A history of cranial radiotherapy is associated with a higher visceral to subcutaneous fat ratio in men with pituitary insufficiency

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Abstract

Objective: Endocrine deficiencies, like GH and estrogen deficiencies, are likely candidates to explain increased visceral to subcutaneous fat ratio in patients with pituitary insufficiency. However, recent reports pointed to cranial radiotherapy (CRT) as an additional determinant of an unfavorable fat distribution. Therefore, we determined the effect of CRT on abdominal fat distribution in men with treated pituitary insufficiency.

Design: Cross-sectional study.

Methods: Thirty-five consecutive male subjects (16 men with and 19 men without CRT aged 62 ± 12 and 56 ± 14 years respectively, P = 0.175) visiting our Endocrine Outpatient Clinic for pituitary insufficiency were invited to participate in this study. A standardized single-slice abdominal CT scan at the level of fourth lumbar vertebra was performed to determine visceral fat area, subcutaneous fat area, and visceral to subcutaneous fat ratio. In addition, we assessed body mass index, total fat percentage with bioelectrical impedance analysis, resting energy expenditure with indirect calorimetry, calorie intake using a diary, and serum hormone concentrations.

Results: Subjects with CRT had a smaller subcutaneous fat area (225.1 (71.1–480.7) vs 269.0 (133.2–59.9) cm², P = 0.022) and a higher visceral to subcutaneous fat ratio (0.79 (0.39–1.55) vs 0.63 (0.23–0.88), P = 0.001) than subjects without CRT. Both the groups were comparable for body mass index, waist–hip ratio, resting energy expenditure, and calorie intake. Importantly, serum hormone concentrations were similar.

Conclusion: In men treated for pituitary insufficiency, previous CRT is associated with a higher visceral to subcutaneous fat ratio.

Introduction

Patients with pituitary insufficiency are at increased risk for obesity. Although obesity by itself is associated with increased cardiovascular morbidity, the accumulation of visceral fat in particular is an established risk factor for the development of cardiovascular disease and type 2 diabetes mellitus (1). The importance of these metabolic consequences highlights the need to identify the factors responsible for changes in body fat distribution in patients with pituitary insufficiency. Traditionally, suboptimal hormone replacement has been considered an obvious therapy in these patients because the majority of pituitary-controlled hormones affect body fat distribution. For instance, androgens are associated with increased visceral fat mass, with the inverse pattern for estrogens (2, 3), and excess of cortisol or a shortage of GH is associated with visceral obesity as well (4, 5). However, in addition to these endocrine explanations, other factors may be involved. Interestingly, excess visceral fat was recently reported in patients who had received cranial radiation therapy (CRT) as part of their treatment for acute lymphoblastic leukemia (6, 7). Whether this relationship between CRT and body fat distribution is also present in patients with pituitary insufficiency is unclear. To study this, we decided to investigate the effect of CRT on body fat distribution in men currently receiving hormone replacement therapy for pituitary insufficiency.

Materials and methods

Subjects

Consecutive patients visiting our Endocrine Outpatient Clinic (Academic Medical Center of the University of Amsterdam) with pituitary insufficiency, i.e. at least one
A J Borgers and others

anterior pituitary hormone deficiency, who had been treated for a (supra)sellar tumor between 1966 and 2007 were invited to participate in this study. Only men were included because previous studies have demonstrated that body composition is gender dependent and related to pre- and postmenopausal status of women.

All patients were observed on a regular basis by an endocrinologist for clinical and biochemical evaluation. Patients received conventional hormone replacement therapy consisting of t-thyroxine, hydrocortisone, testosterone, recombinant human GH (rhGH), and/or vasopressin analogs when indicated. Excessive production of pituitary hormones had not been present for at least 5 years in subjects with a hormone-producing tumor. Hormone concentrations were measured in venous serum or plasma samples obtained between 0900 and 1000 h after an overnight fast. IGF1 was measured by an immunometric assay (Immulite IGF1; Diagnostic Products Corporation, Los Angeles, CA, USA). Age-specific reference values have previously been determined in a random population sample (n= 296) (8).

The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent before participation in the study.

Physical examination and indirect calorimetry

Physical examination included measurement of height (cm), weight (kg), waist circumference (at the midpoint of the costal margin and iliac crest) (cm), and hip circumference (at the level of great trochanters with the legs close together) (cm). Body mass index (kg/m²) and waist–hip ratio were calculated. Bioelectrical impedance analysis (Maltron BF906, Rayleigh, UK) was used to measure body composition.

Resting energy expenditure was measured over a 30 min period after an overnight fast by indirect calorimetry using the ventilated hood technique (Sensormedics model 2900; Sensormedics, Anaheim, CA, USA). Resting energy expenditure was calculated from oxygen consumption and carbon dioxide production as described by Frayn (9).

Abdominal fat measurement

A standardized single-slice abdominal CT scan (Mx8000Quad; Philips Medical Systems, Best, The Netherlands) using 120 kV, 100 mAs, and a slice thickness of 1 cm was performed. On the survey image, the level of fourth intervertebral lumbar disc was selected because the fat area in a slice at this level is a valid predictor of total abdominal fat in men (10, 11). The area of visceral fat and subcutaneous fat (both in cm²) was determined by adding the area of the voxels with CT values within the range of −170 to −30 HU. Care was taken to exclude intracolonic contents with CT values within the same range (12).

Calorie intake

Energy intake was assessed using a food diary. This involved the patients recording their daily food and drink intake for two weekdays and one weekend day. To estimate the daily calorie intake, the food diaries were analyzed using www.dieetinzicht.nl. Data are expressed as total energy intake per kilogram bodyweight per day.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 16.0; SPSS, Inc., Chicago, IL, USA). Normally distributed variables are presented as mean ± s.d., non-normally distributed variables as median (range), and categorical variables as counts (%). Group differences in numerical variables were evaluated using Student’s t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed parameters. The χ² test was used to analyze the differences between categorical data in both the groups. If the sample size was small or cells had an expected count < 5, the Fisher exact test was used. An analysis of covariance was used to determine the effect of CRT on fat distribution with ‘age’, ‘time between initial diagnosis and this study’, and ‘ADH deficiency’ as covariates. Simple bivariate correlation was performed using the Spearman rank correlation coefficient. A P value of <0.05 was considered significant using two-tailed tests.

Results

Subjects

Thirty-five men were enrolled in this study, of which 16 had been treated with CRT (mean age, 62 ± 12 years) and 19 had not been treated with CRT (mean age, 56 ± 14 years). Within the CRT group, 13 subjects received postoperative CRT, two received CRT following unsuccessful dopamine agonist treatment, and one received CRT to prevent Nelson’s syndrome after bilateral adrenalectomy. Total radiation doses administered to the CRT group ranged from 40 to 50 Gy (mean 45.2 ± 4.6 Gy).

The time between initial diagnosis and this study in the group with CRT was longer than that in the group without CRT (20 ± 9 vs 11 ± 11 years, P= 0.021), but there was no difference between the groups in body mass index, waist–hip ratio, resting energy expenditure, calorie intake, and hypothalamic–pituitary hormone deficiencies (Table 1).
All ACTH-, TSH-, and ADH-deficient patients were on stable doses of hydrocortisone, L-thyroxine, and desmopressin respectively. rhGH therapy was given to five out of ten CRT patients with GH deficiency and all 11 non-CRT patients with GH deficiency. The remaining patients were classified as having an intact GH–IGF1 axis based on age-specific IGF1 between ±2S.D. Testosterone supplementation was given to 11 out of 14 CRT patients with LH/FSH deficiency and 15 out of 17 non-CRT patients with LH/FSH deficiency. The majority of hypogonadal patients received transdermal testosterone therapy (61%). The remaining patients received intramuscular (19%), oral (12%), or buccal (8%) formulas of testosterone.

Serum testosterone, age-adjusted IGF1, and fT₄ levels were not different between patients with and without CRT, nor were urine production and urine osmolality. Hydrocortisone tablets were used two or three times daily by all ACTH-deficient patients. In the CRT group, seven patients received a hydrocortisone dosage of 20 mg/day and one patient received 60 mg/day. In the non-CRT group, one patient received 15 mg/day, 11 patients received 20 mg/day, and two patients received 30 mg/day. The total hydrocortisone dosage did not differ between patients with and without CRT (Table 1).

### Subcutaneous and visceral fat

The visceral to subcutaneous fat ratio was 25.4% higher in men with CRT than in men without CRT (0.79 (0.39–1.55) vs 0.63 (0.23–0.88), \(P = 0.001\)). This difference was caused by a smaller absolute median subcutaneous fat area of 43.8 cm² in men with CRT (225.1 (71.1–480.7) vs 268.9 (133.2–599.1) cm², \(P = 0.022\)) and an absolute median difference in visceral fat area of 44.4 cm², although the latter was not statistically significant (201.1 (50.2–375.3) vs 156.7 (55.3–300.2) cm², \(P = 0.271\)) (Fig. 1).

### Factors influencing the visceral to subcutaneous fat ratio

‘Age’, ‘time between initial diagnosis and this study’, and ‘ADH deficiency’ Controlled for ‘age’, ‘time between initial diagnosis and this study’, and ‘ADH deficiency’, men with CRT still had a higher visceral to

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**Table 1** Clinical characteristics. Data are expressed as mean ± s.d., median (range), or number (%).

<table>
<thead>
<tr>
<th>History of cranial radiotherapy</th>
<th>Yes (n=16)</th>
<th>No (n=19)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 ± 12</td>
<td>56 ± 14</td>
<td>0.175</td>
</tr>
<tr>
<td>Time between tumor diagnosis and this study (years)</td>
<td>20 ± 9</td>
<td>11 ± 11</td>
<td>0.021</td>
</tr>
<tr>
<td>Time between cranial radiotherapy and this study (years)</td>
<td>18.2 ± 8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.1 ± 4.4</td>
<td>30.7 ± 4.5</td>
<td>0.286</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
<td>0.95 ± 0.05</td>
<td>0.93 ± 0.04</td>
<td>0.097</td>
</tr>
<tr>
<td>Lean body mass (%)</td>
<td>70.8 (39.5–77.1)</td>
<td>67.6 (49.2–78.3)</td>
<td>0.302</td>
</tr>
<tr>
<td>Resting energy expenditure (kcal/kg)</td>
<td>17.3 ± 1.96</td>
<td>17.1 ± 1.76</td>
<td>0.704</td>
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<tr>
<td>Calorie intake (kcal/day)</td>
<td>1946 ± 467</td>
<td>1906 ± 491</td>
<td>0.805</td>
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<tr>
<td>Biochemistry*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted IGF1 (S.D.)</td>
<td>−0.63 ± 1.16</td>
<td>−0.45 ± 1.34</td>
<td>0.686</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>13.4 (6.8–60.0)</td>
<td>12.8 (0.04–34.0)</td>
<td>0.659</td>
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<tr>
<td>fT₄ (pmol/l)</td>
<td>14.9 ± 4.5</td>
<td>12.9 ± 2.4</td>
<td>0.132</td>
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<td>Osmolality urine (mOsm/kg)</td>
<td>628.4 ± 153.1</td>
<td>556.8 ± 194.0</td>
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<tr>
<td>Urine volume (ml/24 h)</td>
<td>1863 ± 539</td>
<td>1857 ± 899</td>
<td>0.378</td>
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<td>Histology, no. (%)</td>
<td></td>
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<tr>
<td>Macroadenoma – prolactinoma</td>
<td>5 (31.2)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Macroadenoma – GH producing</td>
<td>1 (6.2)</td>
<td>1 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Macroadenoma – gonadotropinoma</td>
<td>1 (6.2)</td>
<td>1 (5.3)</td>
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<tr>
<td>Macroadenoma – nonfunctioning</td>
<td>8 (50)</td>
<td>8 (42.1)</td>
<td></td>
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<td>Craniopharyngioma</td>
<td>5 (26.3)</td>
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<td></td>
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<tr>
<td>Microadenoma – ACTH producing</td>
<td>1 (6.2)</td>
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<td></td>
</tr>
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<td>Previous therapy, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>13 (81.2)</td>
<td>16 (84.2)</td>
<td>0.582</td>
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<tr>
<td>Hypothalamic–pituitary hormone deficiency, no. (%)</td>
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<tr>
<td>ACTH deficiency(^b)</td>
<td>8 (50)</td>
<td>14 (73.7)</td>
<td>0.149</td>
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<tr>
<td>GH deficiency</td>
<td>10 (62.5)</td>
<td>11 (57.9)</td>
<td>0.782</td>
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<tr>
<td>TSH deficiency</td>
<td>13 (81.2)</td>
<td>13 (68.4)</td>
<td>0.319</td>
</tr>
<tr>
<td>LH/FSH deficiency</td>
<td>14 (87.5)</td>
<td>17 (89.5)</td>
<td>0.630</td>
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<tr>
<td>ADH deficiency</td>
<td>1 (6.2)</td>
<td>7 (43.8)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

\(^a\)Reference values: testosterone, 11.0–35.0 nmol/l; fT₄, 10.0–23.0; and osmolality urine, 300–900 mOsm/kg.

\(^b\)Hydrocortisone tablets were used two or three times daily by all ACTH-deficient patients and their total daily dosage did not differ between patients with and without CRT (20 (20–60) vs 20 (15–30); \(P = 0.815\)).
subcutaneous fat ratio than men without CRT ($F(1.30)=11.76$, $P=0.002$).

**Relationship between IGF1 and body composition**

We did not find a correlation between serum IGF1 concentration and visceral to subcutaneous fat ratio ($r^2=0.007$, $P=0.644$), nor between IGF1 and visceral or subcutaneous fat ($r^2=0.000$, $P=0.987$; $r^2=0.004$, $P=0.719$ respectively).

**Hypopituitarism**

In our study population, some men were untreated for their GH or testosterone deficiency. As untreated hormonal deficiencies are implicated in the regulation of fat distribution, we analyzed a subgroup containing men with intact and/or hormonal supplemented axes exclusively. In this separate analysis, the difference in visceral to subcutaneous fat ratio in men with and without CRT was even more pronounced ($0.97$ (0.52–1.55) vs $0.57$ (0.23–0.88), $P=0.001$), again mainly accompanied by a smaller subcutaneous fat area (233.2 (71.1–480.7) cm$^2$, $P=0.017$), although the visceral fat area tended to be larger in men with CRT (247.1 (50.2–375.3) cm$^2$, $P=0.053$). If we controlled for ‘age’, ‘time between initial diagnosis and this study’, and ‘ADH deficiency’, men with CRT still had a higher visceral to subcutaneous fat ratio than men without CRT ($F(1.21)=16.46$, $P=0.001$).

Of note, in this analysis, there were no differences in hydrocortisone treatment regimen and doses between the groups (20 (20–60) vs 20 (20–30); $P=0.702$), nor in serum testosterone, age-adjusted serum IGF1, serum $\Delta^4$-testosterone, urine production, or urine osmolality.

**Discussion**

This is the first report on the relationship between CRT and body fat distribution measured by CT in patients with pituitary insufficiency caused by a tumor in the sellar region. Our results indicate that CRT is associated with a higher visceral to subcutaneous fat ratio in men with pituitary insufficiency. This finding is consistent with the previous observations in survivors of childhood acute lymphoblastic leukemia ($6,7$).

Changes in body fat distribution in patients with pituitary insufficiency are usually attributed to hormonal deficiencies. However, our results suggest that CRT contributes to compartment-specific modulation of adipose tissue accumulation independent of pituitary deficiencies because patients with and without CRT had a comparable degree of pituitary insufficiency. Additionally, in a smaller subgroup analysis containing men with intact or adequately supplemented hormonal axes, visceral to subcutaneous fat ratio was markedly higher in men with CRT. These observations add strength to the notion that CRT might affect body fat distribution independently of pituitary function.

An intriguing question is how CRT affects body fat distribution. The hypothalamus is an important regulator of food intake and energy balance ($13$), but we did not observe a difference in body mass index, resting energy expenditure or food intake. Apparently, other mechanisms in the brain modulate body fat distribution independently of energy intake and expenditure. Recent experimental studies suggest that neurons in the ventral medial hypothalamus regulate visceral fat content independently of food intake by modulating the sympathetic tone ($14$). In addition, distinct subsets of preautonomic neurons within the hypothalamus have been shown to project separately to the visceral and subcutaneous fat compartment via the autonomic nervous system, revealing a neuroanatomical network by which the hypothalamus may control body fat distribution ($15,16,17$). As the hypothalamus is vulnerable to radiation injury ($18$), it is conceivable, but highly speculative at this stage, that CRT impairs hypothalamic nuclei involved in the regulation of body fat distribution, thereby altering body fat distribution in patients after CRT.

Also, tumors invading the hypothalamus, in particular craniopharyngiomas, may inflict damage on the hypothalamus. On imaging, the craniopharyngiomas in our study did not invade the hypothalamus. Clinical evidence of hypothalamic damage is poorly defined in the literature, although most clinicians would agree that the development of massive obesity in patients with craniopharyngioma is indicative of hypothalamic damage. In our study, one out of the five patients with craniopharyngioma had developed hypothalamic obesity. None of the patients had poikilothermia or severe disturbances in their sleep/wake rhythm indicating hypothalamic damage, whereas all patients with craniopharyngioma had diabetes insipidus. Considering the limitations in defining hypothalamic damage, one patient should probably be classified as having hypothalamic damage based on clinical symptoms.
A limitation of this cross-sectional study is that the temporal relationship between CRT and body composition cannot be clearly established. In addition, we studied a relatively small sample, but nevertheless, we were able to demonstrate a statistically significant difference in fat distribution between irradiated and nonirradiated patients. The CRT and non-CRT groups were well matched for the majority of variables except for ‘age’, ‘time between initial diagnosis and this study’, and presence of ‘ADH deficiency’. Statistically controlled for these factors, men with CRT still had a higher visceral to subcutaneous fat ratio. Therefore, it is unlikely that ‘age’, ‘time between initial diagnosis and this study’ or ‘ADH deficiency’ has significantly influenced our results.

In our study, ~60% of patients had GH deficiency. Usually, GH is the first affected hormone, especially if IGF1 between deficiency in our study was defined by an age-specific value. In our study, 83% of patients had a macroadenoma, which may explain why GH deficiency was not the most prevalent pituitary hormone deficiency. The absence of GH deficiency in our study was defined by an age-specific IGF1 between ± 2 S.D. As the gold standard for the diagnosis of GH deficiency is an insulin tolerance test or GHRH arginine test, we may have underestimated the actual proportion of patients with GH deficiency. However, as age-specific IGF1 levels were comparable in both the groups, the effect of potential GH deficiency on the outcome is probably limited.

It is important to note that our results do not necessarily hold for women, as previous studies have demonstrated that body composition is gender dependent and even dependent on pre- and postmenopausal status of women. Therefore, further and larger studies on men and women are needed to clarify the association between CRT and body fat distribution in patients with pituitary insufficiency.

In conclusion, our study demonstrates that CRT in men with pituitary insufficiency is associated with a higher visceral to subcutaneous fat ratio. The outcome adds a new dimension to the several well-known long-term side effects of CRT such as development of pituitary hormone deficiencies, radiation-induced necrosis, optic neuropathy, and secondary malignant tumors (21, 22).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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