Changes in basal and stimulated TSH and other parameters of thyroid function in acromegaly after transsphenoidal surgery

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Abstract. T4 and T3 levels, TSH response to TRH and somatomedin-C levels in 63 patients with acromegaly, were measured before transsphenoidal surgery and during a 4-year follow-up period. Criteria for cure were: mean GH level < 5 mU/l, suppression of GH by oral glucose tolerance test below 2.5 mU/l and normalization of paradoxical GH reaction to TRH. Nine patients underwent radioiodine studies to assess the renal and thyroid clearance of iodide, plasma inorganic iodine level and absolute iodine uptake. Among the patients 40% had goitre, with a male preponderance. T4 and T3 levels were in the normal range both before and after surgery. A transient decrease in T4 levels was found in the immediate postoperative period. Before treatment a diminished or absent TSH response to TRH was exhibited by 64% of the goitre patients and 34% of the non-goitre groups (p < 0.05). Despite normalization of GH and somatomedin-C levels and normal T4 and T3 levels no improvement of the TSH response was found during follow-up. No correlation between the incremental response of TSH to TRH and circulating T4 or T3 levels, basal TSH, GH or tumour size was found. There was, however, a negative correlation (r = −0.765, p < 0.05) between the incremental TSH response to TRH and somatomedin-C levels for females with goitre. Somatomedin-C levels were higher in patients with goitre than in those without goitre (95 ± 26 vs 75 ± 30 nmol/l; mean ± so, p = 0.05). Radioiodine studies showed an increased renal clearance of iodide which was related to the increase in creatinine clearance. The absolute iodine uptake was significantly higher for male acromegalic patients than for controls (7.2 ± 2.2 vs 3.9 ± 2.3, p < 0.05) and decreased significantly postoperatively. From this study we conclude that the increased incidence of goitre in acromegaly is not caused by iodine deficiency, but is probably related to a stimulatory effect of GH or somatomedin-C on thyroid growth and function. In contrast to patients with other pituitary tumours, the impaired TSH response in acromegalics is not associated with hypothyroidism, and the TSH response to TRH does not normalize postoperatively, despite normalization of GH levels.

In patients with acromegaly, several abnormalities related to the thyroid and the pituitary-thyroidal axis, such as goitre formation, changes in plasma iodothyronine levels and impaired TSH response to TRH, have been described (1–5). The exact mechanism of goitre formation in acromegaly is not known. In most studies normal values for T4, free T3 and TSH are found. Inada & Sterling (6) suggested that GH might stimulate peripheral thyroid hormone metabolism. Later studies of children on GH therapy because of GH-deficiency (7,8) as well as in vitro studies (9, 10) demonstrated that GH stimulates 5’-deiodination.

Reports on the TSH response to TRH are conflicting (2–4, 11–13). Basal TSH is reported to be normal in most studies and hypothyroidism is an infrequent finding. Hall et al. (13) showed that in pituitary disease other than acromegaly a lack of TSH response to TRH is associated with hypothyroidism. A major drawback of all studies is the small number of patients tested, the poor definition of a ‘normal’ TSH response, the lack of differentiation between males and females in TSH response to TRH, the different therapeutic modalities (surgery, irradiation and bromocriptine
therapy), and the scarcity of long-term follow-up data.

In this study we investigated several aspects of thyroid function and the pituitary-thyroid axis in a large group of patients with acromegaly during active disease and for 4 years after transsphenoidal surgery. A distinction was made between males and females because of the difference in normal TSH response and between patients with and without goitre. All patients with evidence of tumour remnants after surgery underwent additional irradiation and were evaluated separately.

Patients and Methods

Between 1977 and 1986, 68 patients underwent transsphenoidal surgery for acromegaly. Five patients were excluded from the present study: 2 patients took thyroxine because of hypothyroidism and the preoperative thyroid function tests were incomplete in 3. The patient group thus consisted of 63 patients: 35 males and 28 females, mean age 46 years, range 24–69. None of the patients used drugs known to influence thyroid function tests. All patients were euthyroid according to the clinical and biochemical studies.

Pre-operative investigations included daytime GH levels (blood samples taken at 08:00, 11:30, 16:30 and 23:00 h), a 100 g oral glucose tolerance test (blood samples for determinations of glucose, insulin and GH taken at 0, 30, 60, 90 and 120 min) and a 200 μg iv TRH (protireline, Hoechst AG, Frankfurt am Main) test (blood samples for determination of TSH and GH taken at 0, 20 and 60 min). In addition, blood samples were taken for measurement of T₄, T₃, T₉ resin uptake and somatomedin-C (IGF-I). The pituitary tumour was staged by CT scan and findings at surgery, according to the Hardy-Wilson classification system (14). The same investigations were repeated 2 weeks after surgery and subsequently at yearly intervals. Pituitary irradiation was considered necessary if the mean GH level (calculated from the 4-day time samples) exceeded 5 mU/l, GH suppression by oral glucose loading was insufficient, or a paradoxical GH reaction to TRH was still present after surgery. The patients were divided into 4 groups according to sex and presence of goitre. The latter was determined by palpation and defined as an enlargement of the thyroid to at least twice the normal size. Group 1 consisted of 19 males without goitre, group 2 of 16 males with goitre, group 3 of 19 females without goitre, and group 4 of 9 females with goitre.

Total T₄, T₃, GH, TSH and somatomedin-C levels were measured with conventional radioimmunoassays as described previously (15,16). Normal values for GH (calculated from the mean level of 4-day time samples; controls N = 30) are ≤5 mU/l; normal suppressed GH levels during the oral glucose tolerance test are <2.5 mU/l; a paradoxical GH reaction to TRH was present when the increase exceeded the basal level by 100% or more and the stimulated level exceeded 5 mU/l (15). Normal range for somatomedin-C is 12–35 nmol/l (16). The TSH response was regarded as normal when a rise of more than 4 mU/l for males and more than 8 mU/l for females was measured 20 min after TRH injection. Differentiation between males and females was made because the TSH response is higher in normal females than in normal males (7). The radioiodine uptake of the thyroid gland was estimated in 9 patients pre-operatively and one year after surgery. The patients were told not to consume products from a list of iodine-rich food 48 h before the test. A 24 h urine collection of iodide and creatinine estimation was completed the day before the test. The next day patients drank 10 ml/kg distilled water in 20 min 2 h before the test, and urinary losses were matched in order to ensure a constant creatinine clearance of 2 μCi of Na¹²³I. The measurements were done with a single collimator NaI-detector with a diameter of 3 × 1 inches and two single channel spectrum analysers (Ortec, Oakridge, USA). From previous studies it was known that at a detector-to-skin distance of 20 cm volumes of up to 125 ml can be seen as a point source. The two analyser channels were set for the K-X ray (28 KeV) and the γ-rays (159 KeV) of ¹²³I, respectively. As standard sample the same activity was injected into a 30 ml vial that was placed in a water phantom (diameter: 15 cm) and counted at the same distance. Corrections were made for geometry and absorption by using the differences in attenuation of the K-X ray and γ-ray of ¹²³I, as described by Martin & Rollo (17). At 0.5 and 2.5 h after an iv dose of 2 μCi Na¹²³I, the uptake of radioactivity at neck and thigh was measured. Since the background activity in patients who had undergone total thyroidectomy was twice the activity measured at the thigh (unpublished data), the thyroidal uptake was calculated as: uptake at the neck minus twice the uptake at the thigh. All urine was collected between 0.5 and 2.5 h to count ¹²³I activity and measure inorganic iodide (Technicon) and creatinine. The thyroid and renal clearances were estimated and the plasma inorganic iodide and absolute iodide uptake were calculated as described by Wayne et al. (18). Data were statistically analysed, as appropriate, with the Wilcoxon matched pairs rank sum test, the Mann-Whitney U-test, analysis of variance, and Student’s t-test.

Results

Postoperatively, GH levels were normal in 44 patients and still elevated in the remaining 19 patients (range 6–70 mU/l). One patient of the latter group was treated with a somatostatin analogue (SMS 201-995), the others underwent pituitary ir-
radiation. Eleven patients with normal postoperative GH levels still exhibited a paradoxical GH response to TRH or had an invasive tumour. They also underwent postoperative irradiation in order to prevent recurrence (15). In total, therefore, 29 patients underwent pituitary irradiation.

Goitre was present in 16 of the 35 (45.7%) males and 9 of the 28 (32.1%) females. The somatotropin-C level was 95 ± 26 nmol/l (mean ± sd) for patients with goitre and 75 ± 30 nmol/l for patients without goitre (p < 0.05). The mean GH levels for these patients, however, did not differ.

In Table 1 the total T₄ (TT₄) and T₃ (TT₃) levels, T₃ resin uptake and incremental response of TSH to TRH are shown. There was no difference in total T₄ levels between males and females, irrespective of the presence of goitre. Total T₃ levels were slightly elevated in females with goitre (p < 0.05), but no differences in T₃ resin uptake between the 4 groups were found.

The TSH response to TRH was about 50% lower (p < 0.01) in all groups compared with controls. Pre-operatively, there was no significant difference between patients who underwent only surgery and those subjected to surgery and postoperative irradiation. Twenty-nine patients (46%) had a diminished TSH response to TRH, 16 (64%) with goitre and 13 (34%) without goitre (p < 0.05).

No correlation was found between tumour size and ΔTSH. The TSH response to TRH was significantly lower for males than females, irrespective of the presence of goitre, but the presence of goitre in males led to a significantly lower response of TSH to TRH. No correlation was found between the circulating T₄ or T₃ levels on the one hand and basal TSH and ΔTSH and the pre-operative GH levels. However, a significant negative correlation was found between the somatotropin-C levels and the TSH response to TRH for females with goitre (r = −0.765, p < 0.05), but not for the other 3 groups. The follow-up data are shown in Figs. 1 and 2. Since no large differences between subjects with and without goitre were present, the patients were classified according to treatment, i.e. with or without radiation therapy. T₄ and T₃ resin uptake levels remained constant during the 4-year follow-

Table 1.

Iodothyronine levels and TSH response to TRH in untreated patients with acromegaly and controls.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Goitre</th>
<th>No.</th>
<th>T₃ (nmol/l)</th>
<th>T₄ (nmol/l)</th>
<th>T₃ resin uptake (%)</th>
<th>TSH (mU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>−</td>
<td>19</td>
<td>100 ± 17</td>
<td>1.9 ± 0.4</td>
<td>26 ± 2</td>
<td>6.4 ± 4.6</td>
</tr>
<tr>
<td>Male</td>
<td>+</td>
<td>16</td>
<td>107 ± 25</td>
<td>2.0 ± 0.6</td>
<td>27 ± 2</td>
<td>4.5 ± 3.0</td>
</tr>
<tr>
<td>Female</td>
<td>−</td>
<td>19</td>
<td>102 ± 26</td>
<td>1.9 ± 0.5</td>
<td>26 ± 4</td>
<td>11.6 ± 4.8</td>
</tr>
<tr>
<td>Female</td>
<td>+</td>
<td>9</td>
<td>115 ± 32</td>
<td>2.4 ± 0.3b</td>
<td>27 ± 4</td>
<td>12.0 ± 12.0</td>
</tr>
<tr>
<td>Male</td>
<td>control</td>
<td>30</td>
<td>104 ± 14</td>
<td>1.8 ± 0.4</td>
<td>29 ± 3</td>
<td>11.2 ± 4.2</td>
</tr>
<tr>
<td>Female</td>
<td>control</td>
<td>35</td>
<td>110 ± 16</td>
<td>2.0 ± 0.3</td>
<td>29 ± 3</td>
<td>21.6 ± 5.3</td>
</tr>
</tbody>
</table>

Results are shown as mean ± sd. Statistical significance compared with the control groups:
a: p < 0.001, b: p < 0.01.

Fig. 1.

Total T₄ and T₃ levels before surgery and during the 4-year follow-up period. The results are expressed as mean ± sd. Irradiated patients are shown by the open symbols, non-irradiated by the closed symbols, T₄ levels by circles, and T₃ levels by squares. In the postoperative period a significant (*p < 0.05, **p < 0.01), but transient, decrease in T₃ levels was found for both irradiated and non-irradiated patients. T₄ levels remained unchanged for irradiated and non-irradiated patients.
TSH response to TRH stimulation before surgery and during the 4-year follow-up period. The results are expressed as mean ± SD. The results for male patients are shown in the left-hand panel, for female patients in the right-hand panel. Non-irradiated patients are indicated by closed symbols, irradiated patients by open symbols. The incremental TSH response (ΔTSH) decreased significantly in male and female patients after surgery, but subsequently improved to pre-operative levels in the non-irradiated patients, in contrast to irradiated patients. Statistical significance (difference with pre-operative levels) is given by asterisks: * p < 0.05, ** p < 0.01.

In contrast to what we expected, the TSH response decreased significantly after surgery (Fig. 2). The non-irradiated male and female patients, however, exhibited a significant rise towards pre-operative levels during long-term follow-up, in contrast to irradiated subjects (Fig. 2). Five irradiated patients developed hypothyroidism after 2 to 4 years and therefore required substitution therapy. Other pituitary dysfunctions in this group were: 9 patients with ACTH deficiency requiring hydrocortisone substitution and 5 patients with gonadotropin insufficiency. Only one patient developed hyperthyroidism. Pituitary functions in the non-irradiated patients remained intact.

The clinical data and levels of FT₃ index, TSH response to TRH, GH and somatomedin-C for the 9 patients of iodine clearance studies are shown in Table 2. The results of the clearance studies are listed in Table 3. Unfortunately, patients No. 7 and 9 did not show normalization of GH parameters and were not tested postoperatively. The creatinine clearance was higher in active acromegaly than in controls and a decline was seen postoperatively in almost all patients.

The radiiodine uptake (median 14.0%, range 6.9–17.4) was not significantly different from that for controls (median 13.4%, range 8.8–25.4). No change was seen postoperatively (median 12.1%, range 7.1–14.9). The thyroid clearance in our patients before surgery was not significantly different from that for controls; no change was seen after surgery. The renal clearance of iodide was higher

### Table 2.
Clinical and biochemical data for patients who underwent the clearance studies.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Goitre</th>
<th>FT₃ index</th>
<th>ΔTSH (mU/l)</th>
<th>Somatomedin-C (nmol/l)</th>
<th>GH* (mU/l)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre-operative</td>
<td>Post-operative</td>
<td>Pre-operative</td>
</tr>
<tr>
<td>1</td>
<td>53</td>
<td>m</td>
<td>+</td>
<td>127</td>
<td>4.3</td>
<td>2.9</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>m</td>
<td>–</td>
<td>150</td>
<td>5.8</td>
<td>3.9</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>m</td>
<td>–</td>
<td>113</td>
<td>5.8</td>
<td>0.9</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>m</td>
<td>–</td>
<td>126</td>
<td>2.2</td>
<td>1.0</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>m</td>
<td>+</td>
<td>85</td>
<td>2.6</td>
<td>1.0</td>
<td>104</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>f</td>
<td>+</td>
<td>121</td>
<td>12.4</td>
<td>8.5</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>f</td>
<td>–</td>
<td>113</td>
<td>5.5</td>
<td>2.8</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>f</td>
<td>+</td>
<td>111</td>
<td>10.3</td>
<td>5.8</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>f</td>
<td>+</td>
<td>88</td>
<td>4.4</td>
<td>2.2</td>
<td>97</td>
</tr>
</tbody>
</table>

* Mean of 4 determinations during the day.
Table 3.
Radioiodine studies of acromegalic patients before and after surgery.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Goitre</th>
<th>Creatinine clearance (ml/min)</th>
<th>Thyroid clearance (ml/min)</th>
<th>Renal clearance (ml/min)</th>
<th>Renal iodide (ug/day)</th>
<th>PII (ug/l)</th>
<th>AIU (ug/h)</th>
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<tr>
<td></td>
<td></td>
<td>Pre-operative</td>
<td>Post-operative</td>
<td>Pre-operative</td>
<td>Post-operative</td>
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<td>Post-operative</td>
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<tr>
<td>1</td>
<td>+</td>
<td>176</td>
<td>120</td>
<td>30.6</td>
<td>23.9</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>120</td>
<td>133</td>
<td>18.7</td>
<td>22.9</td>
<td>49</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>196</td>
<td>146</td>
<td>18.3</td>
<td>21.7</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>195</td>
<td>185</td>
<td>36.1</td>
<td>20.4</td>
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<td>27</td>
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<tr>
<td>5</td>
<td>+</td>
<td>138</td>
<td>119</td>
<td>36.0</td>
<td>31.3</td>
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<td>46</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>137</td>
<td>98</td>
<td>22.9</td>
<td>15.5</td>
<td>59</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>203</td>
<td>–</td>
<td>21.7</td>
<td>–</td>
<td>42</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>102</td>
<td>157</td>
<td>18.0</td>
<td>21.2</td>
<td>39</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>114</td>
<td>–</td>
<td>20.8</td>
<td>–</td>
<td>49</td>
<td>–</td>
</tr>
</tbody>
</table>

Mean males ± sd
165 ± 34 | 141 ± 27 | 30 ± 8 | 24 ± 4 | 42 ± 13 | 37 ± 9 | 271 ± 38 | 238 ± 25 | 3.9 ± 1.3 | 3.8 ± 1.8 | 7.22 ± 2.19 | 5.28 ± 1.93
Mean females ± sd
139 ± 45 | 127 ± 42 | 21 ± 2 | 18 ± 4 | 47 ± 9 | 48 ± 3 | 144 ± 48 | 145 ± 60 | 2.0 ± 0.3 | 2.59 ± 0.36 | 1.21 ± 0.27

Male controls
121 ± 10 | 25 ± 11 | 38 ± 5 | 157 ± 48 | 2.4 ± 0.2 | 3.9 ± 2.3
Female controls
103 ± 25 | 21 ± 40 | 28 ± 8 | 114 ± 23 | 1.0 ± 0.8 | 2.2 ± 0.5

PII: plasma inorganic iodine,  AIU: absolute iodine uptake.

* This patient had iodine contamination caused by a contrast medium: pre-operative values not included in calculations.
in acromegalic patients compared with the control group, but the difference was only statistically significant for females (p < 0.05). After therapy, a decrease was seen in 5 out of 7 patients. Plasma inorganic iodine was higher than in controls and decreased after therapy, although the difference did not reach statistical significance. For patient No. 7, a CT-scan one week before the study influenced plasma inorganic iodine and probably thyroid clearance. The pre-operative results for this patient were not included in the calculations. The absolute iodine uptake was higher in males than in controls (p < 0.05) and a significant decrease was seen after therapy.

Discussion
In this study we found a goitre in 40% of the patients, which is consistent with the studies of Mukhtar et al. and Lamberg et al. (1, 2). The lower prevalence (10.5%) found by Nabarro (5) can probably be explained by the fact that in that study the goitre had to be visible. In contrast to the normal population, the incidence of goitre was higher among males than females, suggesting that specific factors are responsible for goitre formation in acromegaly.

Evans et al. (19) showed that GH has a stimulatory effect on the thyroid in the presence of TSH, a finding also reported by Cobb et al. (20). In contrast, in the present study no differences in GH levels existed between goitrous and non-goitrous patients, whereas the somatomedin-C levels differed. The specific effect of somatomedin-C on the thyroid has been demonstrated by in vitro studies, which showed that somatomedin-C (IGF-I) and TSH are markedly synergistic in stimulating DNA synthesis (21, 22, 23). While the effect of TSH is cAMP-dependent and TSH down-regulates its own receptor, the effect of IGF-I is cAMP-independent and IGF-I does not have a down-regulatory effect on either its own or TSH receptors (21).

In our study we could confirm the finding of Mukhtar et al. (1) that the absolute iodine uptake for acromegalic patients is significantly higher than that for controls. The renal iodide clearance was higher in patients compared with controls. If related to the increased creatinine clearance, however, renal clearance was in the normal range, suggesting that the renal handling of iodide is not changed in acromegaly. The increase in the renal clearance of iodide did not lead to a decrease in plasma inorganic iodine. This, in combination with high absolute iodine uptake levels, indicates that iodine deficiency is not present in acromegaly and that more iodide is supplied via an increased food-intake and/or the extrathyroidal tissues, for example an increased thyroid hormone metabolism, as was suggested by Inada & Sterling (6).

Several later studies support this hypothesis. Sato et al. (7) showed that administration of hGH to children with isolated GH deficiency resulted in a decrease in T4 and an increase in T3. Gacs & Banos (8) found an acute rise in T3 and a reciprocal decrease in T4 and rT3 during GH therapy in GH-deficient children, suggesting stimulation of 5'-deiodinase activity. In a study of rats we showed that intravenous human GH infusions result in an increased conversion of T4 to T3 in the liver, kidney and anterior pituitary (24). Direct evidence for increased hepatic 5'-deiodinase activity in animals after stimulation of GH was reported by Kühn et al. (9, 10). Although Corrigan et al. (11) found a normal TSH response to TRH in 11 patients with active acromegaly, others have reported a diminished response in acromegalic patients and during hGH treatment of children with isolated GH deficiency (2, 3, 25–27). In this study we found that the pre-operative TSH response was much lower in all groups than in normal controls. Among our patients, 43% had a subnormal or absent TSH response, 64% of whom had a goitre. This percentage of patients with a pre-operatively diminished response is higher than that reported by both Lamberg et al. (2) and Carmina et al. (3), who found 23 and 28%, respectively. The difference might be explained by the higher percentage of females tested by both authors, since it is known that the TSH response is higher in females than in males, especially in the follicular phase (28, 29). If only the value for a normal TSH response in males (4 mU/l) is used as reference in our study, a diminished response is found in 32% of our patients. In contrast to the findings of Lamberg et al. (2) we found a higher percentage of subnormal responses in the goitre groups, which is in accordance with the data of Hall et al. (13). In this latter study, the TSH reserve in acromegalic patients was impaired twice as often as the ACTH reserve, especially in patients with goitre, and this could not be associated with hypothyroidism. In other pituitary tumours, however, the TSH and ACTH reserves were impaired
with equal frequency and the impairment correlated with hypothyroidism.

Several factors have been suggested that might be responsible for the impaired TSH response to TRH in acromegaly: 1) An inhibition of TSH production by somatostatin; 2) a compromised TSH reserve owing to the tumour mass; 3) limited availability of TRH to the thyrotropes because of TRH binding to tumour somatotropes; 4) the enhanced peripheral conversion of T₄ to T₃, leading to elevated intracellular T₃ levels in the pituitary or 5) autonomous thyroid function. Studies of both rats and humans have demonstrated that somatostatin can inhibit the release of TSH from the pituitary (30,31). Since it has been shown that in rats GH can stimulate the release of somatostatin from the rat hypothalamus, it was postulated that GH may be subject to a positive feedback control via the hypothalamic secretion of somatostatin (31, 32). If inhibition of TSH production is due to high somatostatin levels in acromegaly, one would expect the TSH response to TRH to increase after successful therapy. In our study the TSH response decreased further in the immediate postoperative period and returned to pre-operative levels in the non-irradiated patients. Although Lamberg et al. (2) suggest that normalization occurs, the postoperative rise in the TSH response to TRH in 7 out of 10 patients during 2 years of follow-up only reflects a return to the pre-operative levels, which were already lower than those for normal controls. It is doubtful whether ‘normalization’ of the TSH response is the correct terminology for these patients.

Like Klijn et al. (4) we also showed that the impaired TSH response to TRH in acromegaly is independent of tumour size, basal TSH or GH levels, and GH response to TRH as well as the somatomedin-C and iodothyronine levels.

Hypothetically, the persistently impaired TSH response might be explained by the long-term suppression of TSH secretion by normal thyrotrope cells in the pituitary, which could have made them less sensitive to TRH stimulation. In a long-term follow-up study of surgically removed prolactinomas, Arafah et al. (33) showed that one week after surgery both the prolactin and the TSH response to TRH were significantly lower in successfully treated patients than in normal controls. After 3 months the TSH response was the same as in controls, whereas it took one year or more to achieve normalization of the prolactin response to stimulation tests. In patients with other successfully treated pituitary tumours, such as Cushing’s disease and endocrine-inactive tumours, the postoperative TSH response to TRH is normal or returns to normal, unless pituitary insufficiency occurs (33–37). If one of the other explanations, such as limited availability of TRH to the thyrotropes owing to binding to the tumour cells or an increased intracellular T₃ concentration as a result of increased intracellular conversion of T₄ is correct, normalization should occur postoperatively. Some evidence for autonomous thyroid functioning in acromegaly was provided by Klijn et al. (4), since they found no correlation between either basal TSH or the magnitude of TSH response to TRH and plasma T₄ and T₃ levels. The higher incidence of hyperthyroidism reported by Nabarro (5) and the low incidence of hypothyroidism in acromegaly might support this hypothesis. However, we did not find a high incidence of hyperthyroidism during long-term follow-up of these patients.

In conclusion, it appears that excessive GH production in acromegaly is associated with a high incidence of goitre which cannot be explained by iodine deficiency owing to an increased renal clearance of iodide. A direct trophic effect of GH and/or somatomedin-C excess on the thyroid and an increased peripheral conversion of T₁ to T₃ leading to increased T₄ production are more likely explanations. Studies of rats, at present in progress, may teach us more about the intracellular effect of GH on thyroid hormone metabolism, since we already know from other studies that plasma thyroid hormone levels do not always reflect intracellular events (38).

The impaired TSH response to TRH stimulation found pre-operatively is not changed by elimination of the GH excess, suggesting that either the factor responsible for the impaired TSH response to TRH has not been removed or autonomous thyroid functioning has developed.

References


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