Maturitas 103 (2017) 3–7

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Serum ferritin level is positively associated with insulin resistance and metabolic syndrome in postmenopausal women: A nationwide population-based study

Mi-Ra Cho, Jin-Kyung Park, Won-Jun Choi, A-Ra Cho, Yong-Jae Lee*

Department of Family Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Ferritin
Inflammation
Insulin resistance
Metabolic syndrome
Menopause

ABSTRACT

Objective: Serum ferritin, a marker of iron metabolism, has recently emerged as a biomarker of chronic low-grade inflammation. After menopause, there is a remarkable increase in insulin resistance (IR) and metabolic syndrome (MetS), which is increasingly being viewed as an inflammatory disease. Thus, we examined the associations of serum ferritin with insulin resistance and MetS in postmenopausal women.

Methods: A nationwide cross-sectional study was conducted to examine the relationship between serum ferritin and IR and MetS in 2734 postmenopausal women using data from the 2010–2012 Korean National Health and Nutrition Examination Survey. The odds ratios (ORs) and 95% confidence intervals (CIs) for insulin resistance (HOMA-IR ≥ 75th percentile, 3.04) and MetS were calculated using multiple logistic regression analyses across serum ferritin quartiles (Q1, ≤ 36.25; Q2, 36.56–56.56; Q3, 56.57–85.98; and Q4 ≥ 85.99 ng/ml).

Results: The mean values of most cardiometabolic variables tended to increase proportionally with serum ferritin quartiles. The proportion of women with IR and MetS significantly increased in accordance with serum ferritin quartiles. Compared to individuals in the lowest quartile, the ORs (95% CIs) in the highest quartile were 2.06 (1.23–3.45) for IR and 1.92 (1.44–2.55) for MetS after adjusting for age, cigarette smoking, alcohol intake, and regular exercise.

Conclusion: Serum ferritin levels were positively and independently associated with IR and MetS in postmenopausal women. These findings suggest that serum ferritin level in postmenopausal women may help to identify the presence of IR and MetS.

1. Introduction

Metabolic syndrome (MetS) is characterized by a cluster of several cardiometabolic disorders including abdominal obesity, glucose intolerance, elevated blood pressure, and atherogenic dyslipidemia [1]. The prevalence of MetS in adults has increased globally in recent decades and this upward trend is becoming a significant threat to public health due to its association with increased risk for cardiovascular disease (CVD) and type 2 diabetes mellitus [2,3].

Although the pathophysiology of MetS is not fully understood, insulin resistance and subclinical low-grade inflammation play a key role in the development and progression of MetS [4,5]. Moreover, recent epidemiological studies have suggested that menopause is another factor contributing to MetS in women. Postmenopausal women are susceptible to increased weight gain and fat redistribution accompanied by marked changes in estrogen levels [6,7]. Decreased estrogen levels also influence lipid metabolism in vascular smooth muscle and the endothelium. Thus, menopause is characterized by various detrimental metabolic and vascular changes that lead to insulin resistance and MetS [8–11].

Ferritin is a major iron storage protein that plays an important role in the homeostasis of intracellular iron. Serum ferritin is secreted by all ferritin-producer cells and it is traditionally regarded as an indicator of iron deficiency or overload. Emerging evidence shows that serum ferritin levels are modestly increased in cardiometabolic diseases such as hypertension, type 2 diabetes and dyslipidemia, which are increasingly being seen as inflammatory diseases. In view of these novel findings, we hypothesized that there would be a positive association between serum ferritin and insulin resistance and metabolic syndrome in postmenopausal women. Thus, we sought to identify associations between serum ferritin levels and insulin resistance and MetS in a representative sample of postmenopausal women in Korea.

* Corresponding author at: Department of Family Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul, Republic of Korea.
E-mail address: ukyjhome@yuhs.ac (Y.-J. Lee).

http://dx.doi.org/10.1016/j.maturitas.2017.06.004
Received 20 April 2017; Received in revised form 25 May 2017; Accepted 2 June 2017

2. Methods

2.1. Survey overview and study population

This cross-sectional study used data obtained from the 2010–2012 Korean National Health and Nutrition Examination Survey (KNHANES-V), which was conducted by the Korea Centers for Disease Control and Prevention. The KNHANES is a nationwide, representative, population-based survey performed to evaluate the health and nutritional status of Koreans. The survey consists of a health interview survey, a nutrition survey, and a health examination survey. Sampling units were a stratified, multistage, probability-sampling design that was based on the sex, age and geographical area using household registries. A total 25,533 participants were included in the KNHANES-V. The present analysis was restricted to postmenopausal KNHANES-V participants (n = 6387). Menopause was defined by amenorrhea for 12 consecutive months in the absence of a clear biological or physiological cause. We excluded women with the following medical conditions: hormone replacement therapy, a previous history of hysterectomy, oophorectomy, thyroid disease, liver disease, chronic kidney disease, rheumatologic disease, coronary artery disease, cerebrovascular diseases or cancer. We also excluded individuals who had anemia, had not fasted for 12 h prior to blood sampling, and whose ferritin and MetS components, and/or insulin data were missing. Of the remaining participants, those with a leukocyte count < 3000 cells/μL or ≥10,000 cells/μL were excluded to rule out the possibility of infection, inflammatory disorder, or bone marrow suppressive illness. After these exclusions, a total 2754 postmenopausal women were included in our final analysis. The KNHANES received ethical approval by the Institutional Review Board of the Korea Centers for Disease Control and Prevention (IRB No: 2010-02-CON-04-P, 2011-04EXP-01-C, 2012-01CON-03-2C) and written consent was obtained from all of the participants. In addition, the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

2.2. Data collection

Trained medical staff obtained anthropometric measurements following a standardized procedure. Height was measured to the nearest 0.1 cm with a measuring rod attached to a balanced beam scale (Seca 225, Seca, Germany) using a Frankfurt horizontal plane with subjects standing as straight as possible and inhaling deeply. Body weight was measured using a digital electronic scale, with the subjects wearing light indoor clothing without shoes after adjusting the scale to zero before the measurement (GL-6000-20, G-tech, Korea). Body mass index (BMI) was calculated as the ratio of weight (kg) to height^2 (m^2). Waist circumference (WC) was measured by a trained technician to the nearest 0.1 cm in a horizontal plane at the level midway between the lower rib margin and the iliac crest after normal expiration. Smoking status was assigned to current smoker (a person who smokes cigarettes daily) or not current smoker (a person who has never smoked or who smoked in the past, but who does not smoke cigarettes currently). Alcohol drinking was categorized as two categories: current drinker (a person who drinks alcohol at least twice a month) or not current drinker (a person who drinks less than twice a month). Subjects completed the International Physical Activity Questionnaire (IPAQ) to determine the frequency of physical activity. Regular exercise was defined as physical activity ≥1 day/week regardless of exercise intensity. Systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) were assessed 3 times in the right upper arm using a standard mercury sphygmomanometer (Baumanometer, Baum, Copiague, NY), and the mean of the second and third blood pressure readings was used for analysis. Blood samples were obtained from the antecubital vein after each participant had fasted overnight for a minimum of 12 h. Leucocyte counts were determined by an automated blood cell counter (XE-2100D, Sysmex, Kobe, Japan). Fasting plasma glucose, total cholesterol, triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were measured using an Automatic Analyzer (Hitachi 7600, Hitachi Co., Tokyo, Japan). Fasting serum insulin and ferritin levels were assessed using a 1470 WIZARD gamma-counter (PerkinElmer, Turku, Finland).

2.3. Definition of insulin resistance and MetS

Insulin resistance was determined using the homeostasis model assessment (HOMA) for insulin resistance using the following formula: fasting plasma glucose (mg/dL) x fasting insulin (μIU/mL)/405. Insulin resistance was defined as the value greater than the 75th percentile of HOMA-IR ≥ 3.04 in the present study. Metabolic syndrome, which is a complex disorder, was defined as the presence of at least three of the

Table 1
Clinical and biochemical characteristics of the study population according to serum ferritin quartiles[a].

	Ferritin quartiles (ng/mL)					*P*-value[b]
	Total	Q1 (≤36.25)	Q2 (36.26–56.56)	Q3 (56.57–85.98)	Q4 (≥85.99)	
N	2734	683	684	683	684	
Age (years)	58.7 (0.4)	53.8 (0.8)	58.9 (0.6)	60.4 (0.6)	62.3 (0.6)	< 0.001
BMI (kg/m^2)	24.1 (0.1)	23.6 (0.1)	24.0 (0.1)	24.4 (0.1)	24.6 (0.1)	< 0.001
WC (cm)	81.9 (0.2)	80.2 (0.4)	81.3 (0.4)	82.5 (0.4)	83.6 (0.4)	< 0.001
SBP (mmHg)	124.2 (0.5)	120.9 (0.9)	123.4 (0.8)	126.5 (0.9)	126.2 (0.8)	< 0.001
DBP (mmHg)	76.1 (0.2)	75.1 (0.5)	75.6 (0.4)	77.1 (0.4)	76.5 (0.5)	0.019
FPG (mmol/L)	5.47 (0.02)	5.24 (0.04)	5.44 (0.05)	5.46 (0.04)	5.78 (0.07)	< 0.001
T-C (mmol/L)	5.24 (0.02)	5.17 (0.05)	5.24 (0.04)	5.25 (0.04)	5.30 (0.05)	0.286
TG (mmol/L)	1.53 (0.02)	1.43 (0.05)	1.47 (0.04)	1.51 (0.04)	1.72 (0.05)	0.001
HDL-C (mmol/L)	1.34 (0.01)	1.38 (0.03)	1.37 (0.02)	1.34 (0.03)	1.28 (0.03)	< 0.042
LDL-C (mmol/L)	3.23 (0.05)	3.15 (0.09)	3.21 (0.10)	3.26 (0.08)	3.29 (0.09)	< 0.001
HOMA-IR	2.6 (0.1)	2.3 (0.1)	2.4 (0.1)	2.5 (0.1)	3.1 (0.1)	0.006
Current smoking (%)	4.7 (0.5)	4.0 (0.9)	4.4 (1.0)	4.6 (1.2)	5.9 (1.2)	0.633
Alcohol drinking (%)	45.0 (1.2)	37.4 (2.3)	43.6 (2.5)	48.1 (2.5)	51.6 (2.4)	< 0.001
Regular exercise (%)	44.0 (1.3)	42.1 (2.3)	45.1 (2.4)	48.7 (2.4)	40.4 (2.4)	0.072
Diabetes mellitus (%)	12.8 (0.8)	9.0 (1.4)	10.7 (1.3)	13.4 (1.4)	18.3 (1.9)	< 0.001
Hypertension (%)	44.9 (2.3)	45.4 (4.1)	40.7 (4.3)	44.4 (4.8)	48.8 (4.1)	0.015

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; T-C, total cholesterol; TG, triglycerides; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance.

[a] Data are expressed as the mean (SE) or percentage.

[b] *P*-values were calculated using one-way ANOVA or chi-square test.