

Plasma Leptin Levels Before and After Bromocriptine Treatment in Female Patients with Prolactinoma

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Both It is known that increased body weight is associated with prolactinomas. However, effects of bromocriptine treatment on plasma leptin levels is not clear yet. The aim of this is to evaluate leptin levels before and after bromocriptine treatment in patients with prolactinoma. Twenty female patients with prolactinoma and twenty normoprolactinemic, age- and body mass index (BMI)- matched healthy females were involved in the study. Plasma leptin levels were measured before and eight weeks after bromocriptine treatment in patients with prolactinoma. Bromocriptine treatment resulted in a significant decrease in prolactin levels (from 119.3 ± 45.7 to 55.4 ± 25.2 , $p=0.001$), and a significant increase in leptin levels (from 28.3 ± 15.8 to 32.2 ± 18.3 ng/ml, $p<0.001$). There was a significant decrease in BMI (from 27.0 ± 5.8 to 25.8 ± 1.5 kg/m², $p<0.001$) and waist/hip ratio (from 0.91 ± 0.16 to 0.88 ± 1.14 , $p<0.001$) with treatment. There was a moderate negative correlation between the change in leptin levels and the change in BMI ($r= -0.50$, $p<0.03$) in prolactinoma patients , but, there was no significant correlation between change in leptin levels and either the change in prolactin levels ($r= -0.13$, $p<0.6$) or the change in W/H ratio ($r= -0.38$, $p=0.1$). Our data suggest that hyperprolactinemia may be regarded as a reversible cause of weight gain and leptin has an important role in the weight loss observed during treatment with bromocriptine.

Key words: Prolactinoma, leptin, weight, bromocriptine

Introduction

Obesity is a commonly encountered disease in all parts of the world. In only a minority of obese patients, endocrine disorders are involved in the pathogenesis. The most frequently observed, and thus screened, endocrine problems are Cushing's syndrome and hypothyroidism (1). Prolactin excess is also claimed to be associated with obesity in a few reports (2-4). Central prolactin administration has been found to increase food intake in several animal species (5). The ob gene product leptin is a hormone of adipose tissue that is known to be

increased in patients with obesity. Koshaka et al showed that leptin plays an important role in the generation of steroid induced luteinizing hormone (LH) and prolactin (PRL) surges in female rats (6); and Gualillo et al reported that prolactin, acting on the adipose tissue, increases leptin synthesis and secretion in rats (7). In humans, Greenman et al reported a significant weight loss with normalization of prolactin levels in patients with prolactinoma (2). However, the relation between prolactin and leptin is not clear, yet. This study is conducted in order to clarify this relation, and to show the effect of bromocriptine therapy on plasma leptin levels and body mass index in female patients with prolactinoma.

Materials and Methods

Twenty female patients with prolactinoma were involved in the study. None of the patients had ever

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received any kind of treatment for prolactinoma on entry to the study. Patients who had ever received any kind of treatment for hyperprolactinemia; those who are pregnant or currently nursing; those with chronic pulmonary, heart, liver or renal disease; those with chest trauma or any other chest disease (mastitis, zona, burn, etc.); and, those who are on any medication that could affect prolactin levels are excluded. Patients who had a specific anterior pituitary hormone deficiency or hypothyroidism were also excluded.

Detailed physical examination is performed, and weight, height, calculated BMI values are recorded for each patient. The presence of pituitary adenoma is confirmed with magnetic resonance imaging. Patients are started on bromocriptine treatment with a daily dose of 5 mg with weekly increases of 5 mg up to 20 mg/day. On the eighth week of treatment the same detailed physical examination and measurements are performed.

Twenty normoprolactinemic, age- and BMI- matched female subjects formed the control group. Above-mentioned physical and laboratory examinations are performed only once for the subjects in the control group.

The purpose of the study protocol was explained to all patients, and informed consent was obtained. The study protocol was approved by the local ethical committee of Gulhane School of Medicine.

The design of the study rules out any interference by the diurnal variation in leptin levels, because all samples were collected at 08.00 hours after overnight fasting in all subjects. Plasma samples are collected before and after 2 months of bromocriptine treatment. After a prompt centrifugation the plasma of patients were taken immediately and stored at -70°C until leptin assay was performed. All samples were run in the same assay.

Plasma leptin is determined using a commercially available radioimmunoassay kit (Human Leptin RIA kit; Linco Research Inc., St. Louis, MO, USA). Duplicate leptin determinations were made from each sample. The assay sensitivity was 0.5 ng/ml. The intraassay coefficient of variation (CV) of the assay at 7.0 ng/ml was 6.3% (n=13).

Statistical Analysis

All results are expressed as mean \pm standard deviation (SD). Statistical package for social sciences (SPSS,

version 9.0) software is used for the analyses. We used paired and unpaired student-t test, where necessary, to compare groups. Correlation analyses are performed according to Pearson and Spearman as appropriate. Partial correlation analysis is used in some correlation analysis to control for body mass index. A two-tailed p value of less than 0.05 is considered of statistical significance.

Results

Four (20 %) of the 20 patients with prolactinoma had macroadenoma (adenoma diameter > 1 cm in the greatest dimension), and 16 (80 %) had microadenoma.

The patient group (n=20) was comparable to control group with regard to age (34.6 ± 4.8 vs. 36.5 ± 4.4 years respectively, $p > 0.05$), BMI (27.0 ± 5.8 vs. 25.9 ± 5.9 kg/m², respectively; $p > 0.05$), and waist/hip (W/H) ratio (0.91 ± 0.16 vs. 0.89 ± 0.16 , respectively; $p > 0.05$). Although mean leptin level was higher in the patients than the controls, this difference was not statistically significant (28.3 ± 15.8 vs. 24.4 vs. 15.0 ng/ml, respectively; $p > 0.05$) (Table 1).

Table 1. Pretreatment characteristics of the patient and the control groups.

	Patients (n=20)	Controls (n=20)	p
Age (years)	34.6 ± 4.8	36.5 ± 4.4	NS*
BMI (kg/m ²)	27.0 ± 5.8	25.9 ± 5.9	NS
Prolactin (ng/ml)	119.3 ± 45.7	10.9 ± 5.1	<0.001
Leptin (ng/ml)	28.3 ± 15.8	24.4 ± 15.0	NS
Wasit/Hip	0.91 ± 0.16	0.89 ± 0.16	NS

*NS: Not significant

Table 2. Changes in laboratory and anthropometric measures in prolactinoma patients.

	Basal	After treatment	p
BMI (kg/m ²)	27.0 ± 5.8	25.8 ± 1.5	<0.001
Prolactin(ng/ml)	119.3 ± 45.7	55.4 ± 25.2	0.001
Leptin (ng/ml)	28.3 ± 15.8	32.2 ± 18.3	<0.001
Waist/Hip ratio	0.91 ± 0.16	0.88 ± 1.14	<0.001

Two months of bromocriptin treatment resulted in a significant decrease in prolactin levels (from 119.3 ± 45.7 to 55.4 ± 25.2 , $p = 0.001$), and a significant increase in leptin levels (from 28.3 ± 15.8 to 32.2 ± 18.3 ng/ml, $p < 0.001$). There was a significant

decrease in BMI (from 27.0 ± 5.8 to 25.8 ± 1.5 kg/m², $p < 0.001$) and waist/hip ratio (from 0.91 ± 0.16 to 0.88 ± 0.14 , $p < 0.001$) with treatment. There was a moderate negative correlation between the change in leptin levels and the change in BMI ($r = -0.50$, $p < 0.03$) in prolactinoma patients (Figure 1). But, there was no significant correlation between change in leptin levels and either the change in prolactin levels ($r = -0.13$, $p < 0.6$) or the change in W/H ratio ($r = -0.38$, $p = 0.1$).

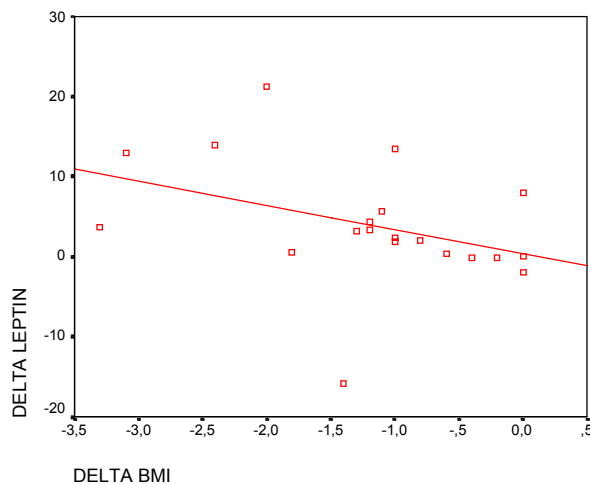


Figure 1. Correlation between change in leptin levels and the change in BMI after bromocriptine treatment in patients ($r = -0.50$, $p < 0.03$)

In this study we showed that bromocriptine treatment results in a decrease in BMI concomitant with a decrease in plasma prolactin in female patients with prolactinoma. An increase in serum leptin concentrations was also followed these changes. There was also a significant negative correlation between the change in leptin levels and the change in BMI with bromocriptine treatment. Thus, it seems likely that a decrease in leptin levels may be due to the weight loss in these patients. Absence of a relation between prolactin and leptin levels, and, prolactin and BMI may suggest that leptin as the sole determinant of BMI change. It is hard to explain why leptin increases in response to a decrease in prolactin with bromocriptine treatment. There are a few reports in the literature concerning the interaction of leptin and prolactin. It has been reported that leptin increased PRL secretion in vitro only at high concentration (1/107 to 1/105 M) (6). Recently, Gualillo et al. demonstrated that

prolactin stimulates leptin secretion by rat white adipose tissue (7). This PRL-induced leptin release

appear to be mediated by an increase in Ob mRNA content of fat cells. Therefore, the higher incidence of obesity in hyperprolactinemic patients is likely to be mediated by a leptin-resistant state. While Mukherjea et al. found prolactin level as an important determinant of leptin levels (8), Butte et al. could not find an important difference in leptin levels in lactating women (9). The latter study was also reported an inverse relationship between leptin and PRL. Another possibility may be a direct effect of bromocriptin on leptin secretion, but this issue is not clear yet.

There is a mutual relation between prolactin and body weight, but this relation is not characterized well yet (2). Wang et al. have reported a positive correlation between prolactin levels and body weight (10). Ferreira et al supported the data of Wang et al by showing higher, albeit within normal range, prolactin levels in normal women with a recent history of weight gain compared to those without a recent weight gain (11). Rousso et al have shown that normal decline of prolactin in response to oral glucose tolerance test is disrupted in obese patients with polycystic ovary syndrome (12). But two other studies reported a decrease in prolactin response to insulin induced hypoglycemia (13) and TRH stimulation (14). These data suggest that hyperprolactinemia is associated with a relatively high rate of obesity, and interestingly weight is lost after normalization of serum prolactin levels as observed in our study and in other studies (15).

A possible excess in the prevalence of overweight subjects among hyperprolactinemic patients has been previously described (2, 15), but relation of leptin with prolactin levels and changes in BMI has been described in only one study (16). Our findings support the findings of Doknic et al (16) that bromocriptine treatment in prolactinomas may influence body weight by reducing hyperprolactinemia.

Our data suggest that hyperprolactinemia may be regarded as a reversible cause of obesity in female patients, and leptin has an important role in the weight loss observed during treatment with bromocriptin. Further studies are needed to clarify the relationship between prolactin and leptin in physiological (normal, pregnant, nursing, etc.) and disease (e.g. prolactinoma) states.

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