Increased prevalence of high Body Mass Index in patients presenting with pituitary tumours: severe obesity in patients with macroprolactinoma

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Introduction: Prolactinoma has been associated with obesity. As opposed to ACTH- and GH-secreting adenoma, the mechanism by which macroprolactinoma causes obesity has not been fully understood. Having seen patients with both prolactinoma and obesity and more recent literature on brain dopamine, dopamine 2 receptors and obesity, we re-evaluated the potential relationship between prolactinoma and obesity.

Methods: Data of patients with pituitary adenomas were collected retrospectively over a period of 20 years. 399 patients with well-documented pituitary adenomas and information about pre-treatment body mass index (BMI), age, sex, and tumour type were analysed.

Results: Elevated BMI (≥30 kg/m²) was observed in 8/36 patients (22.2%) with ACTH-producing tumours, in 15/70 (21.4%) with GH-producing tumours, in 25/100 (25%) with macroprolactinoma, in 8/81 (9.9%) with microprolactinoma, and in 18/105 (17.1%) with inactive macroadenomas. Macroprolactinoma patients had a mean BMI value (27.5 ± 7.7 kg/m²) similar to that of patients with Cushing’s disease (27.2 ± 5.9 kg/m²) and acromegaly (27.4 ± 4.4 kg/m²) and on average a significantly higher BMI value compared to that of patients with inactive macroadiomas (25.8 ± 4.4 kg/m²) (95% CI 1.2, 4.4; p-value <0.001). Compared to the general population, the proportion of BMI ≥30 kg/m² in patients with macroprolactinoma was significantly higher (95% CI 0.1, 0.29; p-value <0.001).

Conclusions: Average BMI in macroprolactinoma patients is significantly higher than BMI in patients with inactive adenomas. Macroprolactinoma is associated with increased frequency of obesity compared to the general population. We propose that in a subgroup of individuals obesity and macroprolactinoma may share a common basis, namely decreased dopamine 2 receptor-mediated actions.

Key words: macroprolactinoma; obesity; dopamine; dopamine agonist

Summary

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Introduction

Obesity is frequently present in patients with newly diagnosed pituitary tumours. An increased prevalence of obesity was not only observed in pituitary tumour patients with Cushing’s disease, acromegaly or hypopituitarism but also in patients with hyperprolactinaemia [1, 2]. Whereas the pathogenesis of weight gain in patients with GH or cortisol excess is known [3–5], the mechanisms of the underlying association between prolactinoma and obesity are still poorly understood.

Dopamine is a neurotransmitter which increases energy expenditure and downregulates food intake and lactotroph cell function [6] by acting through dopamine D2 receptors (D2R). Dopamine agonists are the treatment of choice in patients with prolactinoma; dopaminergic drug treatment often also results in weight loss [7, 8]. In contrast, dopamine receptor antagonists such as neuroleptics often cause hyperprolactinaemia and may result in weight gain [9]. More recently, D2R mutations have been linked to obesity. Several polymorphisms have been identified in the D2R
gene. However, the association between D2R gene polymorphism and obesity remains controversial [10, 11]. It has also been suggested that a reduction in D2R was associated with addictive behaviour, and severely obese individuals were found to have lower numbers of D2R available, as measured in striatum with positron-emission tomography [12]. In a more recent study, spontaneous prolactin secretion was found to be enhanced in obese subjects and was strongly associated with BMI, in particular with the size of the visceral fat depot [13]. The recent observation of a severely obese woman (38 years old, body weight 220 kg, height 1.70 m, BMI 76 kg/m²) with a macroadenoma (prolactin level, 756 μg/litre; pituitary tumour diameter of 12 mm on MRI) prompted us to re-evaluate a potential relationship between prolactinoma, other pituitary adenomas and obesity [1, 2, 8, 14]. We hypothesised that patients with macroadenoma have on average a higher BMI than patients with microprolactinoma and patients with endocrine inactive macroadenoma and the prevalence of obesity (BMI >30 kg/m²) is higher in macroadenoma patients compared to the general population.

### Subjects and methods

#### Patients

We looked for BMI values in patients with prolactinoma and other pituitary adenomas referred to the University Hospital in Zurich between 1982 and 2001. 399 patients with well-documented pituitary adenomas were included in this retrospective study. Pretreatment BMI, age, sex, tumour type and tumour size were assessed in all patients. A pituitary adenoma with a tumour size greater than 1 cm in diameter was defined as macroadenoma. 270 patients had macroadenomas. Diagnosis of the tumour type was usually confirmed by histological examination; for non-operated prolactinoma, where the diagnosis was not histologically confirmed, a prolactin level >10-fold the upper limit of normal was requested for classification as macroadenoma.

#### Statistics

Mean and standard deviation were used for descriptive statistics. Associations between BMI and tumour types adjusted for age and sex were assessed with analysis of variance using a general linear model procedure (GLM). Differences within the tumour types were assessed with a least square means multiple comparison procedure test. The association of obesity (BMI >30 kg/m²) in subjects with pituitary adenoma compared to the general population (based on estimations from published Swiss data) without a pituitary tumour, adjusted for age-and sex, was assessed by the Mantel-Haenszel chi-square test. 95% confidence intervals were demonstrated where appropriate. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS Version 8.2 (SAS institute Inc., Cary, NC, USA).

### Results

Among the 181 patients with prolactinoma, 100 had macroadenoma and 81 had microprolactinoma. 112 patients had a clinically non-functioning or glycoprotein hormone (gonadotropin, TSH, or subunit) -producing pituitary adenoma, 105 macro- and 7 micro-adenomas. 101 of the 105 overweight or obese patients were referred to the University Hospital in Zurich. 81 patients had macroadenomas and 20 had microadenomas. The recent observation of a severely obese woman (38 years old, body weight 220 kg, height 1.70 m, BMI 76 kg/m²) with a macroadenoma (prolactin level, 756 μg/litre; pituitary tumour diameter of 12 mm on MRI) prompted us to re-evaluate a potential relationship between prolactinoma, other pituitary adenomas and obesity [1, 2, 8, 14]. We hypothesised that patients with macroadenoma have on average a higher BMI than patients with microprolactinoma and patients with endocrine inactive macroadenoma and the prevalence of obesity (BMI >30 kg/m²) is higher in macroadenoma patients compared to the general population.

#### Table 1

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Tumour n</th>
<th>Sex (f / m)</th>
<th>age (years)</th>
<th>BMI (kg/m²)</th>
<th>% BMI &gt;30 (kg/m²)</th>
<th>BMI means adjusted (kg/m²)</th>
<th>95% confidence interval of BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>36</td>
<td>20 / 16</td>
<td>40.8 (12.9)</td>
<td>27.2 (5.9)</td>
<td>22.2</td>
<td>27.3</td>
<td>25.5–29.1</td>
</tr>
<tr>
<td>GH</td>
<td>70</td>
<td>38 / 32</td>
<td>46.2 (13.8)</td>
<td>27.4 (4.4)</td>
<td>21.4</td>
<td>27.1</td>
<td>25.8–28.4</td>
</tr>
<tr>
<td>PRL Macro</td>
<td>100</td>
<td>52 / 48</td>
<td>37.7 (13.8)</td>
<td>27.5 (7.7)</td>
<td>25.0</td>
<td>27.9</td>
<td>26.8–28.9</td>
</tr>
<tr>
<td>PRL Micro</td>
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<td>74 / 7</td>
<td>31.9 (8.3)</td>
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<td>9.9</td>
<td>24.5</td>
<td>23.2–25.9</td>
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<tr>
<td>Inactive</td>
<td>Macro</td>
<td>105</td>
<td>51 / 54</td>
<td>52.1 (14.8)</td>
<td>25.8 (4.4)</td>
<td>17.1</td>
<td>25.0</td>
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</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Pre-treatment BMI (kg/m²)</th>
<th>Treatment</th>
<th>Follow-up (years)</th>
<th>Tumour and Prolactin control</th>
<th>BMI (kg/m²) (at time of follow-up)</th>
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<tr>
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<td>48</td>
<td>f</td>
<td>41</td>
<td>cabergoline</td>
<td>5.0</td>
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<td>33</td>
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<tr>
<td>2</td>
<td>62</td>
<td>f</td>
<td>51</td>
<td>surgery, cabergoline*</td>
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<td>yes</td>
<td>35</td>
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<tr>
<td>3</td>
<td>17</td>
<td>m</td>
<td>42</td>
<td>surgery, radiotherapy</td>
<td>11.0</td>
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<td>53</td>
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<tr>
<td>4</td>
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<td>f</td>
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<td>cabergoline</td>
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<td>58</td>
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<tr>
<td>5</td>
<td>37</td>
<td>m</td>
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<td>bromocriptine</td>
<td>3.0</td>
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<td>34</td>
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<tr>
<td>6</td>
<td>21</td>
<td>f</td>
<td>41</td>
<td>surgery, bromocriptine</td>
<td>2.0</td>
<td>no**</td>
<td>41</td>
</tr>
</tbody>
</table>

* = gastric banding ** = poor compliance
Increased prevalence of high Body Mass Index in patients presenting with pituitary tumours

Patients with clinically non-functioning macro-adenomas were operated and the diagnosis was confirmed histologically (prolactin-negative). 70 had GH-secreting, 36 had ACTH-producing adenomas. Among patients with GH-secreting or ACTH-producing adenomas, mean BMI was identical in those presenting with large and those with small tumours, and, therefore, macro- and microadenomas were combined (table 1).

Figure 1a–c shows the distribution of BMI in relation to age for patients with macroprolactinoma, microprolactinoma, and endocrine inactive macroadenomas.

≥40 were found in 1 patient with Cushing’s disease, in 1 patient with acromegaly, in 6 patients with macroprolactinoma (table 2) and in 1 patient with an inactive tumour.

A significant general association was found between tumour types and BMI (p <0.0001). BMI (adjusted for age and sex) was significantly higher in patients with macroprolactinoma compared to patients with endocrine inactive macroadenoma (95% CI 1.2, 4.4; p = 0.0007). BMI in patients with microprolactinoma was significantly lower compared to patients with macroprolactinoma (95% CI –5.0, –1.6; p = 0.0001) and appeared to have a distribution closer to that of the normal population. Interestingly, BMI in the group with macroprolactinoma was not different from BMI in patients with GH- or ACTH-producing adenomas (95% CI –2.5, 0.9; p = 0.38 and 95% CI –2.7, 1.5; p = 0.59).

In a Swiss control population aged 35–44 (ie in the mean range of the macroprolactinoma patients), a BMI of ≥30 kg/m² has been reported in 5.0% (female 5.5%, male 4.5%) of the individuals according to the Swiss federal office for statistics (health survey 1997) (table 3). After adjusting for age and gender, macroprolactinoma was significantly associated with obesity (BMI ≥30 kg/m²) when compared to the normal general population (p <0.001, 95% CI 0.1–0.29). In contrast, the proportions of BMI ≥30 kg/m² in patients with microprolactinoma were not significantly different from the proportions of BMI ≥30 kg/m² in the Swiss control population (p = 0.06, 95% CI 0.18–1.05).

Table 3

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>n</th>
<th>Age (years)</th>
<th>% BMI &gt;30 (kg/m²) patients</th>
<th>% BMI &gt;30 (kg/m²) female general population</th>
<th>% BMI &gt;30 (kg/m²) male general population</th>
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<tr>
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<tr>
<td>Inactive macro</td>
<td>105</td>
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</tr>
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</table>

Figure 1

Distribution of BMI in relation to age for patients with macroprolactinoma, microprolactinoma, and endocrine inactive macroadenomas.
Discussion

An increased frequency of high BMI values in patients presenting with any kind of pituitary macroadenoma may be due to suprasellar extension of the tumour, due to partial pituitary failure (gonadotropin-, growth hormone-, TSH-deficiency) or due to GH or cortisol excess. Acromegaly, Cushing’s disease and elevated BMI are known risk factors for increased mortality. A recent prospective study has shown an increased mortality in patients with hypopituitarism predominantly from vascular disease; more specifically, untreated gonadotropin deficiency was associated with excess mortality [15].

We found an increased prevalence of obesity in patients presenting with acromegaly, Cushing’s disease or macroprolactinoma compared to the general population. We specifically confirmed the association between macroprolactinoma and obesity compared to the general population [1], apparently due to a higher proportion of individuals exhibiting both macroprolactinoma and obesity (95% CI 0.1, 0.29; p <0.001). Although macroprolactinoma patients were not different from patients with endocrine inactive macroadenomas in terms of tumour size and abnormalities in thyroid function tests, BMI was significantly higher in patients with macroprolactinoma than in patients with endocrine inactive macroadenomas. Trends for a higher frequency of hypogonadism in patients with macroprolactinoma and for more extensive suprasellar growth in patients with inactive macroadenoma are difficult to document and quantify. However, the obese macroprolactinoma patients did not appear to have particularly obvious patterns of pituitary failure such as more frequent or longer lasting secondary hypothyroidism, hypogonadotropic hypogonadism, or growth hormone deficiency than the normal weight macroadenoma patients, and hormone replacement therapy could not normalise their body weight. Therefore, abnormalities in pituitary function cannot fully account for an increase in BMI at the time patients present with macroprolactinoma and obesity.

Thus far, we have not been able to document the long-term cure of a patient from both macroprolactinoma and obesity by pituitary surgery. Despite effective prolactin and tumour control by surgery and radiotherapy, the only patient with a BMI >40 kg/m² not receiving dopaminergic treatment had a further increase in body weight (table 2, patient 3). In contrast, 4 of the 5 patients with a BMI >40 kg/m² receiving bromocriptine or cabergoline lost body weight (table 2). The individual with a BMI >40 kg/m² who did not loose body weight underwent partial resection of her macroprolactinoma, had a poor compliance for bromocriptine and thus, had persistent hyperprolactinaemia (patient 6). The findings of the relationship between decreasing prolactin levels and weight loss are consistent with observations reported by others [8, 16] and may reflect effective dopaminergic treatment, rather than a potential association between prolactin and BMI which we could not find within our group of macroprolactinoma patients as opposed to the association between daily prolactin release and the degree of obesity in individuals without prolactinoma. Nevertheless, the latter observation also supports a link between the activity of prolactin-secreting cells and obesity, and the authors speculated that this may be due to reduced D2R availability in the brain [13].

Among the limitations of our study, two deserve special mention. First, body weights and heights of the control population were obtained by interview and were not measured as in the study population. Therefore, self-reported weights may underestimate the proportion of obese subject in the control population. However, even by multiplying the proportion of obesity in the control population by a factor of two (admittedly, an assumption which is difficult to justify by measured data, as also discussed by Schutz and Woringer [17]), the proportions of BMI ≥30 kg/m² in patients with macroprolactinoma were still significantly different from the proportions of BMI ≥30 kg/m² in the general Swiss control population, adjusted for age and gender (95% CI 0.25, 0.58; p <0.001). According to the EURALIM study [18] obesity rates of 11% were found in men and 9% in women in Geneva in 2000. Unfortunately, however, there is (to the best of our knowledge) a lack of measured body weight data at different ages in the referral area (mostly German speaking, but also Italian speaking; eastern part of Switzerland) during the time our data were collected. However, since the prevalence of obesity in the early eighties (ie the start of our retrospective study) was lower compared to the last few years (late nineties, new millennium), we might not have underestimated BMI in the control group that much. The comparison of BMI between patients with macroprolactinoma and patients with endocrine inactive macroadenoma is still valid; however, it is more difficult to see whether the latter significantly differ from the general population.

Second, we could not assess long-term follow-up of BMI and pituitary function in all 399 patients with pituitary adenoma. Particularly, we could not assess longitudinally prolactin levels, different treatment modalities and pituitary function among all 100 patients with macroprolactinoma.

Although we cannot exclude that prolactin excess per se contributed to obesity in patients with macroprolactinoma, we speculate that there is a more likely explanation for the striking association of macroprolactinoma and severe obesity. There is a subgroup of patients who are prone to develop both severe obesity and prolactinoma for which decreased D2R-mediated actions may be a common cause.
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