Jane C-J Chao PhD[1], Yi-Chun Chen PhD[1], Wen-Harn Pan PhD[3,4], Chyi-Huey Bai PhD[2]

[1]*School of Nutrition and Health Sciences, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan. ROC*
[2]*Department of Public Health, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC*
[3]*Institute of Biomedical Science, Academia Sinica, Taipei, Taiwan, ROC.*
[4]*Institute of Population Health Sciences, National Health Research Institutes, Taiwan, ROC*

血清鐵蛋白與代謝症候群危險性：族群基礎研究

血清儲鐵蛋白可在健康成年人中反應體內鐵含量，但是最近的研究發現血清儲鐵蛋白為發炎指標因子。此外，血清儲鐵蛋白濃度也是預測代謝症候群的獨立危險因子。本次研究的主要目的是利用 2005 年至 2008 年國民營養調查資料庫分析臺灣成年人血中儲鐵蛋白指標與代謝症候群的相關性。本次研究總共分析 2654 位參加 2005-2008 國民營養調查，年齡≥19 歲的成年人。儲鐵蛋白平均值為 173±282 ng/mL (男性 229±349 ng/mL，女性 119±180 ng/mL)。代謝症候群的盛行率為 34.6% (男性 43.1%，女性 26.5%)。鐵質過量的盛行率為 18.6% (男性 21.5%，女性 15.8%)。缺鐵性貧血的盛行率為 5.2% (男性 2.0%，女性 8.3%)。血清儲鐵蛋白於最高三等分位的族群與最小三等分位的族群相比，攝取較多動物性蛋白質(p=0.001)與檳榔(p=0.004)以及較少量的碳水化合物(p<0.0001)。在多變項校正後的全人口分析中，血清儲鐵蛋白於最高三等分位的族群與最低三等分位的族群相比，得到代謝性症候群的危險對比值為 1.7 倍(OR=1.724，95% CI：1.21-2.45)。進一步分析儲鐵蛋白與代謝症候群的五個障害分群後發現，高儲鐵蛋白與得到任一障害都具有風險，其中以空腹血糖過高(OR=2.16，95% CI：1.75-2.65)及高三酸甘油酯(OR=2.58，95% CI：1.07-3.22)的風險為最高，且達顯著。總結而言，本研究顯示臺灣健康成年人中，血清儲鐵蛋白與代謝症候群發展可能有重要關聯。

關鍵字：代謝症候群、血清儲鐵蛋白、臺灣國民營養調查、膳食鐵攝取、肥胖