

## Serum Adiponectin and Leptin in a Patient with Cushing's Syndrome Before and After Adrenalectomy

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### Abstract

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We measured the serum adiponectin and leptin concentrations before and after successful removal of a left adrenal adenoma in a 46-year-old woman with Cushing's syndrome. The serum adiponectin level was 6.0 µg/ml before the operation and rose to 8.1 µg/ml after adrenalectomy. However, the serum leptin level was markedly high (24.8 ng/ml) before the operation and decreased to within the normal range (6.0 ng/ml) 6 months after adrenalectomy, concomitant with weight reduction and normalization of the serum cortisol level.

**Key words:** Cushing's syndrome, adiponectin, leptin, obesity

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### Introduction

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Obesity is a major risk factor for the development of hypertension, type 2 diabetes, dyslipidemia and metabolic syndrome (1, 2). Recent evidence suggests that adipose tissue functions not only as an energy storage tissue but it also functions as an endocrine organ producing a number of bioactive substances. These substances, including adiponectin and leptin, are referred to as adipokines. Adiponectin is produced exclusively by adipocytes and is considered a major factor in obesity-related insulin resistance. Adiponectin differs from other adipocytokines in that its production and plasma concentrations are significantly decreased in insulin-resistant subjects, such as obese, type 2 diabetes patients (3). On the other hand, leptin is an important component in the regulation of body weight and energy expenditure (4). The plasma leptin concentration is correlated with body fat content and is elevated in obesity and decreased during fasting (4, 5).

Cushing's syndrome is characterized by obesity, impaired glucose tolerance, and hypertension due to excessive synthesis of glucocorticoid. We encountered a case of Cushing's syndrome whose serum adiponectin and leptin levels were available both before and after successful adrenalectomy. Further, these levels were compared to those of patients with metabolic syndrome who had a body mass index (BMI)

similar to this patient.

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### Case Report

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A 46-year-old Japanese woman with a left adrenal mass was referred to our department on May 9, 2005, for further evaluation of hypertension. She had a family history of hypertension in her parents. The patient had been medicated with oral antihypertensive drugs for more than ten years. When the patient was 44, her body weight increased by 10 kg per year and she was pointed out to have glucosuria. At the age of 45, a left adrenal mass was incidentally detected by abdominal echogram.

On physical examination, she was 148.2 cm tall and weighed, 58.2 kg and her waist circumference was 93.5 cm. Her blood pressure was 160/96 mmHg, pulse rate was regular at 66 beats/min. Examination of her heart and lungs was unremarkable. Centripetal obesity, hirsutism, abdominal cutaneous striae and peripheral edema were observed.

Chest X-ray and electrocardiogram were unremarkable. The abdominal CT revealed that the left adrenal gland was replaced by a 3-cm mass with low attenuation. Hematological tests showed a RBC,  $427 \times 10^4/\mu\text{l}$ ; hemoglobin, 14.3 g/dl; hematocrit, 52.5%; WBC,  $8,200/\mu\text{l}$ ; platelet,  $20.9 \times 10^4/\mu\text{l}$ . Urine analysis demonstrated a glucosuria (3+). Analysis of blood chemistry was as follows: total protein, 6.3 g/dl; sodium, 146 mEq/l; potassium, 3.1 mEq/l; chloride, 109

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**Figure 1.** Resected left adrenal gland including adrenal tumor (left) and its serial section (right). The adrenal gland was 6.5×3.5×2.1 cm, 17g and tumor was 3.0×3.0×2.1cm in size.

**Table 1.** Characteristics of the Patient before and after 6 Months of Adrenalectomy Comparing with the Patients with Metabolic Syndrome aged 40 to 64

	Patient		Metabolic syndrome	
	pre ope	post ope	Male(n=9)	Female(n=9)
Age(y.o.)	45	46	56.1±5.4	56.9±5.8
SBP(mmHg)	160	130	163.4±20.5	171.3±29.3
DBP(mmHg)	96	86	93.7±10.5	93.1±11.8
BMI(kg/m <sup>2</sup> )	26.5	21.6	26.1±2.4	27.6±2.1
Adiponectin(μg/mL)	6.0	8.1	7.0±2.4	8.4±3.1
Leptin(ng/mL)	24.8	6.0	6.5±2.0	17.9±7.3

mEq/l; urea nitrogen, 10 mg/dl; creatinine, 0.5 mg/dl; aspartate aminotransferase (AST), 19 IU/l; alanine aminotransferase (ALT), 33 IU/l; creatinine phosphokinase (CK), 80 IU/l; total cholesterol, 231 mg/dl; triglycerides, 123 mg/dl; fasting blood sugar, 161 mg/dl; HbA1c, 6.9%. Serum adiponectin and leptin level were 6.0 μg/ml and 24.8 ng/ml, respectively. They were measured by SRL Inc, Tokyo, Japan, with the normal range of adiponectin being 4.1-18.9 μg/ml and that of leptin, 8-12 ng/ml.

To determine the etiology, further endocrinological tests were performed. Plasma cortisol concentration at 8:00 A.M. was 22.3 μg/dl and at 23:00, 22.3 μg/dl, and diurnal variation was not observed. Neither 1 mg overnight (23.7 μg/dl) nor 8 mg standard (20.6 μg/dl) dexamethasone suppressed excess cortisol production from the tumor. Plasma ACTH was markedly suppressed (<5 pg/ml) and urinary 17-ketosteroids were not elevated, suggesting that the adrenal tumor was an adenoma.

On June 20, 2005, the patient underwent a left adrenalectomy using laparoscopic techniques. The tumor was 3.0×3.0×2.1 cm in size and histopathologically compatible with an adenoma (Fig. 1).

Six months after the operation (December 2005), her body weight had decreased to 47.5 kg and her waist circumference was 86.0 cm. The antihypertensive drugs, candesartan 8 mg/day, amlodipine 5 mg/day and doxazosin 2 mg/day were discontinued and blood pressure was controlled below 130/85 mmHg with only 2.5 mg/day of amlodipine. Sec-

dary diabetes and dyslipidemia were also improved even after discontinuation of 0.6 mg/day of voglibose and 10 mg/day of atorvastatin and under supplement 10 mg/day of hydrocortisone. Laboratory data at the outpatient clinic was as follows: fasting blood sugar, 100 g/dl; HbA1c, 5.2%; total cholesterol, 165 mg/dl; triglyceride, 79 mg/dl; cortisol, 8.9 μg/dl (9:00 AM); ACTH, 20.0 pg/ml.

Serum adiponectin rose to 8.1 μg/ml (December 2005), 9.8 μg/ml (March 2006) and serum leptin markedly decreased to 6.0 ng/ml (December 2005), 7.7 ng/ml (March 2006). The adiponectin and leptin levels among patients with metabolic syndrome aged 40 to 64 whose BMI was the same level as this patient are shown in Table 1. Adiponectin and leptin levels in female patients with metabolic syndrome (56.9±5.8 y.o.) was 8.4±3.1 μg/ml and 17.9±7.3 ng/ml, respectively.

## Discussion

We reported a patient with Cushing's syndrome whose serum adiponectin and leptin were measured before and after successful removal of an adrenal adenoma. Serum adiponectin was 6.0 μg/ml before the operation and it rose to 8.1 μg/ml after adrenalectomy. Several reports are available regarding the regulation of adiponectin by glucocorticoids. Dexamethasone reduced adiponectin gene expression in murine 3T3-L1 adipocytes (6), and glucocorticoid negatively regulated adiponectin mRNA in human visceral adipose tissue (7). Moreover adiponectin expression in white adipose tissue was stimulated by adrenalectomy in *ob/ob* mice (8). Fallo et al reported the adiponectin level in 21 Cushing's syndrome (15: pituitary-dependent Cushing's disease, 4: adrenal adenoma, 1: adrenal carcinoma, 1: ACTH ectopic production) (9). They divided them into obese Cushing's patients and non-obese Cushing's patients. Adiponectin was lower in non-obese Cushing's patients than in non-obese controls. Interestingly, adiponectin levels were not different in obese Cushing's patients and in obese controls. Furthermore, exogenous administration of glucocorticoids to healthy subjects produced a decrease in adiponectin. These

data suggested that obesity per se acts as a predominant factor masking the relationship between adiponectin and cortisol. Also, in this case, an increase of serum adiponectin was observed along with the concomitant decrease of body weight and cortisol.

On the other hand, serum leptin was extremely high (24.8 ng/ml) before the operation and it decreased to within the normal range (6.0 ng/ml) following adrenalectomy. Leptin is known to be markedly increased after glucocorticoid administration and in Cushing's syndrome (10, 11). Leptin levels in patients with Cushing's syndrome were significantly elevated compared to those in nonobese healthy subjects and obese subjects without any metabolic or endocrine diseases (10). In the patients with pituitary-dependent Cushing's disease, serum leptin levels were reduced after tumor resection, with concurrent decreases in serum cortisol, insulin, and BMI (11). These reports indicated that glucocorticoids act

not only directly on the adipose tissue and increase leptin synthesis, but also have an indirect effect via the associated hyperinsulinemia and/or impaired insulin sensitivity.

Krsek et al reported that among leptin, adiponectin and resistin, only the resistin level is significantly higher in female Cushing's syndrome patients than in control subjects, however curative surgery significantly reduced only the leptin level (12). On the other hand, Libe et al demonstrated that neither adiponectin nor leptin is statistically reduced by transsphenoidal surgery in patients with Cushing's disease (13). It was difficult to determine the difference in adipocytokine levels between Cushing's syndrome and metabolic syndrome because this data was obtained from only one case report, however, the adiponectin level was rather smaller than that of a normal control subject and the leptin level was even larger than that of metabolic syndrome.

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