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Association of serum ferritin levels with metabolic syndrome and subclinical coronary atherosclerosis in postmenopausal Korean women

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ABSTRACT

Background: Several studies have suggested that increased iron storage may promote the development of atherosclerotic coronary heart disease. In the present study, we aimed to investigate the association of serum ferritin levels with metabolic syndrome and subclinical coronary atherosclerosis in postmenopausal women.
Methods: We examined 280 postmenopausal women who visited the health promotion center of our hospital for a routine health checkup. Metabolic syndrome was diagnosed by using the revised criteria of the National Cholesterol Education Program Adult Treatment Panel III. The presence of coronary atherosclerosis was indicated by 64-row multi-detector computed tomography.
Results: The proportion of postmenopausal women with metabolic syndrome and coronary atherosclerosis in the highest ferritin quartile was significantly higher compared with that in the lowest quartile. Serum ferritin levels were independently associated with the presence of metabolic syndrome (adjusted odds ratio for the highest quartile versus the lowest quartile, 3.313; 95% confidence interval, 1.251–8.775) and coronary atherosclerosis (adjusted odds ratio for the highest quartile versus the lowest quartile, 3.047; 95% confidence interval, 1.026–9.051), after adjusting for confounding factors.
Conclusions: Elevated serum ferritin levels may be associated with an increased risk of metabolic syndrome and subclinical coronary atherosclerosis in postmenopausal women.

1. Introduction

Coronary heart disease (CHD) is the leading cause of mortality in postmenopausal women. The loss of ovarian function and subsequent estrogen deprivation in these women has long been recognized to play an important role in promoting CHD [1–3]. Further, estrogen deficiency may increase the risk of CHD in a direct manner or by negatively influencing the established risk factors for CHD, such as being overweight or the presence of dyslipidemia, hypertension, and diabetes mellitus at the time of menopause [4].

The cessation of menstruation with a decline in estrogen production is a part of the natural aging process in women. Due to the absence of monthly bleeding after the later perimenopausal stage, iron accumulates in the body [5,6]. This accumulation results in a two- to three-fold increase in the levels of serum ferritin, which are known to reflect body iron stores, during menopausal transition [7,8]. Although these increased serum ferritin levels are considered to be within the normal physiologic range, they may be associated with various health problems in postmenopausal women [7].

Iron plays an important role in many essential cellular functions such as oxygen sensing and transport [8]. Nevertheless, several studies have suggested that increased iron storage may promote the development of atherosclerotic CHD [9–13]. This association is known as the iron hypothesis. Excessive iron in tissues may catalyze the formation of highly reactive forms of oxygen free radicals, which can cause oxidation of low density lipoprotein (LDL), a trigger for development of atherosclerotic CHD. In fact, a few studies demonstrated that postmenopausal women have elevated serum levels of oxidized LDL [14,15]. Although estrogen deficiency has been established as a risk factor for CHD, increased iron levels remain an unexplored risk factor of CHD in postmenopausal women. Moreover, little is known about the association

Abbreviations: MDCT, multi-detector computed tomography.

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between increased ferritin levels and the risk of coronary atherosclerosis in postmenopausal women.

2. Materials and methods

2.1. Participants

The study was performed at the Gangnam Severance Hospital, Seoul, Korea, from January 2008 to April 2010, and approved by the institutional review board of Gangnam Severance Hospital.

We retrospectively reviewed the medical records of women aged > 40 years who had visited the health promotion center for a routine checkup. A standard questionnaire was used to obtain information on age, smoking history, alcohol consumption, medical history, and medications used. The body weight and height were measured with participants wearing light clothing. The participant's blood pressure was measured after at least 5 min of rest in the sitting position using an automated device (TM-2665P, A&D Co., Ltd.).

The study included data from postmenopausal women who underwent 64-row multi-detector computed tomography (MDCT). Menopause was defined retrospectively as the time of the last menstrual period followed by 12 months of amenorrhea and was confirmed by the presence of serum follicle-stimulating hormone (FSH) levels of >40 IU/l. None of the participants had a current smoking status. Participants who had cardiovascular disease or any malignancy, or those receiving hormone therapy or medication that would directly affect the serum ferritin levels including iron supplementations or blood transfusions were excluded from the study. Finally, 280 postmenopausal women were included in our analysis.

The participants were divided into drinkers and nondrinkers, depending on the frequency of consuming alcohol. If one consumed alcohol ≥ once in a week, we considered that person as a drinker. In addition, participants were divided into regular and non-regular exercise groups, depending on the amount of physical activity. An individual who performed regular exercise was defined as a person who exercised ≥ 3 times per week for >30 min.

2.2. Blood analysis

After a 12-h overnight fasting, blood samples were collected from participants from the antecubital vein. Levels of fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured using a 7600-110 Chemistry Autoanalyzer (Hitachi, Tokyo, Japan). Serum ferritin levels were measured by immunoradiometric assay using a 1470 Wizard gamma-counter (Perkin-Elmer, Turku, Finland). The CV for serum ferritin was <4.0%.

2.3. Coronary atherosclerosis assessment

Cardiac computed tomography (CT) was performed using a 64-row MDCT scanner (Philips Brilliance 64; Philips Medical System) as previously described [16]. A β-blocker (40–80 mg of propranolol hydrochloride) was administered orally 1 h before the scan to decrease the heart rate in women with a heart rate of ≥70 beats/min. We used a prospective electrocardiography-gating protocol that involved a step-and-shoot technique. The scanning parameters were as follows: step-and-shoot axial scanning direction, 400-ms gantry rotation time, 120 kV, 210 mA, 64 × 0.625-mm slice collimation, and 2-mm table feed per rotation, with the center of the imaging window set at 75% of the R–R interval. Image reconstruction was performed on the scanner's workstation using commercially available software (Extended Brilliance Workstation; Philips Medical System). Coronary atherosclerosis was defined as any size of calcified or non-calcified atherosclerotic plaque with luminal narrowing.

2.4. Metabolic syndrome

Metabolic syndrome was diagnosed using the definition of the National Cholesterol Education Program Adult Treatment Panel III criteria, with minor modifications [17]. Because waist circumference was not assessed in our participants, body mass index (BMI) was used instead of waist circumference, as in previous studies [18,19]. Participants with ≥3 of the following 5 components were classified as having metabolic syndrome: (1) obesity (body mass index [BMI] ≥ 25 kg/m^2), (2) low HDL cholesterol level (<50 mg/dl), (3) elevated TG level (≥150 mg/dl) or current antidyslipidemic medication use, (4) elevated blood pressure (BP; systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg) or current use of antihypertensive medication, and (5) high glucose level (fasting glucose level ≥ 100 mg/dl) or current use of insulin or oral hypoglycemic agents.

2.5. Statistical analysis

Data are expressed as the mean ± SD for continuous variables or n (%) for categorical variables. Clinical and laboratory characteristics of the participants according to ferritin quartiles were compared using one-way analysis of variance (ANOVA) with a post hoc Scheffe test for continuous variables and the χ^2 test for categorical variables. The χ^2 test was also used to compare the proportion of patients with metabolic syndrome, its components, and coronary atherosclerosis according to serum ferritin quartiles.

Multiple logistic regression analysis was used to investigate the risk of metabolic syndrome according to the quartile of serum ferritin levels. The analysis was adjusted for age (continuous); alcohol ingestion (categorical); exercise (categorical); hemoglobin levels (categorical); liver enzyme levels (aspartate aminotransferase [AST] and alanine transaminase [ALT] levels, continuous); and hormone status (continuous) including estradiol (E_2), total testosterone, FSH, and thyroid-stimulating hormone (TSH).

Multiple logistic regression analysis was also used to evaluate the risk of coronary atherosclerosis according to the quartile of serum ferritin levels. Age (continuous), alcohol ingestion (categorical), exercise (categorical), obesity (yes/no), elevated BP (systolic BP/diastolic BP ≥ 130/85 mm Hg or current use of antihypertensive medication, yes/no), high glucose level (fasting glucose ≥ 100 mg/dl or current use of insulin or oral hypoglycemic agents, yes/no), low HDL cholesterol level (HDL cholesterol < 50 mg/dl, yes/no), high TG level (triglyceride ≥ 150 mg/dl or current antidyslipidemic medication use, yes/no), hemoglobin level (continuous) and hormone status were used for confounding factors.

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc.). A P value of <0.05 was considered statistically significant.

3. Results

Table 1 shows the clinical and laboratory characteristics of participants according to their serum ferritin level quartiles. There was no significant difference in age, systolic blood pressure (SBP), diastolic blood pressure (DBP), and lipid profiles, including total cholesterol, LDL cholesterol, and triglycerides, among the 4 groups. The average BMI and hemoglobin levels were significantly higher among women with serum ferritin levels in the fourth quartile than among women with serum ferritin levels in the first quartile (Table 1).

Table 2 shows the proportion of patients with metabolic syndrome, its components, and coronary atherosclerosis according to the ferritin level quartiles. Increasing ferritin level quartiles were associated with a higher proportion of postmenopausal women with metabolic syndrome, obesity, and low HDL cholesterol. The proportion of postmenopausal women with coronary atherosclerosis was significantly higher in the fourth quartile than in the first quartile.