Serum soluble leptin receptor levels and free leptin index in women with polycystic ovary syndrome: relationship to insulin resistance and androgens

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Objective: To evaluate levels of soluble receptor (sOB-R) and free leptin in women with polycystic ovarian syndrome (PCOS) and note any relationships with insulin resistance, adiposity, and androgens. Leptin is an adipokine that circulates in a free form and bound to an sOB-R. Only free leptin is biologically active.
Design: Prospective, case-control study.
Setting: University-based reproductive endocrinology practice.
Patient(s): Forty women with PCOS and severe insulin resistance and 15 body mass index (BMI)-matched ovulatory controls.
Intervention(s): Measurements of serum insulin, leptin, sOB-R at fasting and during a standard oral glucose tolerance test (OGTT), and measurements before and after treatment with rosiglitazone.
Main Outcome Measure(s): Fasting glucose, insulin, leptin, sOB-R, T, and DHEAS levels in women with PCOS and controls were measured to investigate the relationship of sOB-R and the free leptin index (FLI) to insulin, adipocity, and androgens and to investigate the effect of acute hyperinsulinemia during OGTT and the effect of improvement of insulin resistance with rosiglitazone on the leptin system. FLI was calculated by dividing leptin levels by sOB-R.
Result(s): Total leptin and FLI correlated significantly with BMI in both patients with PCOS and in controls. There was a significant negative correlation between DHEAS and sOB-R in PCOS. Leptin, sOB-R, and FLI were not significantly different in the two groups, and neither sOB-R nor FLI correlated with insulin or glucose levels. The sOB-R levels increased significantly 3 hours after oral glucose ingestion, resulting in a significant decline in FLI.
Conclusion(s): [1] Adiposity rather than insulin resistance appears to be the main determinant of leptin levels and FLI. [2] Acute increase in insulin levels during OGTT is associated with an increase in levels of sOB-R. [3] DHEAS may play a role in leptin bioavailability by modulating sOB-R levels. (Fertil Steril® 2006;85: 1441–7. ©2006 by American Society for Reproductive Medicine.)

Key Words: Leptin, soluble leptin receptor (sOB-R), free leptin index, polycystic ovarian syndrome (PCOS)

Leptin, a 167-amino acid protein, is a product of the obesity (*ob*) gene and is primarily produced by adipocytes (1). Leptin plays a role in body weight homeostasis through possible neuroendocrine pathways and has an impact on reproduction (1–3). Leptin receptors belong to the cytokine I receptor family and can be classified into the long and short isoforms (4–6). Recently, a soluble leptin receptor (sOB-R) was identified in the circulation (7). Leptin is found in the circulation in the free form and bound to sOB-R, which could affect the bioavailability of free leptin. Bound leptin and leptin binding capacity have been found to vary physiologically in relation to increasing adiposity, with free leptin more accurately reflecting body fat mass (8, 9). The sOB-R is derived from the ectodomain shedding of the long isoform leptin receptor (10, 11). sOB-R appears to be the main binding protein for leptin in human circulation (11). It binds to leptin with affinity similar to that of membrane bound receptor, and it modulates serum leptin levels by delaying its clearance and inhibiting the ability of leptin to bind and activate the membrane bound receptor (12, 13).

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases, affecting 4%–10% of women of reproductive age in the developed world (14, 15). Patients with PCOS display hyperandrogenism and anovulation, and a significant number of these women are obese (16). Periph-

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TABLE 1

Clinical and hormonal characteristics of women with PCOS and controls.

Characteristic	PCOS (n = 40)	Controls (n = 15)	Significance
Age (y)	28.4 ± 0.9	34.6 ± 1.9	$P<.05$
BMI	38.5 ± 1.3	34.5 ± 2.6	NS
Total T (ng/dL)	90.2 ± 5.1	71.4 ± 9.0	$P<.05$
DHEAS (ng/mL)	1,630.3 ± 184.9	1,075.3 ± 199.7	$P<.05$
LH (mIU/mL)	7.9 ± 0.7	3.5 ± 1.2	$P<.05$
Fasting insulin (μU/mL)	33.1 ± 3.0	10.1 ± 1.2	$P=.00002$
Insulin AUC	536.6 ± 58.1	158.2 ± 16.1	$P=.0002$
Fasting glucose (mg/dL)	87.9 ± 1.9	86.5 ± 2.2	NS
Glucose AUC	379.4 ± 13.4	314.1 ± 19.5	NS
Leptin (ng/dL)	87.9 ± 4.2	81.4 ± 7.8	NS
sOB-R (ng/dL)	23.0 ± 1.2	21.3 ± 1.6	NS
FLI	4.5 ± 0.4	4.4 ± 0.64	NS

Note: AUC = area under the curve; BMI = body mass index; FLI = free leptin index; NS = not significant.

Sepilian. Soluble leptin receptor and free leptin in PCOS. Fertil Steril 2006.

eral insulin resistance with consequent hyperinsulinemia appears to play a key role in the pathogenesis of this disorder (17). Total leptin concentrations in women with PCOS have shown conflicting results. Some investigators observed increased leptin levels in women PCOS (18–20), while others found no difference (21–24). Free leptin and sOB-R have never been studied in women with PCOS.

Since women with PCOS display obesity, insulin resistance, and hyperandrogenism, this is a good model to study the effects of hyperinsulinemia and hyperandrogenism on the leptin system. The aim of the present study is to evaluate levels of leptin, sOB-R, and free leptin in women with PCOS and to investigate the role of adiposity, insulin resistance, and hyperandrogenism on sOB-R and free leptin.

MATERIAL AND METHODS

Subjects

Forty women with PCOS were recruited to participate in the study. All women had acanthosis nigricans, a cutaneous finding that is associated with severe insulin resistance in women with PCOS (25, 27). The National Institutes of Health/National Institute of Child Health and Human Development criteria were used to establish PCOS (26). The diagnosis of PCOS was made by the presence of anovulation accompanied by hyperandrogenism, after excluding other conditions that could present in a similar fashion. All of the women had normal thyroid-stimulating hormone and PRL levels, and subjects with possible ovarian tumors (T > 200 ng/dL) and congenital adrenal hyperplasia (17-hydroxyprogesterone levels > 2 ng/mL) were excluded from the study. All women had polycystic-appearing ovaries on ultrasound. Fifteen women with regular ovulatory cycles who matched the body mass index (BMI) of the PCOS subjects were recruited as controls. Patient characteristics are shown in Table 1. All the studies in the control ovulatory women were performed in the early follicular phase of the cycle. In women with PCOS who were anovulatory and had irregular cycles, the tests were performed after their period except when they had long periods of amenorrhea. The study was approved by the Institutional Review Board of the University of Texas Medical Branch at Galveston, and all participants signed an informed consent form.

Methods

Height and weight were measured and the BMI was calculated in all patients and controls. Fasting levels of leptin and sOB-Rs were measured and the free leptin index (FLI) was determined by dividing the leptin levels by the soluble leptin receptors. Levels of total T, DHEAS, and LH were also measured. After a high-carbohydrate diet for 3 days, a standard oral glucose tolerance test (OGTT) was performed. Blood samples were collected for insulin and glucose before and at 1, 2, and 3 hours after 75 g oral glucose intake. The area under the curve (AUC) for insulin and glucose was calculated by the trapezoid method. Leptin and sOB-R levels were measured during OGTT in 15 women with PCOS and eight normal controls to evaluate the effects of acute increase in insulin and glucose levels on sOB-R and free leptin. Women with impaired glucose tolerance or overt diabetes were excluded from the study.

To further investigate the role of insulin resistance on the leptin system, we offered the women with PCOS treatment with the insulin sensitizing agent rosiglitazone for 6 months. Ten of the women with PCOS enrolled and agreed to undergo treatment with rosiglitazone (4 mg/day for 6 months). Fasting insulin, leptin, and s-OBr were measured before and after treatment. The BMI and the FLI were determined before and after treatment.