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

Po-Chun Ko^{a,1}, Shih-Yi Huang^{b,1}, Ching-Hung Hsieh^c, Ming-I Hsu^{a,*,2}, Chun-Sen Hsu^{a,2}^a Department of Obstetrics and Gynaecology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan^b School of Nutrition and Health Sciences, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan^c Department of Obstetrics and Gynecology, Clinic of Fu Jen Catholic University, Taipei, Taiwan

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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.

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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

* Corresponding author. Department of Obstetrics and Gynaecology, Wan Fang Hospital, Taipei Medical University, 111 Section 3, Xinglong Road, Taipei 11696, Taiwan.

E-mail address: hsumingi@yahoo.com.tw (M.-I. Hsu).

¹ P.C. Ko and S.Y. Huang contributed equally to this work.

² M.I. Hsu and C.S. Hsu contributed equally to this work.

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 non-obese 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 <3 years 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 μ g/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/m². 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 \pm 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.

Table 2

A comparison of biochemical characteristics of obese and non-obese women with high and low ferritin.

	Obese			Non-obese		
	Low ferritin ^a	High ferritin ^a	<i>p</i>	Low ferritin ^a	High ferritin ^a	<i>p</i>
Case number	89	144		180	126	
Ferritin (ng/mL)	25.1 ± 12.5	117.4 ± 99.2	<0.001*	25.6 ± 12.1	82.0 ± 38.8	<0.001*
Age (y/o)	29.0 ± 6.7	27.8 ± 6.5	0.180	27.6 ± 6.3	26.5 ± 6.6	0.143
Menstrual cycle length (days)	64.1 ± 64.1	113.4 ± 116.0	<0.001*	61.1 ± 66.5	83.9 ± 81.4	0.008*
BMI ^a (kg/m ²)	31.3 ± 5.2	31.3 ± 4.8	0.951	20.5 ± 2.1	20.6 ± 2.0	0.579
PCOS	44%	62%	0.007*	44%	63%	0.001*
Hyperandrogenism	53%	69%	0.014*	55%	69%	0.013*
Polycystic ovaries	57%	63%	0.433	56%	58%	0.752
Oligo/amenorrhea	66%	76%	0.094	52%	74%	<0.001*
SHBG ^a (nmol/L)	32.0 ± 17.2	23.0 ± 12.9	<0.001*	58.9 ± 28.8	47.4 ± 26.9	<0.001*
hsCRP ^a (mg/dL)	0.30 ± 0.31	0.47 ± 0.44	0.012*	0.10 ± 0.22	0.17 ± 0.37	0.051
Systolic pressure (mmHg)	120.6 ± 15.5	125.4 ± 18.7	0.051	106.8 ± 13.7	104.9 ± 11.9	0.225
Diastolic pressure (mmHg)	83.6 ± 11.8	87.1 ± 14.2	0.062	71.9 ± 10.0	71.4 ± 9.9	0.688
Anthropometric measurements						
Weight (kg)	81.8 ± 15.1	81.3 ± 13.0	0.766	52.5 ± 6.0	52.9 ± 6.3	0.496
Height (cm)	161.0 ± 5.3	161.0 ± 5.7	0.444	160.0 ± 4.7	160.0 ± 5.7	0.908
Waist (cm)	96.6 ± 12.6	98.2 ± 12.0	0.331	73.2 ± 6.9	73.8 ± 7.1	0.446
Hip (cm)	111.0 ± 9.1	109.3 ± 8.7	0.154	91.7 ± 5.3	92.0 ± 6.3	0.685
Waist to hip ratio	0.87 ± 0.08	0.90 ± 0.08	0.007*	0.80 ± 0.08	0.80 ± 0.08	0.591
Androgens						
Total testosterone (ng/mL)	0.64 ± 0.25	0.76 ± 0.33	0.003*	0.51 ± 0.24	0.62 ± 0.30	0.001*
Androstenedione (ng/mL)	2.5 ± 1.3	2.9 ± 1.3	0.017*	2.4 ± 1.1	3.0 ± 1.4	<0.001*
Free androgen index ^a	10.1 ± 9.3	15.0 ± 10.2	<0.001*	3.9 ± 3.1	6.2 ± 5.2	<0.001*
DHEAS ^a (ng/dL)	185 ± 82	210 ± 118	0.076	186 ± 99	195 ± 101	0.448
17-OH PRG ^a (ng/dL)	0.9 ± 0.6	1.1 ± 0.7	0.131	1.1 ± 0.9	1.3 ± 1.0	0.283
Insulin sensitivity and glucose tolerance						
Fasting insulin (uIU/mL)	16.1 ± 11.7	21.9 ± 18.7	0.010*	8.8 ± 10.8	8.5 ± 4.5	0.705
Fasting glucose (mg/dL)	94.0 ± 10.0	101.1 ± 27.5	0.020*	87.7 ± 7.3	89.4 ± 16.3	0.235
2-hour glucose (mg/dL)	116.0 ± 33.9	148.8 ± 64.0	<0.001*	98.0 ± 23.9	100.8 ± 33.7	0.404
Hemoglobin A1c, %	5.5 ± 0.3	5.9 ± 1.0	0.004*	5.4 ± 0.3	5.4 ± 0.4	0.646
HOMA-IR ^a	3.8 ± 3.0	5.7 ± 5.5	0.004*	1.9 ± 2.1	1.9 ± 1.1	0.866
Impaired glucose tolerance, %	16%	32%	0.009*	6%	5%	0.603
Diabetes mellitus, %	3%	16%	0.003*	1%	2%	0.378
Hormonal components						
LH (mIU/mL)	7.8 ± 6.1	9.2 ± 8.8	0.215	10.3 ± 13.3	11.2 ± 8.3	0.487
FSH (mIU/mL)	5.9 ± 2.1	5.8 ± 1.7	0.831	6.5 ± 2.4	7.0 ± 2.2	0.081
TSH (mIU/mL)	1.9 ± 1.2	2.2 ± 1.3	0.121	1.8 ± 1.1	2.0 ± 1.2	0.311
Prolactin (mIU/mL)	14.1 ± 5.1	13.3 ± 5.2	0.227	14.2 ± 5.3	14.2 ± 5.4	0.999
Liver function						
GOT ^a (IU/l)	24.0 ± 10.1	32.0 ± 20.9	0.001*	20.5 ± 6.9	20.5 ± 5.6	0.938
GPT ^a (IU/l)	24.0 ± 13.9	41.5 ± 34.5	<0.001*	16.7 ± 9.7	17.9 ± 9.3	0.291
Lipid profiles and blood pressure						
Cholesterol (mg/dL)	184.4 ± 32.4	194.7 ± 39.3	0.039*	179.0 ± 33.1	186.0 ± 32.3	0.069
Triglycerides (mg/dL)	103.6 ± 60.5	142.6 ± 125.3	0.006*	60.6 ± 28.0	78.6 ± 71.0	0.003*
HDL ^a (mg/dL)	44.8 ± 12.5	42.6 ± 11.3	0.156	60.0 ± 14.8	59.8 ± 15.1	0.914
LDL ^a (mg/dL)	118.7 ± 26.5	125.7 ± 32.0	0.087	100.0 ± 28.6	105.2 ± 28.4	0.118
Metabolism						
Metabolic syndrome	43%	66%	<0.001*	3%	6%	0.337
Hypertension	47%	53%	0.354	11%	12%	0.695
HDL ^a < 50 mg/dl	74%	83%	0.091	25%	26%	0.914
Triglycerides ≥ 150 mg/dL	12%	32%	0.001*	1%	6%	0.012*
Waist > 80 cm	94%	96%	0.622	19%	19%	0.964
FPG ^a ≥ 100 mg/dL	19%	36%	0.007*	5%	7%	0.331

Note: Data are either mean ± SD or are percentage; * *p* < 0.05.

^a Low ferritin = serum ferritin level < 45.5 ng/mL; high ferritin = serum ferritin level ≥ 45.5 ng/mL; BMI = body mass index; PCOS = polycystic ovary syndrome; PCOM = polycystic ovary morphology; SHBG = sex hormone-binding globulin; hsCRP = high-sensitivity C-reactive protein; free androgen index (FAI) = T (nmol/L) × 100/SHBG (nmol); DHEA-S = dehydroepiandrosterone sulfate; 17-OH PRG = 17- α -OH progesterone; HOMA-IR = homeostasis model assessment insulin resistance index; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; FPG = fasting plasma glucose.

and total cholesterol in both obese and nonobese women. Fasting insulin, fasting glucose, glycated hemoglobin, homeostasis model assessment insulin resistance index, glutamic oxaloacetic transaminase, and high-density lipoprotein were correlated with serum ferritin levels among obese women, but not among nonobese women. However, a strong correlation between serum ferritin levels and triglycerides was observed in both obese and nonobese women. Obese women had significantly higher serum ferritin (82.1 ± 90.3 vs. 48.8 ± 38.3 ; *p* < 0.001) and hs-CRP (0.39 ± 0.41 vs. 0.13 ± 0.30 ; *p* < 0.001) levels than nonobese women.

Table 2 compares the clinical and biochemical characteristics of women with low and high ferritin level in the obese and nonobese subgroups. Women with high ferritin levels had a greater risk of PCOS and hyperandrogenism than women with low ferritin levels. Furthermore, women with high ferritin levels had longer menstrual interval, lower sex hormone-binding globulin, and higher serum androgens and triglycerides than women with low ferritin levels in both obese and nonobese women. Obese women with high ferritin levels had higher insulin resistance, impaired glucose tolerance, and liver enzymes than obese women with low ferritin levels.

However, among nonobese women, insulin resistance and metabolic disturbances were not significantly different between the high and low ferritin groups.

Discussion

Ferritin is the cellular storage protein for iron, and reduced serum ferritin provides unequivocal evidence of diminished iron stores. In women, a serum ferritin concentration ≥ 150 ng/mL is usually defined as hyperferritinemia [19], but increased serum ferritin concentrations in nonpathological conditions, reflecting subclinical iron overload, are associated with insulin resistance and an increased risk of type 2 diabetes mellitus [3]. This is probably due to the fact that the normal ranges of serum ferritin are too wide, and the criteria for iron overload are too high [20]. To study the effect of serum ferritin levels in this study, women were classified into high and low serum ferritin groups according to the median ferritin levels in our samples.

Obese women tended to have higher hemoglobin and ferritin concentrations and lower transferrin saturation compared with the nonobese women [11,21]. Previous studies have reported that ferritin is elevated in inflammatory conditions, even in the presence of true iron deficiency [22]. To consider whether body status may impact the pathological effects of ferritin, we separately analyzed obese and nonobese women. Although high serum ferritin was associated with insulin resistance and metabolic disturbance in obese women, we did not observe any association between serum ferritin levels and parameters of insulin resistance in nonobese women. This result could explain why a study of nonobese Korean women determined no significant differences in the homeostasis model assessment insulin resistance index in various serum ferritin levels [23].

Prolonged menstrual cycle length was correlated with higher serum ferritin levels. Factors contributing to potential iron overload might result from reduced menstrual losses, secondary to oligo- or amenorrhea, or from hyperinsulinism, secondary to insulin resistance, because insulin favors the intestinal absorption and the tissue deposition of iron [10]. Regular blood loss during menstruation is a physical characteristic of reproductive-aged women. Serum ferritin concentration is directly related to reticuloendothelial iron stores, and normally, 1 μ g/L of serum ferritin corresponds to approximately 8 mg of storage iron [22]. Our results indicate that prolonged menstrual cycle length is an important factor for iron overload resulting from reduced menstrual losses in reproductive-aged women. Furthermore, serum ferritin levels and disturbances in insulin resistance were observed in obese women, but not nonobese women. However, the pathogenesis of increased iron stores on insulin resistance among obese and nonobese premenopausal women might be different. Increased iron stores in obese women could be a consequence of insulin resistance [24], whereas reduced menstrual losses in women with oligomenorrhea might be a major factor contributing to increased iron stores in nonobese women.

Independent of obesity, women with higher ferritin levels have a greater risk of hypertriglyceridemia. The mechanism underlying increased serum ferritin hypertriglyceridemia is not clear. Iron accumulation results from the downregulation of the iron-export protein, ferroportin-1, which increases the levels of cytokines, such as tumor necrosis factor- α . Tumor necrosis factor- α is involved in hyperferritinemia, and the observed high ferritin concentration could be an inflammatory manifestation. A study by Mateo-Gallego et al [25] suggested that genetic mechanisms underlying hypertriglyceridemia also favor iron overload. An elevated triglyceride level is a predictor of cardiovascular disease (CVD) in women [25–27]. The American Heart Association recently issued a

scientific statement that enforced the pivotal role of triglycerides in lipid metabolism, reaffirming that triglycerides are not directly atherogenic, but represent an important biomarker of CVD risk [28]. In terms of metabolic syndrome, the risk of hypertriglyceridemia was significantly increased in women with high ferritin levels. A previous study reported that elevated serum ferritin levels may be employed as a marker of metabolic syndrome in nonobese women [23]; however, the association between serum triglycerides and ferritin might be used to understand metabolic disturbances in nonobese women with elevated ferritin levels. Because serum ferritin levels might be a good indicator of menstrual pattern and metabolic disturbance, measuring serum ferritin levels might be useful for evaluating cardiovascular risk in women of reproductive age.

There are several limitations to our study. Serum ferritin concentrations differ significantly according to sex, body status, and ethnicity. Therefore, we classified our population into two subgroups (high and low ferritin groups) based on the median (45.5 ng/mL) of our data. The cut-off points employed in this study to determine higher and lower ferritin levels might not apply to other studies. This is a cross-sectional, retrospective study, and the participants were Taiwanese patients who visited our reproductive endocrine outpatient department during a fixed interval. The average body weight of Taiwanese women is lower than that of western women; therefore, our results should be applied to the general population with caution.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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