CLINICAL STUDY

Dopaminergic tone and obesity: an insight from prolactinomas treated with bromocriptine

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Abstract

Objective: It has recently been shown that increased body weight is associated with prolactinomas and that weight loss occurs with normalization of prolactin levels. On the other hand, decreased dopaminergic tone in humans is well correlated with obesity. The objective of this study was to correlate changes in prolactin levels with leptin and body mass index (BMI) in patients with prolactinomas treated with the long-acting dopamine agonist bromocriptine (BC).

Methods: Eleven female and twelve male patients, aged 36.7 ± 2.6 years with BMI in males of $30.4 \pm 1.7 \, \text{kg/m}^2$ and in females of $24.4 \pm 1.2 \, \text{kg/m}^2$, were evaluated after 1 and 6 months and 11 patients were further evaluated after 2 years of BC therapy. Plasma prolactin is presented as the mean of four samples taken daily. Serum leptin was determined in the pooled serum from three samples taken at 15-min intervals at 0800 h after an overnight fast. Multivariate linear regression and repeated measures analysis of covariance were used.

Results: In males, pretreatment prolactin levels were $71\,362 \pm 29\,912 \, \text{mU/l}$ while leptin levels were $14.9 \pm 1.8 \, \mu\text{g/l}$. In females, pretreatment prolactin levels were $11\,395 \pm 5839 \, \text{mU/l}$ and leptin levels were $16.7 \pm 2.5 \, \mu\text{g/l}$. The sexual dimorphism of serum leptin levels at initial presentation was preserved after adjusting for BMI and prolactin-induced hypogonadism. After 1 month of therapy, prolactin levels significantly decreased (males: $17\,618 \pm 8736 \, \text{mU/l}$, females: 3686 ± 2231; $P < 0.05$), BMI did not change (males: $30.2 \pm 1.7 \, \text{kg/m}^2$, females: $24.1 \pm 1.2 \, \text{kg/m}^2$; $P > 0.05$), while serum leptin levels decreased (males: $12.5 \pm 1.5 \, \mu\text{g/l}$, females: $13.6 \pm 2.1 \, \mu\text{g/l}$; $P < 0.05$). After 6 months of treatment, prolactin further decreased (males: $3456 \pm 2101 \, \text{mU/l}$, females: $677 \pm 360 \, \text{mU/l}$; $P < 0.05$) as did BMI (males: $28.6 \pm 1.6 \, \text{kg/m}^2$, females $23.1 \pm 1.0 \, \text{kg/m}^2$; $P < 0.05$). The difference was more pronounced in male patients. Leptin levels were $12.8 \pm 2.8 \, \mu\text{g/l}$ in males and $12.9 \pm 1.8 \, \mu\text{g/l}$ in females ($P < 0.05$). After 2 years of BC treatment, prolactin levels were near normal (males: $665 \pm 439 \, \text{mU/l}$, females $447 \pm 130 \, \text{mU/l}$; $P < 0.05$) and BMI remained $26.5 \pm 1.9 \, \text{kg/m}^2$ for males and $23.6 \pm 0.8 \, \text{kg/m}^2$ for females ($P < 0.05$). Leptin levels were $9.5 \pm 2.2 \, \mu\text{g/l}$ in males and $18.7 \pm 3.1 \, \mu\text{g/l}$ in females ($P < 0.05$). There was a gradual increase in the gender difference in serum leptin levels over time. Changes in serum leptin levels significantly correlated with changes in BMI ($r = 0.844$, $P < 0.001$) but did not correlate with changes in plasma prolactin levels after 1 month ($r = 0.166$), 6 months ($r = 0.313$) and 2 years ($r = 0.234$, $P > 0.05$).

Conclusion: The long-acting dopamine agonist BC, by increasing dopaminergic tone, may influence body weight and likely body composition by mechanisms in addition to reducing hyperprolactinemia in patients with prolactinomas.

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Introduction

The prevalence of obesity is increasing worldwide. Hyperprolactinemia in humans may be associated with a relatively high rate of obesity but the nature of the link between prolactin and increased body weight is unclear. There are reports that in the pathological setting, such as sustained hyperprolactinemia, a relatively high rate of obesity is followed by weight loss after normalization of serum prolactin levels with dopamine agonists (1, 2). On the other hand, drugs that block dopamine D2 receptors increase appetite and result in significant weight gain. Healthy subjects treated with antipsychotic drugs (dopamine antagonists) gain weight (3). Furthermore, of particular interest is the recent report that dopamine deficiency in obese

individuals may perpetuate pathological eating and strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals (4). Prolactin is a positive feedback stimulus for central dopamine synthesis and release whereas sustained hyperprolactinemia down-regulates 'normal' effects by reducing central dopaminergic tone (5).

Leptin, the 16 kDa protein produced by the adipocytes, has been shown to affect appetite, metabolism and reproduction. Leptin circulates in proportion to adiposity and thus leptin levels are raised in obesity (6). The effects of leptin are mediated by leptin receptors in the brain and are targeted to the hypothalamus where it acts on discrete neuronal circuits to promote negative energy balance. Thus, for the long-term tonic regulation of energy homeostasis, leptin is of utmost importance.

In rodents, prolactin regulates leptin secretion (7) and prolactin-induced leptin release appears to be mediated by an increase in leptin gene expression in the fat cell. Increased serum prolactin levels, obtained by pituitary graft or exogenous injected ovine prolactin, significantly stimulate serum leptin concentrations in the rat. These data demonstrate that prolactin acts on adipose tissue by increasing leptin synthesis and secretion, further suggesting a new role for this lactogenic hormone in the regulation of food intake in rodents.

In humans, the only physiological setting where a clear association of prolactin and leptin is found is pregnancy and lactation. In pregnancy, where energy demands are increased, the needs may be met through partitioning of nutrients for energy utilization which is under hormonal control (8).

The purpose of this study was to investigate the relation between prolactin, body weight and leptin before and after treatment of patients with prolactin-secreting pituitary adenomas with bromocriptine (BC) in an attempt to answer the questions as to whether sustained hyperprolactinemia *per se* promotes adiposity or whether the change in dopaminergic tone directly correlates with obesity rather than indirectly by decreasing prolactin levels.

Subjects and methods

Study subjects

Twenty-three patients with prolactinomas treated at the Institute of Endocrinology of the University Clinical Center from 1998 to 2001 were included in this study. There were 11 female and 12 male patients, mean age 36.7 ± 2.6 years (range 17–59 years).

Inclusion criteria for the study were as follows. (a) Persistent hyperprolactinemia which could not be attributed to drug therapy, stress, hypothyroidism, end-stage renal disease or other causes of increased circulating prolactin. Prolactin levels greater than 500 mU/l were considered to be elevated. (b) Magnetic resonance imaging (MRI) of the hypothalamic–pituitary region confirming pituitary adenoma.

Fifteen patients had macroprolactinomas and eight had microprolactinomas. All except one man had macroprolactinomas as opposed to women (five micro-adenomas and six macroadenomas). Mean pretreatment prolactin levels were $71\,362 \pm 29\,912$ mU/l in males and $11\,395 \pm 5839$ mU/l in females. All patients were treated with the dopamine agonist BC (Bromergon Leic, Ljubljana, Slovenia) at a dose of 15–20 mg daily. Mean follow-up time was 6 months, while 11 patients with prolactinomas were evaluated after 2 years of BC therapy. Treatment significantly reduced prolactin levels in all patients after 1 month of therapy, with near normal prolactin after 6 months of follow-up and normal prolactin levels after 2 years of therapy.

Data on body weight before and during treatment, history of weight fluctuation, tumor size as measured by MRI, modalities of and response to treatment were recorded. Pituitary function was assessed prior to starting treatment and during medical therapy. Thyroid and adrenal axis testing were normal. Growth hormone status was not assessed.

Prolactin is presented as the mean of four samples taken at 0900, 1100, 1300 and 1900 h. Leptin was determined in the pooled serum from three samples taken at 15-min intervals at 0800 h in the morning after an overnight fast. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2).

Hormone measurements

Plasma prolactin levels were measured using immunoradiometric assay INEP (Zemun) kits with intra-assay coefficient of variation (CV) values 4.6% (250 mU/l), 6.1% (670 mU/l) and 2.6% (815 mU/l), and with interassay CV values 7.9% (219.5 mU/l) and 5.8% (756.1 mU/l). Serum leptin levels were assayed by commercial radioimmunoassay kits (Linco, St Louis, MO, USA). Estradiol was assayed by chemiluminescent methods (IMMULITE estradiol; DPC, Los Angeles, USA), with intra-assay CV values 15% (46 pg/ml), 9.5% (116 pg/ml), 8.6% (266 pg/ml), 7.1% (422 pg/ml) and 6.3% (480 pg/ml), and with interassay CV values 16% (56 pg/ml), 9.3% (151 pg/ml) and 6.4% (482 pg/ml). Testosterone was assayed by electrochemiluminescence immunoassay (Boehringer Mannheim Elecsys 1010/2010, Roche, Basel, Swtizerland), with intra-assay CV values 4.6% (0.24 ng/ml), 1.4% (2.75 ng/ml), 1.1% (7.01 ng/ml), 0.9% (6.20 ng/ml) and 1.7% (1.95 ng/ml), and with interassay CV values 7.4% (0.018 ng/ml), 2.2% (0.061 ng/ml), 1.7% (0.118 ng/ml), 1.6% (0.097 ng/ml) and 2.6% (0.050 ng/ml).

Statistical analysis

Data were analyzed using multivariate ANOVA. Results are expressed as means±s.e. Prolactin values were logarithmically transformed for analysis. Multivariate linear regression analysis and repeated measures analysis of covariance were performed to assess the possible influence of different parameters on weight change and to investigate the contribution of independent variables on leptin levels. A two-tailed P value of less than 0.05 was considered of statistical significance.

Results

Pretreatment weight, BMI, prolactin and leptin levels

Before treatment, 58% of males and 18% of females were obese with BMI $> 27 \, \text{kg/m}^2$. Mean weight and BMI in patients with prolactinomas were significantly higher in males ($101.5\pm5.3 \, \text{kg}$ and $30.4\pm1.7 \, \text{kg/m}^2$) than in females ($68.6\pm3.3 \, \text{kg}$ and $24.4\pm1.2 \, \text{kg/m}^2$; $P < 0.01$; Table 1). Pretreatment prolactin levels were significantly higher in males ($71\,362\pm29\,912 \, \text{mU/l}$) than in females ($11\,395\pm5839 \, \text{mU/l}$; $P < 0.01$). Covariable prolactin and BMI were not co-linear. Leptin levels were $16.7\pm2.5 \, \mu\text{g/l}$ in females and $14.9\pm1.8 \, \mu\text{g/l}$ in males. Sexual dimorphism in serum leptin concentrations was preserved in patients with prolactinomas after adjusting for BMI and hypogonadism induced by hyperprolactinemia.

Effect of 1 month of BC therapy on weight, BMI, prolactin and leptin levels

After 1 month of therapy, PRL levels significantly decreased from $71\,362\pm29\,912 \, \text{mU/l}$ to $17\,618\pm8736 \, \text{mU/l}$ in males and from $11\,395\pm5839 \, \text{mU/l}$ to $3686\pm2231 \, \text{mU/l}$ in females; $P < 0.05$ (Table 1). Body weight and BMI did not significantly change after 1 month of therapy (males: from $101.5\pm5.3 \, \text{kg}$ to $100.9\pm5.3 \, \text{kg}$ and from $30.4\pm1.7 \, \text{kg/m}^2$ to $30.2\pm1.7 \, \text{kg/m}^2$, females: from $68.6\pm3.3 \, \text{kg}$ to $67.8\pm$

$3.3 \, \text{kg}$ and from $24.4\pm1.2 \, \text{kg/m}^2$ to $24.1\pm1.2 \, \text{kg/m}^2$ respectively; $P > 0.05$). Serum leptin decreased both in females and in males (females: from $16.7\pm2.5 \, \mu\text{g/l}$ to $13.6\pm2.1 \, \mu\text{g/l}$, males: from $14.9\pm1.8 \, \mu\text{g/l}$ to $12.5\pm1.5 \, \mu\text{g/l}$; $P < 0.05$). Leptin levels correlated with BMI ($r = 0.575$, $P = 0.004$). Changes in leptin levels did not correlate with changes in prolactin levels ($r = 0.166$, $P > 0.05$; Fig. 1A), but did correlate with changes in BMI ($r = 0.716$, $P < 0.001$; Fig. 2A).

Effect of 6 months of BC therapy on weight, BMI, prolactin and leptin levels

After 6 months of treatment, PRL levels further decreased (males: from $71\,362\pm29\,912 \, \text{mU/l}$ to $3456\pm2101 \, \text{mU/l}$, females: from $11\,395\pm5839 \, \text{mU/l}$ to $677\pm360 \, \text{mU/l}$; $P < 0.01$). Body weight and BMI significantly decreased (males: from $101.5\pm5.3 \, \text{kg}$ to $95.3\pm4.8 \, \text{kg}$ and from $30.4\pm1.7 \, \text{kg/m}^2$ to $28.6\pm1.6 \, \text{kg/m}^2$; $P < 0.05$, females: from $68.6\pm3.3 \, \text{kg}$ to $65.0\pm3.1 \, \text{kg}$ and from $24.4\pm1.2 \, \text{kg/m}^2$ to $23.1\pm1.0 \, \text{kg/m}^2$; $P < 0.05$; Table 1 and Fig. 3B). Leptin levels decreased in females from $16.7\pm2.5 \, \mu\text{g/l}$ to $12.9\pm1.8 \, \mu\text{g/l}$ and in males from $14.9\pm1.8 \, \mu\text{g/l}$ to $12.8\pm2.8 \, \mu\text{g/l}$; $P < 0.05$; Fig. 3A). Leptin levels significantly correlated with BMI ($r = 0.546$, $P = 0.009$). Changes in leptin levels did not correlate with changes in prolactin levels ($r = 0.313$, $P > 0.05$; Fig. 1B), but significantly correlated with changes in BMI ($r = 0.459$, $P < 0.05$; Fig. 2B).

Effect of 2 years of BC therapy on weight, BMI, prolactin and leptin levels

Prolactin was near normal in 11 patients with prolactinomas after 2 years of chronic BC therapy (males: from $71\,362\pm29\,912 \, \text{mU/l}$ to $665\pm439 \, \text{mU/l}$, females: from $11\,395\pm5839 \, \text{mU/l}$ to $447\pm130 \, \text{mU/l}$; $P < 0.01$). Body weight and BMI remained decreased (males: from $101.5\pm5.3 \, \text{kg}$ to $88.3\pm4.3 \, \text{kg}$ and from $30.4\pm1.7 \, \text{kg/m}^2$ to $26.5\pm1.9 \, \text{kg/m}^2$; $P < 0.05$, females: from $68.6\pm3.3 \, \text{kg}$ to $65.4\pm2.8 \, \text{kg}$ and from

Table 1 Effects of bromocriptine (BC) therapy on body weight, BMI, prolactin and leptin levels in patients with prolactinomas. Values are (mean±s.e.)

| Characteristics		Pretreatment ($n = 23$)	BC treatment		
			1 month ($n = 23$)	6 months ($n = 23$)	2 years ($n = 11$)
Body weight (kg)	Female	68.6±3.3	67.8±3.3	65.0±3.1*	65.4±2.8*
	Male	101.5±5.3	100.9±5.3	95.3±4.8*	88.3±4.3*
BMI (kg/m²)	Female	24.4±1.2	24.1±1.2	23.1±1.0*	23.6±0.8*
	Male	30.4±1.7	30.2±1.7	28.6±1.6*	26.5±1.9*
Prolactin (mU/l)	Female	11 395±5839	3686±2231*	677±360*	447±130*
	Male	71 362±29 912	17 618±8736*	3456±2101*	665±439*
Leptin (μg/l)	Female	16.7±2.5	13.6±2.1*	12.9±1.8*	18.7±3.1
	Male	14.9±1.8	12.5±1.5*	12.8±2.8*	9.5±2.2

*$P < 0.05$ compared with pretreatment values.
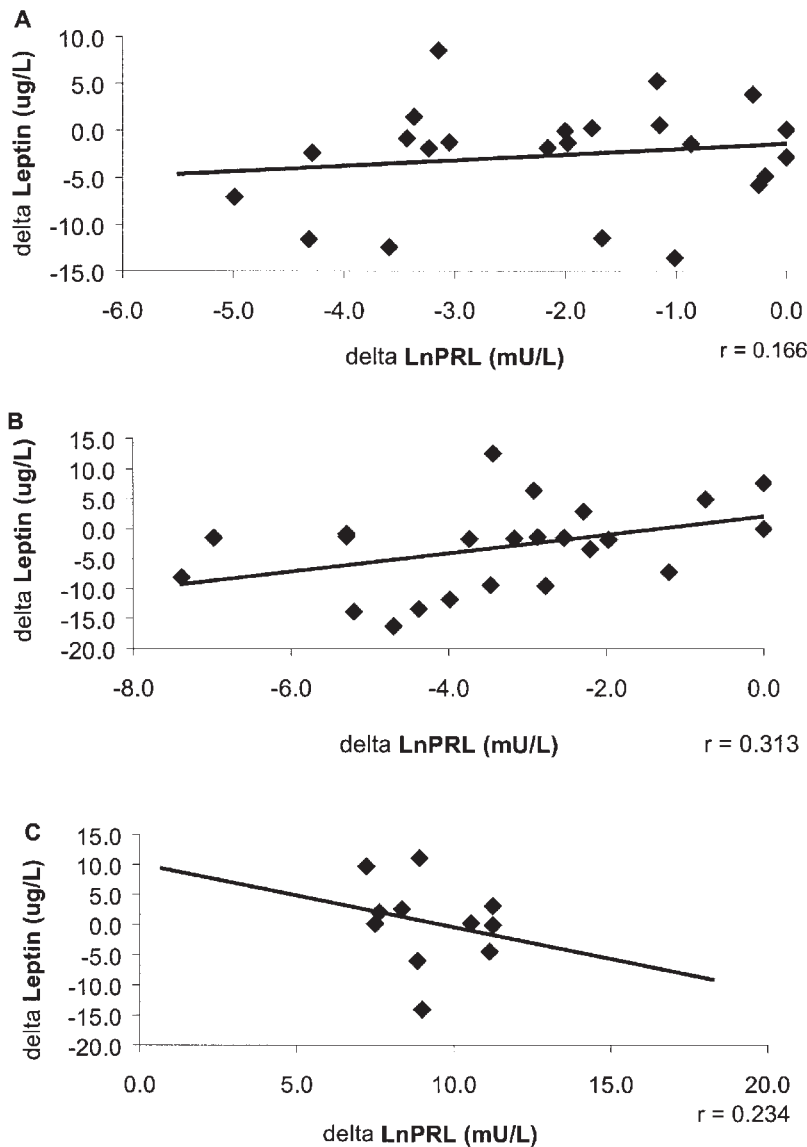
Figure 1 Correlations between the changes in leptin (delta leptin) and logarithmically transformed prolactin (delta LnPRL) levels in patients with prolactinomas after (A) 1 month, (B) 6 months and (C) 2 years of BC therapy.

$24.4\pm1.2\,\text{kg/m}^2$ to $23.6\pm0.8\,\text{kg/m}^2$; $P < 0.05$; Table 1 and Fig. 3B). The change was more pronounced in male patients (Fig. 4). Leptin levels in females increased from $16.7\pm2.5\,\mu\text{g/l}$ to $18.7\pm3.1\,\mu\text{g/l}$ (Fig. 5) and in males they decreased from $14.9\pm1.8\,\mu\text{g/l}$ to $9.5\pm2.2\,\mu\text{g/l}$ ($P > 0.05$; Figs 3A and 4). The change in serum leptin levels significantly correlated with BMI ($r = 0.844$, $P < 0.001$; Fig. 2C) during therapy but not with the change in prolactin levels ($r = 0.234$, $P > 0.05$; Fig. 1C).

Discussion

In our study, 58% of men and 18% of females with pro-lactin-secreting adenomas at initial presentation were overweight (BMI $> 27\,\text{kg/m}^2$). Sustained hyperprolac-tinemia (changed dopaminergic tone) may promote obesity and other studies have confirmed our findings (1, 2). There are several ways by which hyperprolactin-emia might induce fattening: (a) by stimulation of lipo-genesis, (b) by reduction of central nervous system dopaminergic tone and (c) by disruption of circadian neuroendocrine activities within the hypothalamus that regulate dopaminergic tone and thus body compo-sition. Male patients with prolactinomas in our study were obese but the greater than 100-fold decrease in prolactin levels was associated with a reduction in BMI only from 30.4 to 26.5, meaning a weak relation-ship. Female patients presented tremendous prolactin levels before treatment but with a BMI of $24.4\,\text{kg/m}^2$. BC treatment decreased prolactin levels about 25-fold
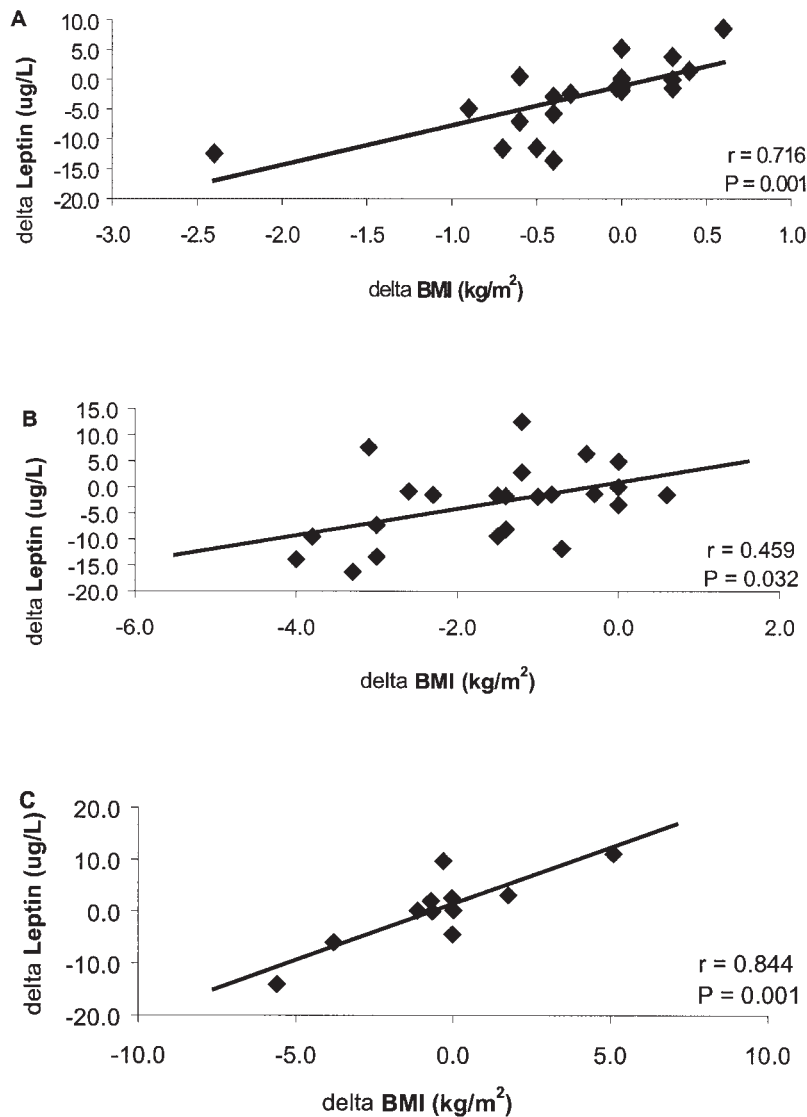
Figure 2 Correlation between the changes in leptin levels (delta leptin) and BMI (delta BMI) in patients with prolactinomas after (A) 1 month, (B) 6 months and (C) 2 years of BC therapy.

yet BMI remained the same. Such data provide good evidence that prolactin is unrelated to BMI in women. Serum leptin levels at initial presentation and during treatment with BC correlated with BMI but not with plasma prolactin levels.

Sexual dimorphism of serum leptin levels was preserved in untreated patients with prolactin-secreting pituitary adenomas after adjusting for BMI and prolactin induced-hypogonadism. This confirms previous findings that, in humans, a clear gender difference exists in leptin levels. The difference may reflect the difference in body composition between men and women. Gonadal function was restored in most patients after 6 months of treatment. Sexual dimorphism of leptin levels gradually increased but was most pronounced after 2 years of therapy with BC when prolactin levels and gonadal functions were normal, implying the influence of testosterone/estrogen on plasma leptin

levels. The gender difference in leptin levels reached twofold higher leptin levels in females after 2 years of treatment. This may be due to the stimulative effect of estrogens and the suppressive effect of androgens which can partially explain the widening of the gender difference in leptin levels.

In rodents, increased plasma prolactin levels obtained by pituitary graft or exogenous injected ovine prolactin significantly stimulated serum leptin concentrations in comparison with controls (7). It has been suggested that prolactin may have a role in energy homeostasis in rodents. To further clarify the roles of prolactin in fuel homeostasis, Freemark *et al.* (9) measured body weight, abdominal fat content and serum leptin in prolactin receptor-deficient mice. These mice showed a reduction of total abdominal fat mass (49% reduction) and a 29% reduction in total fat mass. Females were affected to a greater extent
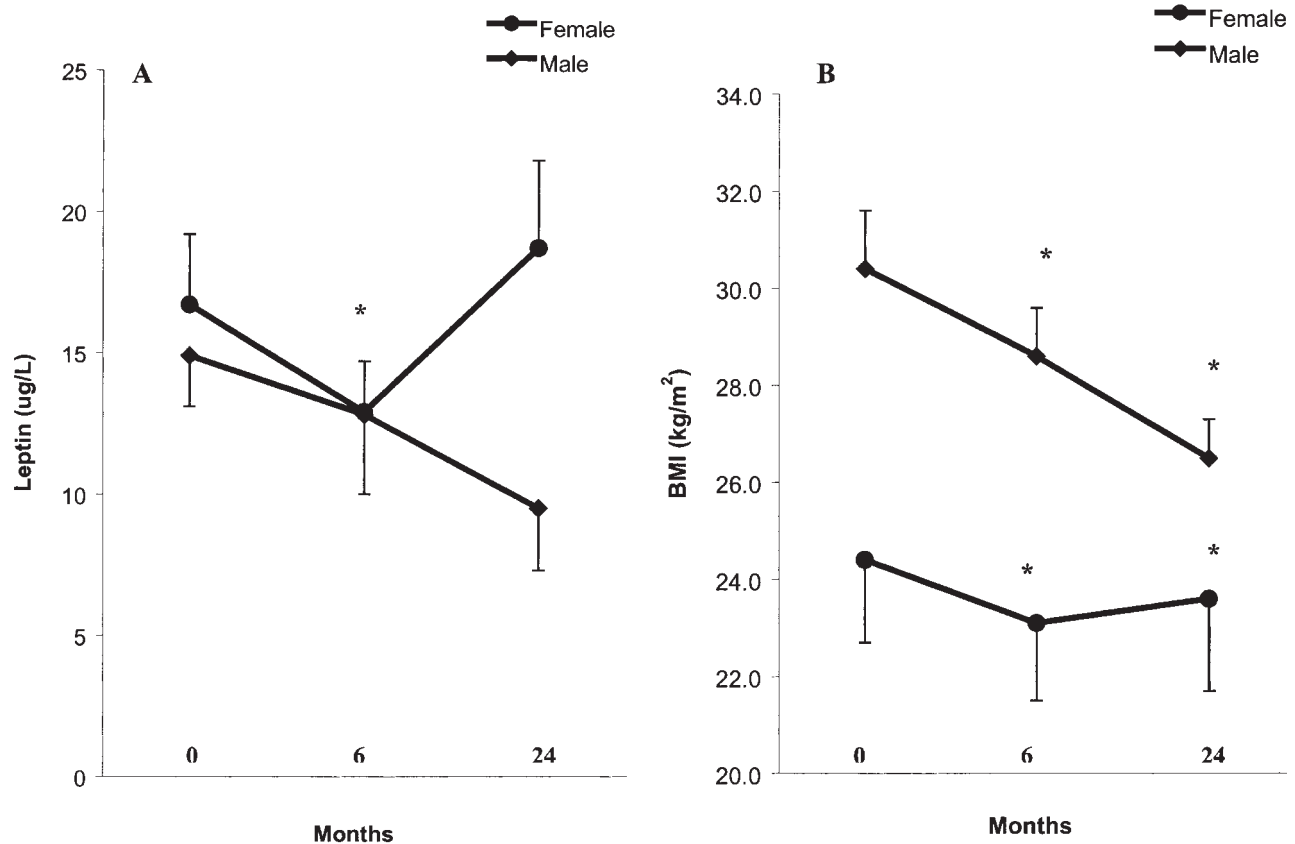
Figure 3 Serum leptin levels and BMI in female and male patients with prolactinomas before and after 6 months and 2 years of BC therapy (means±s.e.; *$P < 0.05$).

than males with reduction in serum leptin levels. Female prolactin receptor-deficient mice are sterile (hypoestrogenic and progesterone deficient) while males have normal testosterone levels. Serum leptin concentrations were reduced in females but not in males. Freemark *et al.* (9) suggest novel roles for the lactogens in adipose tissue growth and metabolism during pregnancy and postnatal life.

In our patients, a significant decrease in plasma prolactin levels during the first month of treatment with BC did not affect body weight or BMI. Thus, changes in prolactin levels *per se* over the short term did not exert any effect on leptin directly. Furthermore, gonadal function was not restored after 1 month of treatment in patients with prolactinomas. The observed reduction in leptin levels at 1 month without change in body weight or BMI may still be indicative of a loss in body fat which has been previously observed in experimental animals (10).

On the other hand, after 6 months and 2 years of therapy, BMI and serum leptin levels decreased in a large proportion of patients. The decrease in body weight was more pronounced in men (-6.2 ± 1.5 kg) but was still significant in women as well (-3.6 ± 1.0 kg). The reduction of prolactin levels did not directly correlate with changes in serum leptin levels

and BMI, suggesting that changes in prolactin levels are not the predominant determinant of changes in body weight, at least in our hyperprolactinemic patients with prolactinomas. Weight loss occurred later than changes in plasma prolactin levels. Furthermore, none of our patients was on special diets that could provide data on daily caloric intake. They were on standard ordinary home diets for the period of the 2 years of follow-up. In non-hyperprolactinemic humans, as in all other vertebrate species examined, the circadian rhythm of and not the absolute level of plasma prolactin is critical in determining the prolactin influence on body fat store level. So, although the correlations of changes in leptin versus changes in prolactin were not significant at any time-point in our study, it is clear that both prolactin and leptin decrease over time as does body weight, suggesting that increased dopaminergic tone may reduce body fat by decreasing lipogenesis in part by decreasing plasma prolactin.

On the other hand, our data do support a role for dopaminergic tone regulating energy balance. Decreased dopaminergic tone in humans is well correlated with obesity (4). Drugs that block dopamine D2 receptors increase appetite and result in significant weight gain as has been reported during short-term (30 days) antipsychotic drug (sulpiride) administration
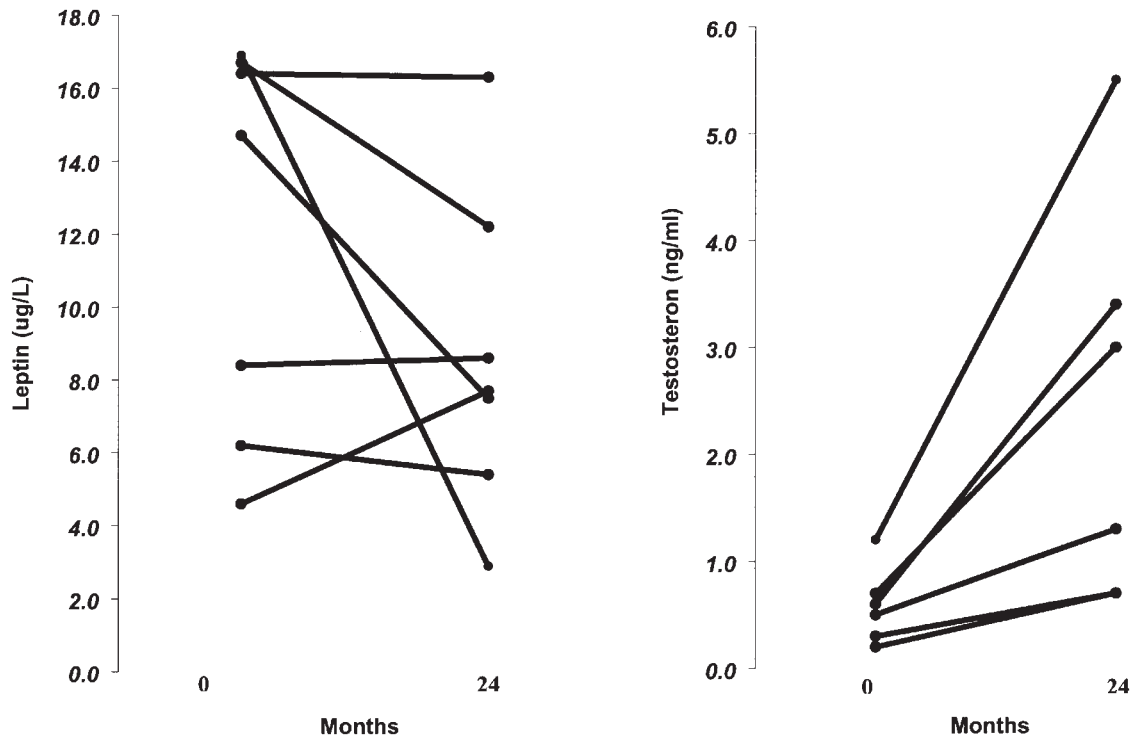
Figure 4 Serum leptin and testosterone concentrations in male patients with prolactinomas before and after 2 years of BC therapy.
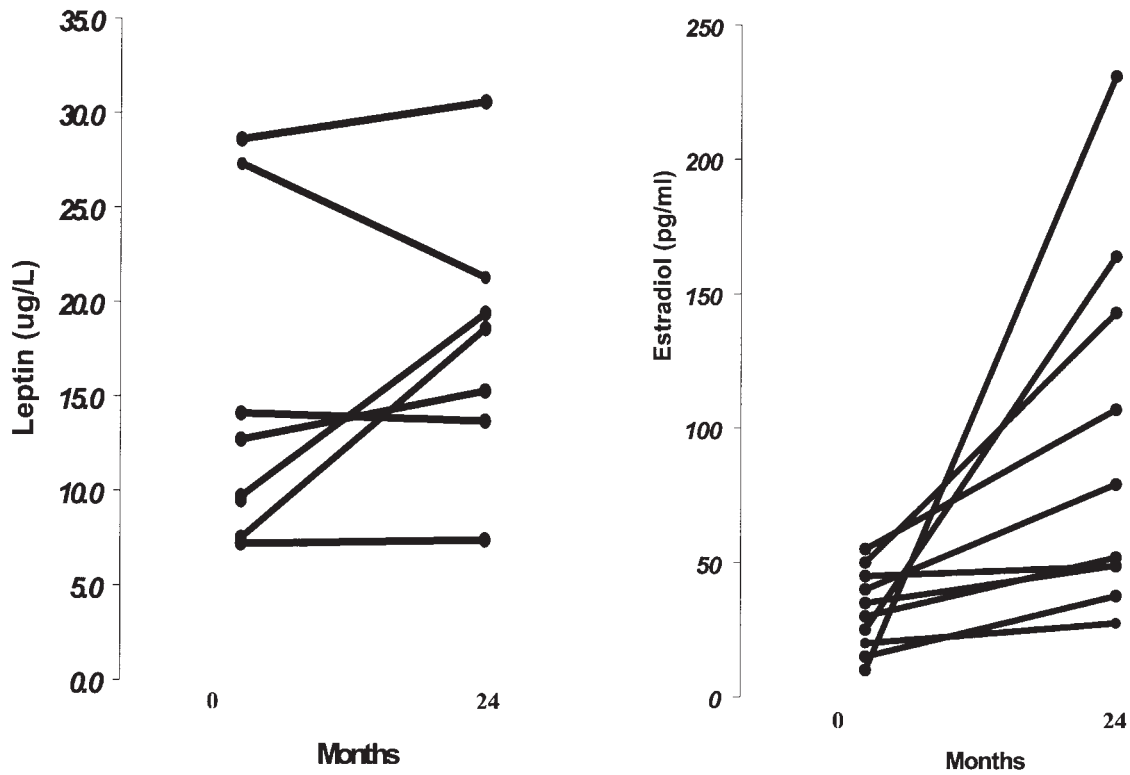

Figure 5 Serum leptin and estradiol concentrations in female patients with prolactinomas before and after 2 years of BC therapy.

to healthy men who gained weight. In addition, amphetamine and sibutramine are drugs that increase dopaminergic tone and are efficacious in treating obesity. Healthy obese subjects treated with BC over an 18-week period showed reduced body weight, loss of body fat and improved glucose tolerance (11). The stimulated area under the oral glucose tolerance test curve was reduced by 46% while the stimulated area under the insulin curve was reduced by 30%. Treatment with SKF 38393 (dopamine D1 receptor agonist) plus BC (dopamine D2 receptor agonist) acted synergistically to normalize hyperphagia, body fat, hyperglycemia and hyperlipidemia in leptin-deficient Ob/Ob mice (12). This treatment not only normalized hyperphagia but redirected several metabolic and endocrine activities independent of its effects on feeding to improve the obese/diabetic syndrome in Ob/Ob mice. Furthermore, a study (13) where the authors examined whether reduction in body fat stores and insulin resistance in Syrian hamsters induced by BC were associated with reductions in daily norepinephrine and serotonin activities showed that BC, a potent dopamine D2 agonist, was effective in decreasing elevated noradrenergic and serotonergic activities centrally within the vetromedial hypothalamus. BC treatment of Syrian hamsters for 2 weeks significantly reduced body fat by 60% and areas under the glucose and insulin curves during glucose tolerance test by 50 and 46% respectively. It has recently been postulated that dopamine regulates food intake by modulating food reward via the meso-limbic circuitry of the brain and that obese individuals have lower dopamine D2 receptor availability in the striatum than normal individuals (4). It has been postulated that compulsive disorders such as drug addiction, gambling and obesity reflect 'rewards deficiency syndrome' which is thought to be due, in part, to a reduction in dopamine D2 receptors. This may have implications for the treatment of obesity aimed at improving dopamine function. Some of our patients reported that BC decreased their food intake, thus being anorexigenic and, furthermore, none of our patients changed their life-style during the 2-year period.

In conclusion, we have to consider the possibility that the long-acting dopamine agonist BC, by increasing dopaminergic tone, may influence body weight and likely body composition by mechanisms in addition to reducing hyperprolactinemia.

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