Body Iron Stores Are Increased in Overweight and Obese Women With Polycystic Ovary Syndrome

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Increased body iron stores are associated with insulin resistance and type 2 diabetes. In conceptual agreement, increased serum ferritin levels are positively associated with the prevalence of the metabolic syndrome in men and adult pre- and postmenopausal women (1) and with an increased risk of type 2 diabetes in both men (2) and women (2,3). Given that insulin resistance and an increased risk of type 2 diabetes are frequent in patients with polycystic ovary syndrome (PCOS) (4,5), we hypothesize that body iron stores might be especially increased in these women.

RESEARCH DESIGN AND METHODS

— We studied 78 patients with PCOS and 43 nonhyperandrogenic control subjects matched for BMI and degree of obesity (6). Women were phenotyped to determine clinical, anthropometrical hormonal and metabolic variables as described previously (7). Serum ferritin and C-reactive protein (CRP) concentrations were measured by automated immunochemiluminescence (Immulite 2000 Ferritin and High Sensitivity CRP; Diagnostic Products, Los Angeles, CA) with lower limits of detection of 0.9 pmol/l and 0.1 mg/l, respectively. None of the women had a history of abnormal glucose tolerance or had taken insulin sensitizers in the previous 6 months. The ethics committee of Hospital Ramón y Cajal approved the study, and informed consent was obtained from all participants.

Data were analyzed by general linear model after ensuring a normal distribution of the variables by logarithmic or square-root transformations, introducing PCOS or control status and degree of obesity or abnormal glucose tolerance as independent variables and age as a covariate. $P < 0.05$ was considered statistically significant.

RESULTS

— Ferritin levels were increased in overweight and obese women with PCOS compared with overweight and obese control subjects, given that a significant interaction ($F = 3.694$, $P = 0.028$) between PCOS status and the degree of obesity was found (Fig. 1*A*). However, no difference independent of obesity was found between the PCOS patients and the control subjects ($F = 1.395$, $P = 0.240$), and no difference independent of PCOS status was found between the lean, overweight, and obese women ($F = 2.244$, $P = 0.111$) (Fig. 1*A*).

Ferritin is considered an inflammatory marker. We therefore measured the serum levels of the inflammatory marker CRP in these women to assess the potential confounding effect of chronic inflammation on the observed increase in ferritin levels.

CRP levels increased steadily from lean women to overweight and obese individuals, irrespective of their PCOS or control status ($F = 29.285$, $P < 0.001$), and no differences were found between PCOS patients and control subjects ($F = 0.545$, $P = 0.462$), suggesting that the increased ferritin levels observed in overweight and obese PCOS patients were independent from chronic inflammation (Fig. 1*B*).

Undiagnosed type 2 diabetes (2-h oral glucose tolerance test serum glucose ≥11.1 mmol/l) was present in three PCOS patients (3.8%) and in no control subjects, whereas glucose intolerance (2-h oral glucose tolerance test serum glucose 7.8–11.0 mmol/l) was found in six PCOS patients (7.7%) and in three control subjects (7.0%). All of the women presenting with a disorder of glucose tolerance were overweight or obese. Ferritin levels were increased in the 12 women with abnormal glucose tolerance compared with the 109 euglycemic subjects ($F = 5.468$, $P = 0.021$), irrespective of PCOS or control status ($F = 0.289$, $P = 0.592$) (Fig. 1*C*).

Because the periodic blood loss resulting from regular menstruation protects premenopausal women against excessive iron accumulation, oligomenorrhea and amenorrhea might contribute to the increase in ferritin observed in overweight and obese PCOS patients. When studying PCOS patients and control subjects as a whole, ferritin levels were increased in women with amenorrhea compared with women with regular menstrual cycles, whereas women with oligomenorrhea presented with intermediate values (means ± SD: amenorrhea 159 ± 144 pmol/l, oligomenorrhea 114 ± 95 pmol/l, and regular menstrual cycles 83 ± 51 pmol/l; $F = 3.295$, $P = 0.040$).

CONCLUSIONS

— Our present findings suggest for the first time that increased body iron stores, expressed as increased serum ferritin concentrations, are present in overweight and obese women with PCOS but not in lean patients. These increased iron stores might contribute to the insulin resistance and β-cell dysfunc-

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Abbreviations: CRP, C-reactive protein; PCOS, polycystic ovary syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

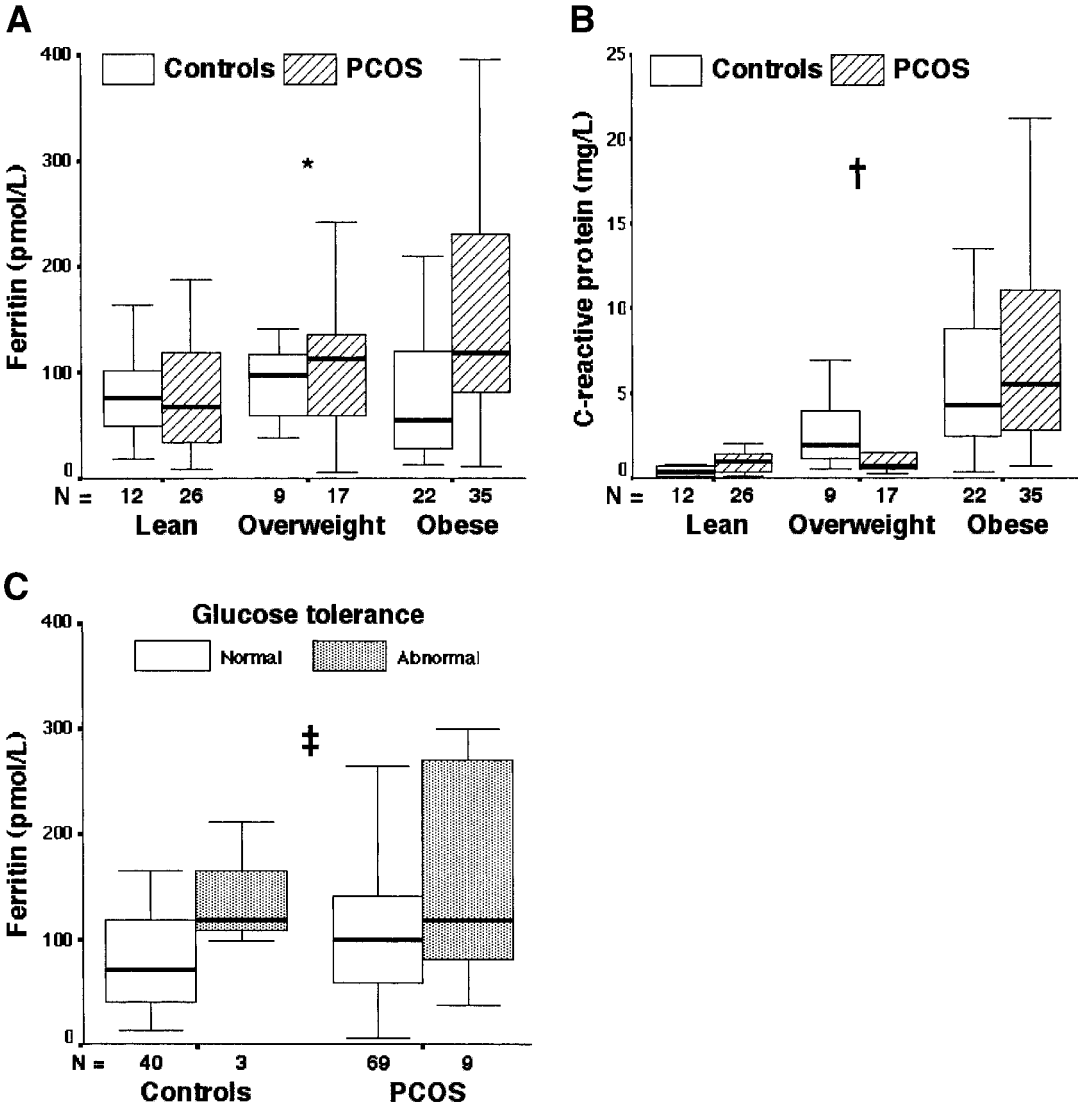

Figure 1—*Serum ferritin (A) and CRP (B) concentrations depending on PCOS status and degree of obesity and serum ferritin levels depending on the presence or absence of disorders of glucose tolerance (C). The box plots include the median (horizontal line) and the interquartile range (box), and the whiskers indicate the 5th and 95th percentiles. The figures below the x-axis indicate the number of subjects in each subgroup.* *$P < 0.05$ *for the interaction between PCOS status and degree of obesity.* †$P < 0.05$ *for the difference between lean (BMI <25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) women.* ‡$P < 0.05$ *for the difference between women with normal or abnormal (glucose intolerance or type 2 diabetes) glucose tolerance.*

tion frequently found in PCOS patients, as has been proposed for insulin resistance, the metabolic syndrome, and type 2 diabetes (1–3,8,9).

However, the increase in serum ferritin levels in PCOS may be a secondary, not a pathogenic, event in PCOS. The absence of regular menstrual blood loss in PCOS patients might contribute to iron overload, as serum ferritin levels were increased in our amenorrheic patients compared with regularly menstruating women. Oxidative stress increases ferritin synthesis, partly to avoid further oxidative damage, given that ferritin neutralizes the highly toxic unbound iron (10), and oxidative stress may be increased in PCOS women (7,11). Also, the hyperinsulinemia resulting from insulin resistance may contribute to increased body iron stores and serum ferritin levels because insulin may stimulate intestinal iron absorption by upregulating activity of hypoxia-inducible factor-1α (12).

Yet several of these factors might collaborate in the increased body stores observed in overweight and obese PCOS patients. As proposed for type 2 diabetes (10), the insulin resistance intrinsic to PCOS, exacerbated by obesity and perhaps dietary influences, may facilitate iron absorption and deposition in tissues, a mechanism possibly amplified by the reduced menstrual losses of PCOS patients. Iron deposition in certain tissues increases insulin resistance, closing the vicious circle of iron overload and predisposing these women to disorders of glucose tolerance and other components of the metabolic syndrome.

In summary, serum ferritin levels are increased in overweight and obese

women with PCOS and are associated with disorders of glucose tolerance in premenopausal women.

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