Increased body weight associated with prolactin secreting pituitary adenomas: weight loss with normalization of prolactin levels

Yona Greenman, Karen Tordjman and Naftali Stern
Institute of Endocrinology, Tel Aviv-Elias Sourasky Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Summary

OBJECTIVE Hyperprolactinaemia in humans may be associated with a high prevalence of obesity but the nature of this link is poorly defined. The aim of this study was to establish the relationship between hyperprolactinaemia and body weight in patients with prolactin-secreting pituitary tumours.

DESIGN We conducted a retrospective study of prolactinoma patients treated at the Endocrine Institute of the Tel Aviv Medical Center, Israel, during the period 1989–1996. Patients with clinically non-functioning pituitary macroadenomas (NFA) served as the control group. Data on demographic parameters, body weight before and during treatment, clinical presentation including history of weight fluctuations, tumour size as measured by computed tomography or magnetic resonance imaging, modalities and response to treatment, and pituitary function before and during treatment were recorded from medical files.

PATIENTS Forty-two patients with prolactinomas (PR) and 36 patients with clinically non-functioning macroadenomas (NFA) comprised the study population.

RESULTS Mean weight was 93 ± 3.4 kg and 78 ± 2.7 kg in male patients with PR and NFA respectively (P = 0.0007). Recent weight gain (8 to 22 kg) was a presenting symptom in 13 PR patients, whereas only one NFA patient had this clinical presentation (P = 0.001). Seventeen PR patients lost weight (mean change –8.3 ± 1.5 kg, range –2–28 kg), during prolactin lowering therapy, 11 of whom had entirely normalized prolactin levels. Fourteen of the 18 patients who did not lose weight still had elevated prolactin levels (P = 0.01). Weight loss in patients with PR could not be attributed to altered pituitary function nor to compression of the third ventricle. In contrast to PR, no significant weight loss was observed in NFA patients.

CONCLUSION Weight gain and elevated body weight are frequently associated with prolactinomas regardless of a mass effect on the hypothalamus or pituitary function. In this series, weight loss was recorded in 70% of prolactinomas patients and in 90% of male patients who normalized their prolactin levels. We propose the inclusion of hyperprolactinaemia in the differential diagnosis of endocrine obesity and weight gain.

Endocrine disorders are involved in the pathogenesis of obesity in a minority of patients (Amatruda & Welle, 1995). Nevertheless, steroid hormone excess and thyroid hormone deficiency are routinely screened for in the evaluation of the obese patient, as early diagnosis and treatment of these disorders prevent the development of serious systemic complications (Amatruda & Welle, 1995).

Hyperprolactinaemia in humans may be associated with a relatively high rate of obesity (Lachelin et al., 1977; Nunes et al., 1980) and in several animal species central prolactin administration has been found to increase food intake (Noel & Woodside, 1993). The nature of the link between high prolactin levels and body weight is poorly defined, so it is not common practice to measure prolactin levels as part of the work-up of overweight patients. To clarify further the relationship between hyperprolactinaemia and body weight, we conducted a retrospective study in patients with prolactin-secreting pituitary adenomas.

Methods

Patients

Prolactinoma (PR) patients treated at the Endocrine Institute of the Tel Aviv Medical Center, Israel, from 1989 to 1996
were included in this analysis. Entry criteria were as follows: (1) unequivocal radiographic documentation of pituitary adenoma by at least three experienced readers, associated with persistent hyperprolactinaemia which could not be attributed to drug therapy, stress, hypothyroidism, end-stage renal disease, or other established causes of increased circulating prolactin; (2) minimal follow-up of 4 months. Patients suffering from clinically nonfunctioning pituitary tumours (NFA) served as the control group. Medical files were reviewed by one of the investigators and data on demographic parameters, body weight before and during treatment, clinical presentation including history of weight fluctuations, tumour size as measured by computed tomography (CT) or magnetic resonance imaging (MRI), modalities of and response to treatment, and pituitary function before and during treatment were recorded. Inquiring about recent weight changes is part of the routine initial assessment of patients in our clinic and this information could be retrieved in the majority of the cases. Specific anterior pituitary hormone deficiencies were defined using standard criteria as previously described (Greenman et al., 1995). Briefly, secondary hypogonadism in men was diagnosed when serum levels of testosterone or bioavailable testosterone were low (testosterone, <10 nmol/l; bioavailable testosterone, <3.5 nmol/l) on at least three different occasions, in the presence of low or normal levels of gonadotrophins (<12 IU/l). In premenopausal women, a deficiency in gonadotrophin secretion was assumed in the presence of amenorrhoea or oligomenorrhoea and infertility and/or when low or normal levels of gonadotrophins (LH, 4–15 IU/l; FSH, 1–10 IU/l) were associated with consistently low oestradiol levels (<37 pmol/l on at least three occasions after day 21 of the menstrual cycle). In postmenopausal women a deficiency of gonadotrophin secretion was diagnosed when serum levels of LH and/or FSH were inappropriately low for age (<30 IU/l). Hypothyroidism was defined when a subnormal serum T4 level (<64 nmol/l) or free T4 level (<9 pmol/l) was associated with a low or normal TSH level (1–5 mU/l). Deficiency of pituitary ACTH secretion or impaired ACTH reserve was diagnosed when the serum 0800 h cortisol levels were low (<140 nmol/l) or low normal (140–280 nmol/l) and failed to increase by at least 200 nmol/l above the baseline, with a peak cortisol level of at least 500 nmol/l after insulin-induced hypoglycaemia or ACTH stimulation. In the patients tested with metyrapone overnight (2–3 g metyrapone given at midnight), ACTH deficiency was diagnosed when the following morning serum 11-deoxycortisol measurement was less than 200 nmol/l in the presence of an adequately inhibited morning cortisol level (<140 nmol/l). The prevalence of GH deficiency in this series could not be assessed reliably because only a few patients have had more than one provocative test of GH secretion. Prolactin levels greater than 425 mU/l were considered to be elevated. Pituitary function was assessed prior to starting treatment, 3 to 6 months post-operatively or into medical therapy and whenever indicated thereafter. Radiographic parameters recorded for the analysis were the presence of micro- (<10 mm) or macroadenomas (>10 mm), suprasellar extension and in particular, evidence of tumour pressure on the hypothalamic area. Weight and pituitary function tests at the last available clinic visit were used in the final analysis. There were 42 PR patients (F/M, 24/18) and 36 patients (F/M, 14/22) in the control group.

Hormone measurements

All hormones were measured in duplicate using commercial assay kits as follows: T3, cortisol, 17β-oestradiol, testosterone, RIA (Diagnostic Products Corp., Los Angeles, CA); TSH, immunoradiometric assay, magnetic solid phase (Serono Diagnostics, Woking, UK); FT4, LH and FSH, RIA (Amerlex, Amersham, Aylesbury, UK); prolactin, enzyme immunoassay (Boehringer, Mannheim, Germany; normal range, 106–425 mU/l). Bioavailable testosterone (BT) was measured by a modification of a method described by Tremblay and Duke, as described by Greenman et al. (1995). Briefly, tracer amounts of tritiated testosterone were added to serum aliquots (0.5 ml), which were then incubated for 30 min at 37°C. An equal volume of a saturated solution of ammonium sulphate was added to precipitate the globulin fraction, which included the sex-hormone binding globulin-bound testosterone. After separation of the sex-hormone binding globulin fraction by centrifugation (1100 g for 3 min), the supernatant was counted. The product of the percentage of labelled testosterone remaining in the supernatant times the concentration of BT. For 11-deoxycortisol determination, samples were analysed using a high-pressure liquid chromatography method as described by Tordjman et al. (1995).

Statistical analysis

Results are expressed as means ± SEM. They were analysed with paired and unpaired Student’s t-test as appropriate. The Mann-Whitney test was used for nonparametric data. Categorical data were analysed by Fisher’s exact test for 2 × 2 tables. Multivariate linear regression analysis was used for evaluation of the influence of different variables on the observed weight change. A two-tailed P-value of less than 0.05 was considered of statistical significance.

Results

Twenty-five patients had macroadenomas and 17 prolactin-secreting microadenomas. As might be expected, the majority
of men had macroprolactinomas (16 macroadenomas and two microadenomas) as opposed to women in whom microprolactinomas predominated (15 microadenomas and nine macroadenomas), \( P = 0.002 \). All 36 patients suffering from NFA had macroadenomas (Table 1). In seven of the 42 patients (16·6%) with PR there was radiographic evidence of pressure on the floor of the third ventricle whereas in 11 of the 36 patients with NFA (30·5%) pressure signs were present on CT or MRI (\( P = \text{NS} \)). Patients with prolactinomas were younger than NFA patients (37 ± 2·4 years vs 60 ± 2 years, \( P = 0.0001 \)). Pretreatment prolactin levels were 481·2 ± 63·6 mU/l, 1250 ± 190·8 mU/l, and 62964 ± 17172 mU/l in patients with NFA, micro- and macroprolactinomas, respectively (\( P < 0.0001 \)).

Thirty-seven PR patients were treated with the dopamine agonist bromocriptine (BC). One of them was subsequently switched to treatment with the non-ergot dopamine agonist quinagolide due to resistance to treatment. One post-menopausal woman received concomitant oestrogen replacement therapy. Of the 10 PR patients who underwent transphenoidal adenomectomy, two received also adjuvant radiotherapy. Five patients did not receive any medical treatment. Thirty-five patients with NFA underwent transphenoidal surgery, eight of whom subsequently received radiation therapy. Three NFA patients were treated with BC and in one of these subjects this was the only therapeutic modality.

**Pre-treatment weight**

Mean weight and BMI were significantly higher in male patients with PR than with NFA (93 ± 3·4 kg and 31·6 ± 1·1 kg/m² vs 78 ± 2·7, \( P = 0.0007 \) and 26·5 ± 1·1 kg/m² \( P = 0.002 \), respectively). This weight excess in male PR patients could not be attributed to differences in age, as they were significantly younger than NFA male patients (46·4 ± 4·1 years vs 61·7 ± 2·8 years, respectively, \( P = 0.0034 \)). Conversely, although female patients with NFA tended to be heavier than hyperprolactinaemic women (79·6 ± 6·1 kg and 31·2 ± 2·5 kg/m² vs 67·5 ± 3·1 kg and 26·1 ± 1·3 kg/m² respectively), this difference was not statistically significant. The expected age-related increase in weight might have played a role in this finding as NFA female patients were older than female PR patients (58 ± 3 ± years and 30 ± 2 years, respectively, \( P = 0.0001 \)). There were no differences in weight between women with micro- or macroprolactinoma.

**Recent weight gain**

Recent weight gain (8 to 22 kg) was a presenting symptom in 13 patients (5 men, 8 women) with PR (31%), whereas only one patient with NFA (2·7%) had this presentation (\( P = 0.001 \)). Clinical history of weight gain in hyperprolactinaemic patients was not related to tumour size (five had microadenomas, five had large macroadenomas, and three had intrasellar macroadenomas) nor to the degree of suprasellar extension as only two of them had imaging evidence of pressure on the hypotalamic area.

**Effect of therapy on weight**

In 35 treated patients with PR and in 34 patients with NFA, follow-up weight records were available. Mean follow up time was 18 ± 3 months and 30 ± 3 months in patients with PR and NFA respectively (\( P = 0.0073 \)). Notable weight fluctuations did not occur during the longer follow up period of NFA patients.

Overall, patients with PR lost an average of 4 ± 1·2 kg whereas NFA patients gained 2 ± 0·7 kg (\( P = 0.0001 \)). The difference was more pronounced in male PR patients with a mean weight loss of 5·7 ± 2·4 kg as opposed to a mean weight gain of 2·8 ± 1·0 kg in NFA (\( P = 0.0009 \)). Only a small weight loss was seen in treated female PR patients (−1·8 ± 0·8 kg vs 0·6 ± 0·5 kg in NFA, \( P = 0·04 \); Table 2). Although male PR patients lost more weight than females, this difference was not significant (\( P = 0·1 \)). Weight loss occurred in 13 (three women, 10 men) out of 23 patients with macroprolactinomas and in four (all female) of 12 patients with microprolactinomas with available follow-up weight records (\( P = \text{NS} \)). Multivariate linear regression analysis was performed to assess the possible influence of different parameters on weight loss. Sex \((P = 0·26, \text{age} (P = 0·6)), \text{evidence of pressure on the}

### Table 1 Clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Prolactinomas</th>
<th>NFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 2·4</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>F/M</td>
<td>24/18</td>
<td>14/22</td>
</tr>
<tr>
<td>Macroadenomas</td>
<td>25 (59·5)</td>
<td>36 (100)</td>
</tr>
<tr>
<td>Pressure on hypothalamus</td>
<td>7 (16·6)</td>
<td>11 (30·5)</td>
</tr>
<tr>
<td>Recent weight gain</td>
<td>13 (31)</td>
<td>1 (2·7)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>18·3 ± 3</td>
<td>30 ± 3</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate percentages.


### Table 2 Weight change (kg) on treatment

<table>
<thead>
<tr>
<th></th>
<th>Prolactinoma</th>
<th>NFA</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>−5·7 ± 2·4</td>
<td>2·8 ± 1</td>
<td>0·0009</td>
</tr>
<tr>
<td>Female</td>
<td>−1·8 ± 0·8</td>
<td>0·6 ± 0·5</td>
<td>0·04</td>
</tr>
<tr>
<td>All</td>
<td>−4 ± 1·2</td>
<td>2 ± 0·7</td>
<td>0·0001</td>
</tr>
</tbody>
</table>
hypothalamic area ($P = 0.34$) and tumour size (micro- vs macroadenoma; $P = 0.07$) had no predictive value on weight changes during treatment. Prolactin normalization (see below) was the only independent variable predictive of weight loss during treatment ($P = 0.013$). Overall recent weight gain or weight loss on therapy were recorded in 28 of the 42 PR patients but in only four of the 36 NFA patients ($P < 0.0001$).

**Weight loss in relation to prolactin levels**

Treatment significantly reduced prolactin levels in all patient groups. Prolactin levels recorded at the last medical visit during treatment were $280 \pm 36$ mU/l, $562 \pm 155$ mU/l and $6084 \pm 3434$ mU/l in NFA, micro- and macroprolactinomas, respectively ($P = 0.02$, 0.01 and 0.002 respectively in relation to pre-treatment values). PR Patients who normalized prolactin levels with treatment lost $7.4 \pm 2$ kg ($P = 0.0033$) as opposed to patients with persistent hyperprolactinaemia who did not significantly lose weight ($-1.1 \pm 1$ kg, $P = NS$; Fig. 1). However, there was no quantitative correlation between the changes in prolactin and weight. Again, the impact of prolactin normalization was much stronger in men ($-10.2 \pm 2.6$ kg in men who normalized prolactin levels vs $0.3 \pm 2.5$ kg in men who did not, $P = 0.0097$) than in women ($-1.9 \pm 1.5$ kg vs $-1.5 \pm 1.2$ kg in women who did and did not normalize prolactin levels, respectively, $P = NS$). In fact, the overall weight loss in PR subjects normalizing their prolactin levels was entirely attributable to this effect in men since the prolactin normalization per se had no notable effect on mean weight changes in women. Overall, 11 of the 15 patients who normalized prolactin levels lost weight as opposed to weight loss in only six of the 20 patients who did not normalize prolactin levels ($P = 0.017$, Fig. 2). Nine of 10 men with normal prolactin levels on treatment lost weight whereas in only two of the seven men who did not normalize prolactin levels was a weight loss recorded ($P = 0.034$). Again in women this relationship was not apparent as only two of the five female patients who normalized prolactin levels lost weight as opposed to four out of seven who remained with elevated prolactin levels ($P = NS$). Weight loss could not be accounted for by variations in treatment regimens as almost all patients received BC. In fact, average BC doses among patients who did not lose weight were higher than in those who did, reflecting therapeutic attempts to further reduce prolactin levels. NFA patients had no significant weight loss following surgery.

![Image](https://example.com/image.png)

**Fig. 1** Weight loss during treatment in relation to prolactin levels. Patients with prolactinoma (PR) who normalized prolactin levels during treatment (●) lost significantly more weight than those who remained hyperprolactinaemic (□). Patients suffering from non-functioning adenomas (NFA) had no significant weight changes following surgery. * $P = 0.0081$; ** $P = 0.0097$.

![Image](https://example.com/image.png)

**Fig. 2** Prevalence of weight loss in prolactinoma (PR) patients during treatment. Eleven of 15 patients who normalized prolactin levels lost weight as opposed to weight loss in only six of the 20 patients who did not normalize prolactin during treatment ($P = 0.017$). High prolactin, normal prolactin, denote prolactin status attained in PR patients during therapy.

Table 3  Prevalence of hypopituitarism in the study population

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>On treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NFA</td>
<td>PR</td>
</tr>
<tr>
<td>Hypogonadism*</td>
<td>17/22 (1)</td>
<td>14/18 (1)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6/36 (5)</td>
<td>2/42 (1)</td>
</tr>
<tr>
<td>Hypoadrenalism</td>
<td>8/36 (8)</td>
<td>1/42 (1)</td>
</tr>
</tbody>
</table>

Nominator denotes number of patients with hypofunction, denominator denotes number of patients in the whole group. * In male patients only. Numbers in parentheses denote number of patients receiving replacement therapy.

**Weight loss in relation to pituitary function**

The prevalence of specific anterior pituitary hormone deficiencies in both groups is summarized in Table 3. In men, hypogonadism was equally frequent in NFA and PRL patients before treatment. Mean total testosterone levels were 8.6 ± 2 nmol/l and 8.3 ± 1.4 nmol/l in NFA and PR patients respectively (P = NS). BT levels were 2.3 ± 0.5 and 2.3 ± 0.2 nmol/l in NFA and PR respectively (P = NS). After treatment, hypogonadism was more prevalent in NFA patients (Table 3, P = 0.0002), but because most of them received replacement therapy there was no functional difference between the two groups. Testosterone and BT were measured 10 days after the intramuscular injection of a depot preparation of testosterone enanthate 250 mg in patients receiving replacement therapy. Total testosterone levels were 14.2 ± 2.4 nmol/l and 13.5 ± 1.7 nmol/l in NFA and PR patients respectively (P = NS). BT levels were 4.6 ± 1 nmol/l and 4.3 ± 0.9 nmol/l in NFA and PR patients after/ on treatment. Normalization of prolactin levels led to recovery of gonadal function irrespective of residual tumour size in all PR male patients but two who required testosterone replacement therapy. Weight loss did not occur in NFA even in subjects in whom normalization of androgen levels was attained.

Most PR female patients were premenopausal, whereas most NFA patients were post-menopausal, thus rendering any comparison between the functional gonadal status of the two groups inappropriate. There was no difference in thyroid status between the two groups either before or after treatment. Secondary hypoadrenalism was more prevalent among NFA both before (P = 0.009) and after treatment (P = 0.04), but all cortisol deficient patients received physiological steroid replacement therapy and had no clinical manifestations of hormone deficiency.

**Discussion**

The mutual relationship between prolactin and body weight has been recognized but so poorly characterized that at the present time very few clinicians are aware of its existence or importance. On one hand, prolactin levels and body weight have been reported to be positively correlated in normal women (Wang et al., 1987). Women with a history of recent weight gain were also found to have higher prolactin levels, albeit still in the normal range, in comparison to control women without such a history (Ferreira et al., 1995). On the other hand, healthy obese subjects have decreased prolactin responses to insulin-induced hypoglycaemia and TRH stimulation (Donders et al., 1985; Weaver et al., 1990). Impairment of the serotoninergic (Bernini et al., 1989; Pijl et al., 1993) and the opioidergic (Argenio et al., 1991) pathways have been implicated in this impaired modulation of prolactin release.

A possible excess in the prevalence of overweight among hyperprolactinaemic patients has been repeatedly described (Wallace et al., 1985; Sobrinho, 1991), but was rarely the focus of the papers in question (Creemers et al., 1991). In the present study, we find a clear association between high prolactin levels and increased body mass in male patients. This is in accordance with a previous study that also found increased body weight in male but not female PR patients, compared with the general population (Creemers et al., 1991). Furthermore, a history of recent weight gain was significantly more frequent among both men and women suffering from prolactinomas than in the control population with NFA. Neither increased body weight nor recent weight gain could be attributed to a tumoural mass effect on the central hypothalamic area, as hypothesized in a previous study (Creemers et al., 1991).

A key finding in the present study is the significant weight loss in the PR population during prolactin-lowering therapy that was more pronounced in men but still significant in women as well. Even more remarkable was the strong association between the occurrence of post-treatment weight loss and prolactin normalization. Thus hyperprolactinaemia emerges as a potentially reversible cause of weight excess.

The potential effect of pituitary hormone deficiency on body weight was also addressed in our analysis. Although the NFA group included more subjects with hypoadrenalism both before and after treatment and of hypogonadism after treatment, once diagnosed all hypocortisolaemic and most hypogonadal patients received appropriate hormonal replacement therapy. Adequate replacement therapy was ensured through measurements of peak and trough testosterone levels after intramuscular injection of testosterone esters, and frequent clinical assessment of sexual function. Most patients requiring adrenal replacement were treated with prednisone, 7.5 mg daily, with close clinical follow-up to detect possible under- or overtreatment in which cases the dose was adjusted individually. Difficulties related to the assessment of adequacy of adrenal replacement therapy have been recently addressed (Monson, 1997; Peacey et al.,...


