Original Article

Profile of leptin, adiponectin, and body fat in patients with hyperprolactinemia: Response to treatment with cabergoline

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ABSTRACT

Introduction: Though hypoadiponectinemia and leptin resistance have been proposed as potential factors for weight gain in patients with hyperprolactinemia (HPL), the effects of HPL and cabergoline on these adipocyte-derived hormones are not clear. Aims of this study were (i) to assess the alterations of body fat, leptin, and adiponectin in patients with HPL (ii) effect of cabergoline treatment on these parameters. **Methods:** Nineteen consecutive patients with prolactinoma (median prolactin [PRL] 118.6 (interquartile range: 105.3) μg/L) and 20 controls were studied in a nonrandomized matched prospective design. The controls were age, gender, and body mass index (BMI) matched. Anthropometric data, metabolic variables, leptin, and adiponectin were studied at baseline and 3 and 6 months after cabergoline treatment. **Results:** Patients with prolactinoma had increased level of fasting plasma glucose ($P < 0.001$) as compared to age-, gender-, and BMI-matched healthy controls. Estradiol concentration of controls was higher than that of patients ($P = 0.018$). Patients with prolactinoma had higher levels of leptin ($P = 0.027$) as compared to healthy controls without a significant difference in adiponectin levels. There was a significant decrease of body weight at 3 months ($P = 0.029$), with a further decline at 6 months ($P < 0.001$) of cabergoline therapy. Furthermore, there was a significant decrement of BMI ($P < 0.001$), waist circumference ($P = 0.003$), waist-hip ratio ($P = 0.03$), total body fat ($P = 0.003$), plasma glucose ($P < 0.001$), leptin levels ($P = 0.013$), and an increase in estradiol concentration ($P = 0.03$) at 6 months of cabergoline treatment. **Conclusion:** Patients with prolactinoma have adverse metabolic profile compared to matched controls. Normalization of PRL with cabergoline corrects all the metabolic abnormalities.

Key words: Adiponectin, body fat, cabergoline, hyperprolactinemia, leptin

INTRODUCTION

Hyperprolactinemia (HPL) affects many metabolic functions in addition to its well-known effects on lactation and gonadal function.[1-3] It has also been associated with weight gain and obesity and in some studies, an improvement in weight after dopamine agonist (DA) treatment has been documented.[4,5] The exact mechanism of weight gain in patients with HPL is not known; however, increased lipoprotein lipase activity, decreased dopaminergic tone, decreased adiponectin level, and hypogonadism are some of the possible responsible factors.[6-8] HPL has also been associated with alteration of lipid and carbohydrate metabolism. In addition to pituitary

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gland, prolactin (PRL) is also produced, and its receptors are expressed in adipose tissue. Role of PRL in inhibiting lipoprotein lipase activity *in vitro* has been suggested.[9,10] Hyperprolactinemic states whether physiological (such as pregnancy and lactation) or pathological such as prolactinomas are associated with an increase in the leptin levels because of its increased release.[11-13] PRL is also known to decrease adiponectin in both *in vivo* and *in vitro*.[8] HPL is also associated with hypoadiponectinemia which results in decrease in insulin sensitivity. However, there are few data with regard to the effect of HPL on adiponectin in patients with prolactinoma. This study was aimed to analyze: (1) The alteration in leptin and adiponectin levels and body fat in people with prolactinoma as compared to age, gender, and body mass index (BMI) matched controls (2) the effect of normalization of PRL with cabergoline treatment on these parameters.

METHODS

Selection of participants
This study was conducted in the Department of Endocrinology at a Tertiary Care Hospital in North India over a period of 1½ years. Twenty eight consecutive patients with HPL because of PRL secreting pituitary adenoma and 20 age, gender, and BMI-matched controls were included in the study. Of 28 patients, 8 women were excluded (4 conceived and 4 were lost to follow-up). One man with prolactinoma and hypogonadism, on testosterone replacement, was also excluded in the final analysis. Thus, the final sample consisted of 19 patients (18 women and 1 man) and 20 controls. The study was approved by the Institutional Ethics Committee and informed consent was obtained from all patients and controls. Patients with elevated PRL levels on at least two occasions and magnetic resonance imaging (MRI) evidence of pituitary adenoma were included. Exclusion criteria were secondary causes of HPL, pregnancy, or patients on medication for dyslipidemia and diabetes mellitus at study entry.

Study protocol
Anthropometric and laboratory measurements in cases and controls were assessed at baseline. Patients with prolactinoma were reassessed at 3 and 6 months after initiation of cabergoline treatment. Blood samples were taken after an overnight fast for the measurement of plasma glucose, hormones (PRL, thyroid stimulating hormone [TSH], T4, estradiol, growth hormone [GH], follicle-SH [FSH], and luteinizing hormone [LH]), and adipocytokines (adiponectin and leptin). All the patients were treated with cabergoline (0.5 mg orally/week) with dosage titration until normalization of serum PRL. Serum PRL was monitored every month until normalization.

During the study period, patients were instructed to continue their routine homemade diets and physical activity.

Anthropometric data
Both cases and controls were examined by measurement of weight and height using standard measurements. BMI was calculated as weight in kg divided by square of height in meters (kg/m²). Measurements of waist and hip were taken to calculate waist-hip ratio. Total body fat was measured by DEXA scan (GE lunar DPX pro) at baseline in both cases and controls and after 6 months of cabergoline treatment in patients with prolactinoma. Obesity was defined as per "Asia-Pacific guidelines of obesity classification."[14]

Biochemical and hormonal assays
Serum PRL was measured using commercial chemiluminescent immunoassay (Beckman Coulter Unicel, DXI), normal range: 1–27 μg/L (women); 1–20 μg/L (men). TSH, T4, FSH, LH, GH, cortisol, and estradiol were also measured using commercial chemiluminescent immunoassay (Beckman Coulter Unicel, DXI). Plasma glucose was measured by enzymatic method using glucose oxidase and peroxidase on an automated chemistry analyzer (HITACHI-912). Serum leptin and adiponectin were estimated using commercially available ELISA Kits (Ani Biotech Orgenium Laboratories, FINLAND) as per the manufacturer's protocol.

Statistical analysis
The statistical software SPSS 21 (IBM SPSS Statistics 21) was used to analyze the data. The continuous variables are shown in terms of descriptive statistics such as mean, standard deviation (SD), median, and inter quartile range. The parametric and nonparametric tests have been used to analyze the data after verifying the distribution of variables with the help of Shapiro-Wilk test. The Student's independent *t*-test and Wilcoxon–Mann–Whitney U-test were used to compare the parameters between cases and controls at baseline. Furthermore, the paired *t*-test and Wilcoxon signed rank test have been used to analyze the data at baseline and 3 and 6 months of cabergoline treatment. All results have been described on 5% level of significance, i.e. $P < 0.05$ considered as significant.

RESULTS

Of nineteen patients, 15 had microadenoma and 4 had macroadenoma. Of 18 women, 1 had primary amenorrhea, 12 had secondary amenorrhea, and the other 5 were eumenorrheic. Four women had primary infertility and two had secondary infertility. Two women had primary hypothyroidism and were on adequate doses of levothyroxine at the time of entry in the study. Two patients with macroprolactinoma had morning cortisol <275.9 mmol/L.

Insulin tolerance test documented normal cortisol and GH response in both these patients. In none of these patients, there was any suggestion of extension of pituitary mass into third ventricle on MRI.

Serum PRL normalized in 18 out of 19 patients after 1 month and in 1 patient within 6 months of cabergoline therapy. Median PRL level decreased from 118.6 ± 105.3 μg/L at baseline to 10.4 ± 20 μg/L at 3 months ($P < 0.001$) and 9.4 ± 5.9 μg/L at 6 months ($P < 0.001$).

Metabolic and anthropometric parameters and adipocytokines in cases and controls

Of 19 patients, 7 (36.8%) were obese, 4 (21%) were overweight, and 2 had impaired fasting glucose. Among controls, 4 (20%) were obese, 4 (20%) were overweight, and none had impaired fasting glucose. Mean (SD) age of

patients was 27.3 (6.2) years and BMI was 24.2 (4) kg/m². With cases and controls comparable in body weight and BMI, patients with prolactinoma had significantly higher trunk fat on DEXA measurement; mean (SD) truncal fat of 11.0 (4.2) kg in cases and 9.3 (2.8) kg in controls ($P = 0.044$), though there was no difference in total body fat. Patients with prolactinoma had significantly higher level of fasting plasma glucose compared to controls (4.8 ± 0.5 mmol/L in cases and 4.2 ± 0.3 mmol/L for controls, $P < 0.001$). Patients with prolactinoma had higher levels of leptin as compared to controls (6.15 ± 2.24 pg/ml in cases and 4.66 ± 1.89 pg/ml for controls, $P = 0.027$), while as there was no significant difference in adiponectin levels [Table 1].

Metabolic and anthropometric parameters and adipocytokines before and after cabergoline treatment

The prevalence of obesity declined from 36.8% at baseline to 21% at 6 months after cabergoline treatment, with a decline in mean (SD) body weight from 57.3 (9.5) kg at baseline to 54.8 (9.2) kg after 6 months ($P < 0.001$). Similarly, there was a significant decrease in mean (SD) BMI from 24.2 (4.0) kg/m² at baseline to 23.2 (3.9) kg/m² ($P < 0.001$) and that of mean (SD) body fat (kg) from 22.4 (7.8) to 21.1 (6.8) after 6 months of cabergoline treatment ($P = 0.003$). Similar trend was noted with mean (SD) fasting plasma glucose from 4.8 ± 0.5 mmol/l to 4.3 ± 0.3 mmol/l ($P < 0.001$) and median (interquartile range) leptin from 6.15 (2.24) pg/ml at baseline to 4.82 (1.51) pg/ml after 6 months of treatment ($P = 0.013$) without any significant change in adiponectin levels. Two patients with impaired fasting plasma glucose were documented to have normal plasma glucose after cabergoline treatment [Table 2].

Hormonal profile of cases and controls
Mean estradiol at baseline in patients with prolactinoma was

Table 1: Baseline characteristics of cases and controls

Parameter	Cases (*n*=19)	Controls (*n*=20)	*P* value
≠Age	27.3 (6.2)	27.1 (5.6)	0.9
Gender (men : women)	1 : 18	2 : 18	
≠Body weight (kg)	57.3 (9.5)	60.3 (11.1)	0.35
≠BMI (kg/m²)	24.2 (4.0)	24.6 (3.9)	0.73
≠Waist (cm)	85.3 (12.0)	83.3 (7.4)	0.52
≠Hip (cm)	91.1 (8.7)	91.4 (9.0)	0.91
Waist-hip ratio	0.94 (0.12)	0.92 (0.09)	0.68
Body fat (kg)	23.4 (10.4)	20.5 (8.3)	0.69
≠Trunk fat (kg)	11.0 (4.2)	9.3 (2.8)	0.044
≠Fasting glucose (mmol/L)	4.8 (0.5)	4.2 (0.3)	<0.001
≠Uric acid (μmol/L)	297.9 (66.6)	206.9 (75.5)	<0.001
≠FSH (IU/l)	5.7(2.6)	5.8(1.8)	0.88
≠LH (IU/l)	5.3(4.4)	5.2(1.5)	0.96
≠Estradiol (pg/ml)	52.7(24.3)	85.7(42.6)	0.018
Leptin(pg/ml)	6.15(2.24)	4.66(1.89)	0.027
Adiponectin(pg/ml)	18.69(5.88)	17.17(4.93)	0.35

≠Normally distributed data are expressed as mean (SD).Other data (non-normally distributed) expressed as median. IQR: Interquartile range

Table 2: Anthropometric, metabolic and hormonal profile of patients at diagnosis and after 3 and 6 months on cabergoline treatment

Parameter	Baseline	Cabergoline treatment		*P* value	
		3 months	6 months	*	†
≠Body weight (kg)	57.3 (9.5)	56.6 (9.1)	54.8 (9.2)	0.029	<0.001
≠BMI (kg/m²)	24.2 (4.0)	23.9 (4.2)	23.2 (3.9)	0.09	<0.001
≠Waist (cm)	85.3 (12.0)	84.9 (11.3)	82.3 (10.0)	0.30	0.003
≠Waist-hip ratio	0.9 (0.06)	0.9 (0.06)	0.9 (0.07)	0.89	0.039
Body fat (kg)	23.4. (10.4)	-	22.3 (11.8)	-	<0.001
PRL (μg/L)	118.6 (105.3)	10.45 (20.0)	9.4 (5.9)	<0.001	<0.001
≠TSH (U/L)	3.4 (1.7)	3.7 (2.0)	4.3 (1.3)	0.60	0.09
≠T4 (nmol/L)	110.5 (25.2)	125.3 (33.9)	114.4 (22)	0.10	0.60
≠Fasting glucose (mmol/L)	4.8 (0.5)	4.6 (0.4)	4.3 (0.3)	0.006	<0.001
FSH (IU/l)	6.0(3.8)	5.6(4.0)	5.6(3.2)	0.87	1.00
LH (IU/l)	5.1(7.4)	5.23(2.7)	5.3(1.3)	0.62	0.54
≠Estradiol (pg/ml)	52.7(24.3)	87.7(54.5)	63.4(167.4)	0.004	0.12
Leptin(pg/ml)	6.15(2.24)	5.80(2.86)	4.82(1.51)	0.67	0.013
Adiponectin(pg/ml)	18.69(5.88)	18.63(5.08)	17.35(4.66)	0.96	0.49

Baseline compared with *3 months and †6 months after cabergoline treatment. ≠Normally distributed data are shown as mean (SD).Other data (non-normally distributed) are expressed as median. IQR: Interquartile range

significantly lower as compared to controls (52.7 ± 24.3 pg/ml in cases and 85.7 ± 42.6 pg/ml for controls, $P = 0.018$) and it increased to 87.7 ± 54.5 pg/ml after 3 months ($P = 0.004$) without any further significant increase after 6 months of cabergoline treatment ($P = 0.12$). Concentrations of FSH and LH were in normal range both at beginning and at the end of treatment [Tables 1 and 2].

DISCUSSION

The metabolic manifestations of HPL are not completely understood. Decreased dopaminergic tone has been hypothesized to play a vital role in promoting weight gain in HPL[6,15] and normalization of PRL with DA treatment has been found to reduce body fat and BMI as a result of activation of type 2 dopamine receptor.[16] Some studies have described HPL associated weight gain predominantly in men with striking weight loss after DA treatment[17,18] whereas others did not reveal any correlation between HPL and body weight, and DA treatment did not lead to weight loss in patients with HPL.[19,20] HPL has been found to be associated with many metabolic abnormalities in both men and women. Patients with HPL have insulin resistance and glucose intolerance compared to normal individuals.[17,18] In the present study, we documented increased level of fasting plasma glucose in patients with prolactinoma compared to age-, gender-, and weight-matched controls. Previously, many case–control studies have documented increased insulin resistance and abnormal glucose tolerance in patients with prolactinoma compared to healthy controls.[5,21-23] In the present study, we documented higher levels of fasting plasma glucose in patients with prolactinoma compared to age-, gender-, and BMI-matched healthy controls implying that diabetogenic effect of HPL may be independent of gender and body weight. There is limited data on the body fat distribution in patients with HPL, though some studies have demonstrated higher body fat mass in patients with HPL in the presence of high prevalence of obesity.[21] Our study results revealed higher trunk fat mass in patients compared to BMI-matched control population, without a significant difference in total body fat mass. Patients with prolactinoma had lower serum estradiol concentration compared to healthy controls which is related to hypogonadism.

In humans, leptin levels are influenced by the amount of body fat, being higher in obese individuals,[24] and the correlation between HPL and leptin levels is not clear. Though some case–control studies have documented higher levels of leptin in patients with HPL compared to matched controls with positive correlation between leptin and PRL, with some studies showing a significant decline in leptin levels in men with prolactinomas, after

DA treatment.[13,17] However, other studies in patients with prolactinomas neither revealed a correlation between these two parameters nor there was a decline of leptin levels on follow-up after cabergoline treatment.[6,25] In our study, patients with prolactinoma had higher levels of leptin compared to age-, gender-, and BMI-matched controls with a significant decline of leptin levels after 6 months of cabergoline treatment.

Hyperprolactinemic states such as pregnancy and lactation have been found to be associated with hypoadiponectinemia.[26,27] The effect of PRL on adiponectin levels in healthy individuals and in patients with HPL is not completely understood. Some case–control studies have documented hypoadiponectinemia in patients with prolactinoma as compared to healthy controls.[28] whereas, other studies did not find correlation between PRL and adiponectin in healthy women.[29,30] In some studies, adiponectin levels did not change after 6 months of treatment with DAs in patients with prolactinomas.[17] In our study, there was no significant difference in serum adiponectin levels in cases and controls and the levels did not change after 6 months of cabergoline treatment.

Conflicts of interest
There are no conflicts of interest.

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