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Original Article

Serum ferritin levels and polycystic ovary syndrome in obese and nonobese women

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ABSTRACT

Objective: The aim of this study is to evaluate serum ferritin levels and polycystic ovary syndrome (PCOS)-related complications in obese and nonobese women.
Materials and methods: This retrospective study included 539 (286 with PCOS and 253 without PCOS).
Results: Serum ferritin correlated with menstrual cycle length, sex hormone-binding globulin, total testosterone, androstenedione, triglyceride, and total cholesterol in both obese and nonobese women. Obese women with high ferritin levels exhibited higher insulin resistance, impaired glucose tolerance, and liver enzymes (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase) than obese women with low ferritin levels. However, among nonobese women, insulin resistance and risk of diabetes were not significantly different between the high and low ferritin groups. Independent of obesity, hypertriglyceridemia was the major metabolic disturbance observed in women with elevated serum ferritin levels.
Conclusion: Elevated serum ferritin levels are associated with increased insulin resistance and risk of diabetes in obese women but not in nonobese women. However, higher serum ferritin levels were correlated with a greater risk of hyperglyceridemia in both obese and nonobese women. Therefore, hypertriglyceridemia in women with PCOS might be associated with iron metabolism.

Introduction

Ferritin is a ubiquitous intracellular protein that is essential for the regulation of iron homeostasis. The serum ferritin level is widely used as a clinical biomarker to estimate body iron status. Iron is a strong pro-oxidant, and high body iron levels are associated with an increased level of oxidative stress, which may elevate the risk of type 2 diabetes [1]. Mildly elevated body iron stores are associated with statistically significant increases in glucose homeostasis indices [2,3]. Furthermore, patients with elevated iron stores present both insulin resistance and metabolic alterations that put them at increased risk for cardiovascular disease (CVD) [4,5].

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects 6–7% of premenopausal women [6]. PCOS is clinically diagnosed by hyperandrogenism and chronic anovulation; however, its morbidity includes insulin resistance, type 2 diabetes mellitus, hypertension, cardiovascular disease, and infertility [7]. Increased serum ferritin levels are frequently observed in women with PCOS [8]. An excess of androgen and menstrual dysfunction are correlated with ferritin levels in premenopausal women [9]. Factors contributing to potential iron overload in women with PCOS include the iron-sparing effect of chronic menstrual dysfunction, insulin resistance, and a decrease in hepcidin, which leads to increased iron absorption [10].

Serum ferritin concentrations differ significantly according to sex, body status, and ethnicity [3,11,12]. A growing number of studies suggest a potential link between obesity and altered iron

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metabolism [11]. Furthermore, the association between serum ferritin levels and certain diagnostic components of metabolic syndrome might be different in men and women [12]. Menstruating women are at risk for iron deficiency; however, obese menstruating women are at low risk of depleting their iron stores [13]. Recently, we reported that obesity is the main factor associated with the prevalence of insulin resistance, impaired glucose tolerance, and metabolic syndrome in women with PCOS [14,15]. The correlation between serum ferritin levels and metabolic components in obese and nonobese women is not well understood. Therefore, we conducted this retrospective study to evaluate the relationship between ferritin levels, insulin resistance, metabolic disturbances, and PCOS-related syndrome among obese and nonobese women.

Materials and methods

This study was approved by the Taipei Medical University Joint Institutional Review Board (Taipei, Taiwan), and registered in the Protocol Registration System of ClinicalTrials.gov (identifier NCT01600833).

We retrospectively reviewed the medical records of female patients who visited our clinic from January 1, 2008 to November 30, 2011. The chief complaints of these patients included menstrual disturbance, dysmenorrhea, infertility, and acne/hirsutism. The following were excluded: (1) women who had been diagnosed with congenital adrenal hyperplasia, androgen-secreting tumor, Cushing's syndrome, or disorders of the uterus; (2) women who experienced menarche <3years before the evaluation or those who were older than 46 years; and (3) women who received hormones or drugs for major medical diseases. A total of 639 women were initially screened. One hundred women were excluded due to hyperprolactinemia ($n = 62$), ovarian failure ($n = 18$), and insufficient data ($n = 20$). Overall, 539 women were included in this study.

Medical histories included detailed menstrual and medical/surgical records as well as anthropometric measurements. Biochemical hyperandrogenemia was defined as total serum testosterone ≥0.8 ng/mL (normal range for female adult 0.1–0.8 ng/mL), androstenedione ≥ 2.99 ng/dL (normal range for female adult 0.10–2.99 ng/mL), or ≥ 275 μg/L [16]. Hirsutism was defined as a modified Ferriman–Gallwey score ≥6. The number of menstrual cycles during the previous year was recorded. Menstrual interval was defined as 365 divided by the number of menstrual cycles in the previous year. Oligomenorrhea/amenorrhea was defined as a menstrual interval of >35 days or fewer than 10 menstruation cycles in the previous year. Obesity was defined as having a body mass index ≥25 kg/m^2. The definition of polycystic ovaries was previously described [17].

PCOS was diagnosed according to the Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome [18], which require the presence of hyperandrogenism and ovarian dysfunction.

Serum ferritin levels were obtained in all 539 women, and the median level was 45.5 ng/mL. To evaluate further the clinical and biochemical characteristics of women with different levels of serum ferritin, the study cases were classified into the following subgroups: high ferritin group (ferritin ≥45.5 ng/mL, $n = 270$) and low ferritin group (ferritin <45.5 ng/mL, $n = 269$).

Metabolic syndrome (2005 National Cholesterol Education Program Adult Treatment Panel III) was defined as the presence of at least three of the following criteria: abdominal obesity, hypertriglyceridemia (triglycerides ≥ 150 mg/dL), serum high-density lipoprotein <50 mg/dL, hypertension, and fasting plasma glucose ≥ 100 mg/dL.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL, USA). We evaluated the correlation between serum ferritin levels and related parameters with Pearson's correlation coefficients using the two-tailed method (Table 1). In Table 2, data are presented as the means ± standard deviation. We used the Chi-square test and Fisher exact test to compare categorical variables, and ANOVA was used to compare continuous variables. Differences between the groups were considered to be significant at $p < 0.05$.

Results

Table 1 illustrates the correlation between serum ferritin levels and related parameters in all, obese, and nonobese women. Serum ferritin correlated with menstrual cycle length, sex hormone-binding globulin, total testosterone, androstenedione, triglyceride,

Table 1
Correlation of ferritin with clinical and biochemical insulin resistance and metabolic syndrome ($n = 539$).

	Total ($n = 539$)		Obese ($n = 233$)		Nonobese ($n = 306$)	
	Correlation	p	Correlation	p	Correlation	p
Parameters correlated with ferritin both in obese and nonobese women						
Menstrual cycle length	0.320	<0.001*	0.378	<0.001*	0.124	0.031*
Sex hormone-binding globulin	−0.249	<0.001*	−0.192	0.003*	−0.197	0.001*
Total testosterone	0.221	<0.001*	0.151	0.021*	0.224	<0.001*
Androstenedione	0.181	<0.001*	0.164	0.012*	0.257	<0.001*
Cholesterol	0.165	<0.001*	0.158	0.016*	0.129	0.026*
Triglyceride	0.334	<0.001*	0.264	<0.001*	0.324	<0.001*
Parameters correlated with ferritin both in obese but not nonobese women						
Fasting insulin	0.257	<0.001*	0.233	0.002*	0.009	0.872
Fasting glucose	0.270	<0.001*	0.258	<0.001*	0.092	0.115
HOMA-IR	0.329	<0.001*	0.306	<0.001*	0.043	0.455
Hemoglobin A1c	0.284	<0.001*	0.258	0.001*	0.068	0.289
GOT	0.561	<0.001*	0.621	<0.001*	0.048	0.411
High-density lipoprotein	−0.196	<0.001*	−0.137	0.037*	−0.045	0.437
Body mass index	0.271	<0.001*	0.149	0.023*	0.044	0.442
High-sensitivity C-reactive protein	0.248	<0.001*	0.229	<0.001*	0.074	0.202
Systolic pressure	0.210	<0.001*	0.167	0.013*	−0.049	0.397
Diastolic pressure	0.220	<0.001*	0.175	0.009*	−0.040	0.497

*$p < 0.05$.
GOT = glutamic oxaloacetic transaminase; HOMA-IR = homeostasis model assessment insulin resistance index.