Stimulation With 0.3-mg Recombinant Human Thyrotropin Prior to Iodine 131 Therapy to Improve the Size Reduction of Benign Nontoxic Nodular Goiter

A Prospective Randomized Double-blind Trial

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Background: Use of recombinant human thyrotropin increases the thyroid radioiodine (iodine 131 [131I]) uptake and may have a role in the context of 131I therapy of benign goiter.

Methods: In a double-blind, placebo-controlled trial, 57 patients with nodular nontoxic goiter (51 women and 6 men) were randomized to receive either 0.3 mg of recombinant human thyrotropin (n=28) or placebo (n=29) 24 hours before 131I therapy. The 131I dose was calculated based on thyroid size (measured by ultrasound), thyroid 131I uptake, and 131I half-life. The follow-up period was 1 year and included measurements of thyroid size and function and patient satisfaction.

Results: Baseline median goiter volume was 51 mL (range, 20-99 mL) in the placebo group and 59 mL (range, 25-92 mL) in the thyrotropin group (P=.75). At 12 months, the mean±SEM relative goiter reduction was 46.1%±4.0% in the placebo group and 62.1%±3.0% in the thyrotropin group (P=.002 between groups). The difference was most pronounced among patients with large goiters. Within each group, there was no significant correlation between retained thyroid 131I dose and goiter reduction. Adverse effects were significantly more frequent in the thyrotropin group (34 vs 12 events; P<.001). Permanent hypothyroidism developed in 3 patients (11%) in the placebo group compared with 16 patients (62%) in the thyrotropin group (P<.001). Patient satisfaction was high and uninfluenced by the use of recombinant human thyrotropin.

Conclusions: Stimulation with recombinant human thyrotropin prior to 131I therapy improves thyroid size reduction by 35%, with a 5-fold higher rate of hypothyroidism. These effects are, at least partially, mediated through mechanisms other than an increase in retained 131I thyroid dose. Further recombinant human thyrotropin dose-finding studies are warranted before routine use.
SUBJECTS AND STUDY DESIGN

From January 2002 through April 2004, 712 patients with NNG were examined at our endocrine outpatient clinic (Figure 1). All patients lived in a moderate iodine-deficient region. The diagnosis was obtained by clinical examination, ultrasonography, and sodium pertechnetate 99m Tc thyroid scintigraphy. In case of a scintigraphically dominant hypoactive nodule, fine-needle aspiration biopsy was performed to exclude malignancy.

Treatment indications were symptoms of cervical compression, cosmetic discomfort, and/or subclinical hyperthyroidism (serum thyroid-stimulating hormone [TSH] <0.10 mU/L and normal serum thyroxine [T4] and serum triiodothyronine [T3] levels). Exclusion criteria are listed in Figure 1. Patients with a 24-hour thyroid RAIU below 20% were excluded because we found it of concern to treat such patients suboptimally, in case they were randomized to the placebo group. Of the 142 eligible patients, 115 accepted 131I therapy, 66 of whom provided signed informed consent. Nine patients dropped out just prior to treatment, leaving 57 patients (6 men and 51 women) for the final analysis (Figure 1).

The study was performed in a randomized, placebo-controlled, double-blinded set-up, in which each patient received either 0.3 mg of recombinant human thyrotropin or isotonic sodium chloride solution injected intramuscularly in the gluteal region 24 hours prior to 131I therapy. Freeze-dried recombinant human thyrotropin (vials containing 0.9-mg recombinant human thyrotropin; Thyrogen; Genzyme Transgenics Corp, Cambridge, Mass) was reconstituted with 3 mL of isotonic sodium chloride solution. Of this dilution, 0.3 mg of recombinant human thyrotropin corresponds to 1 mL. Prior to 131I therapy, pregnancy was ruled out by a urinary test in all female patients of childbearing age not using a safe contraception. The follow-up period was 12 months. The study was approved by the local ethics committee of the county of Funen, Denmark (trial No. 2001-0002) and registered at http://www.clinicaltrials.gov (registration number: NCT00145366).

UPTAKE MEASUREMENTS AND 131I THERAPY

A baseline thyroid RAIU was determined at 24 and 96 hours after oral administration of a tracer activity of 0.5 MBq (14.0 µCi) 131I. Aiming at a thyroid dose of 10 000 rad (100 Gy), the administered therapeutic 131I activity was calculated based on the following algorithm:

\[
\text{Activity (MBq)} = \frac{\text{Thyroid Volume (mL)} \times 22.4 \times (\text{Days} \times \text{MBq/mL}) \times 100}{\text{Half-Life (Days)} \times 24\text{-Hour } 131\text{I Uptake} \%}.
\]

The effective half-life was calculated from the 24- and 96-hour thyroid RAIU measurements.

Iodine 131 therapy was given orally, 10 to 14 days following the last tracer thyroid RAIU measurement. According to the official radiation regulation in Denmark, patients were treated on an outpatient basis, receiving a maximum activity of approximately 600 MBq (16.2 mCi) of 131I. The iodine was administered in a liquid suspension, and an SD of ±10% in administered 131I activity was accepted. After 131I therapy, 24- and 96-hour RAIU measurements were repeated to assess the actual retained thyroid 131I dose. For further details concerning the exact measurements, please see our previously published study.11

THYROID SIZE ESTIMATION

Thyroid size was estimated by ultrasonography before treatment and 3, 6, 9, and 12 months following 131I therapy by a precise and accurate planimetric ultrasonic scanning procedure,11 using a 3.5-MHz compound scanner (type 1846; Brüel & Kjær, Copenhagen, Denmark) mounted with a 5-MHz transducer on a static scanner arm. The average intraobserver variation of this method is around 5%, with a measurement error of 7%.11 The mean ± SD thyroid volume in an adult Danish population without clinically overt goiter is 18.6 ± 4.5 mL (normal range, 10-28 mL).11 The ultrasonic measurements were performed by experienced operators blinded toward the randomization (V.E.N., S.J.B., and L.H.).

THYROID FUNCTION

Thyroid function testing was performed before treatment; 3 and 6 weeks after 131I therapy; and 3, 6, 9, and 12 months after 131I therapy. This included serum TSH, serum total T4, and serum total T3 levels, which were measured at our Department of Clinical Chemistry, Odense University Hospital, Odense, Den-
In subjects who developed thyrotoxicosis after 131I therapy, TSH receptor antibodies (values >60 U/mL are regarded as positive) and thyroid-stimulating hormone antibodies (values >0.01-2.49 UI/L as positive) were measured to detect possible 131I-induced Graves disease. Before and 12 months after 131I therapy, and at the end of follow-up, each individual was registered by a visual analog scale. The score of 0 represented no complaints and 10, the worst possible degree of compression and/or discomfort. The score data were compared by use of the Wilcoxon test. To compare frequencies, the $\chi^2$ test was used. The level of statistical significance was chosen as $P<.05$.

### RESULTS

#### BASELINE DATA

Baseline clinical and laboratory data are given in Table 1. No significant differences were found in any of the baseline variables. Of the randomized patients, 28 received recombinant human thyrotropin and 29 received placebo.

In 12 patients (7 received placebo and 5 received recombinant human thyrotropin), the 131I activity was limited to 600 MBq (16.2 mCi) owing to a significantly lower mean±SD thyroid RAIU (26.3%±9.2% vs 35.2±6.0%; $P<.001$ between groups) and a significantly higher median thyroid volume (67 mL [range, 41-99 mL] vs 51 mL [range, 20-83 mL]; $P=.01$ between groups) compared with the 45 patients given an unrestricted activity. Thus, the calculated 131I activity in the 12 patients was above 600 MBq (16.2 mCi) (median, 1232 MBq [range, 853-2062 MBq] [33.3 mCi [range, 23.1-55.7 mCi]] in the placebo group; median, 929 MBq [range, 780-1632 MBq] [25.1 mCi [range, 21.1-44.1 mCi]] in the thyrotropin group; $P=.34$). Because in-house therapy was not planned, they were only given approximately 600 MBq (16.2 mCi). Thus, the overall median 131I activity was 581 MBq (range, 241-666 MBq) (15.7 mCi [range, 6.5-18.0 mCi]) and 519 MBq (range, 173-658 MBq) (14.0 mCi [range, 4.7-17.8 mCi]) in the thyrotropin group and the placebo group, respectively ($P=.55$ between groups) (Table 2). For further details regarding the exact 131I kinetics after stimulation with 0.3 mg of recombinant human thyrotropin, please see our previously published study.

#### GOITER VOLUME REDUCTION

Baseline median goiter volume was 51 mL (range, 20-99 mL) in the placebo group and 59 mL (25-92 mL) in the thyrotropin group ($P=.75$). At 12 months, the corresponding values were 27 mL (5-82 mL) and 20 mL (8-90 mL). The extent of reduction in goiter volume was statistically significant only in the thyrotropin group ($P<.001$). Hundred and twenty per cent of the patients in the thyrotropin group had a reduction in goiter volume, whereas only 24% of the placebo patients achieved a similar degree of reduction ($P<.001$). When the percentage of goiter volume reduction was compared across the 12 patients who received 131I with a thyrotropin dose of 0.3 mg, a statistically significant difference was found ($P=.03$).

#### STATISTICAL ANALYSIS

Accepting a type 1 error of 5% and a type II error of 10% and assuming an SD of 20% on the percentage of goiter volume reduction, at least 21 patients in each randomization group were required to detect a difference of 20%. The STATA 8 (StataCorp, College Station, Tex) statistical software program was used, and data are presented as median (range) or mean±SD or SEM. Non-parametric or parametric statistical tests were used, depending on the normality of the data. A repeated-measure analysis of variance was performed to test for an overall difference between groups. A 1-way analysis of variance or the Friedman test was used to test within-group differences. Linear regression analysis was used to test for relationships between relevant variables. Visual analog scale score data were compared by use of the Wilcoxon test. To compare frequencies, the $\chi^2$ test was used. The level of statistical significance was chosen as $P<.05$.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eligible, Not Randomized</th>
<th>0.3-mg Recombinant Human Thyrotropin</th>
<th>Placebo</th>
<th>$P$ Value (Nonrandomized vs Randomized)</th>
<th>$P$ Value (Recombinant Human Thyrotropin vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>49</td>
<td>28</td>
<td>29</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age, y</td>
<td>58 (34-77)</td>
<td>52 (32-68)</td>
<td>52 (26-77)</td>
<td>.07</td>
<td>.92</td>
</tr>
<tr>
<td>Female-male ratio</td>
<td>42:7</td>
<td>24:4</td>
<td>27:2</td>
<td>.62</td>
<td>.42</td>
</tr>
<tr>
<td>Goiter size (range), mL</td>
<td>46 (24-96)</td>
<td>59 (25-92)</td>
<td>51 (20-99)</td>
<td>.69</td>
<td>.75</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>NA</td>
<td>68</td>
<td>86</td>
<td>NA</td>
<td>.12</td>
</tr>
<tr>
<td>Previous thyroidectomy, %</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>.86</td>
<td>.75</td>
</tr>
<tr>
<td>Subclinical thyrotoxicosis, %</td>
<td>25</td>
<td>11</td>
<td>14</td>
<td>.50</td>
<td>.60</td>
</tr>
<tr>
<td>Baseline serum TSH, median (range) (mU/L)</td>
<td>0.28 (&lt;0.01-1.64)</td>
<td>0.39 (&lt;0.01-2.15)</td>
<td>0.29 (&lt;0.01-2.49)</td>
<td>.68</td>
<td>.75</td>
</tr>
<tr>
<td>Baseline serum free T4, mean ± SD (nmol/L)</td>
<td>125.0 ± 36.1</td>
<td>120.0 ± 23.0</td>
<td>109.0 ± 27.1</td>
<td>.16</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; T4, thyroxine; TSH, thyroid-stimulating hormone.

*Eleven patients previously had a hemithyroidectomy; TSH, thyroid-stimulating hormone.
†Reference interval, 0.30 to 4.00 mU/L.
‡Reference interval, 70 to 140 nmol/L.
mL (6-59 mL), respectively ($P<.001$, within groups compared with baseline). In relative numbers, the $\Delta$SEM goiter reduction at 3 months after $^{131}$I therapy was $21.0\%\pm 2.1\%$ in the placebo group and $27.0\%\pm 3.0\%$ in the thyrotropin group ($P=.11$); at 6 months, $36.0\%\pm 4.3\%$ and $46.0\%\pm 3.0\%$, respectively ($P=.04$); at 9 months, $42.0\%\pm 4.1\%$ and $55.0\%\pm 3.1\%$, respectively ($P=.01$); and at 12 months, $46.1\%\pm 4.0\%$ and $62.1\%\pm 3.0\%$, respectively ($P=.002$) (Figure 2). Thus, compared with conventional $^{131}$I therapy, the goiter reduction was increased by $35\%$ at 12 months when stimulating with $0.3\, \text{mg}$ of recombinant human thyrotropin. Overall, those who developed hypothyroidism had a significantly higher mean±SD retained thyroid dose compared with those who remained euthyroid ($14\,800\pm 5700\, \text{rad} \, [148.0\pm 57.0\, \text{Gy}]$ and $94\,300\pm 4300\, \text{rad} \, [94.3\pm 43.0\, \text{Gy}]$, respectively; $P<.001$). However, when stratifying according to randomization group, the difference was statistically insignificant ($15\,600\pm 5800\, \text{rad} \, [156.0\pm 58.0\, \text{Gy}]$ and $12\,810\pm 5610\, \text{rad} \, [128.1\pm 56.1\, \text{Gy}]$ in the thyrotropin group [$P=.17$] and $10\,710\pm 3430\, \text{rad} \, [107.1\pm 34.3\, \text{Gy}]$ and $78\,200\pm 2210\, \text{rad} \, [78.2\pm 22.1\, \text{Gy}]$ in the placebo group [$P=.13$]), but this is most likely explained by lack of statistical power. It is worth noting that those

### Table 2. Iodine 131 ($^{131}$I) Kinetics at Baseline and After Therapy Following Prestimulation With $^{131}$I 0.3 mg of Recombinant Human Thyrotropin or Placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>0.3-mg Recombinant Human Thyrotropin (n = 28)</th>
<th>Placebo (n = 29)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h $^{131}$I tracer uptake, mean ± SD, %</td>
<td>34.0±5.5</td>
<td>31.6±11.0</td>
<td>.29</td>
</tr>
<tr>
<td>96-h $^{131}$I tracer uptake, mean ± SD, %</td>
<td>32.3±5.6</td>
<td>31.0±12.0</td>
<td>.53</td>
</tr>
<tr>
<td>24-h $^{131}$I therapy uptake, mean ± SD, %</td>
<td>47.0±13.0</td>
<td>28.7±9.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>96-h $^{131}$I therapy uptake, mean ± SD, %</td>
<td>46.0±13.0</td>
<td>27.4±8.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Therapeutic $^{131}$I activity, median (range), MBq*</td>
<td>581 (241-666)</td>
<td>519 (173-658)</td>
<td>.55</td>
</tr>
<tr>
<td>Retained thyroid dose, mean ± SD, rad†</td>
<td>138,600±55,800</td>
<td>80,600±26,300</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Increase in thyroid dose, mean ± SEM, %</td>
<td>48.1±11.0‡</td>
<td>0.2±9.0§</td>
<td>.002</td>
</tr>
</tbody>
</table>

*To convert to millicurie, divide by 37.
†To convert to gray, divide by 100.
‡95% Confidence interval, 26.0 to 70.0.
§95% Confidence interval, −19.0 to 19.0.

### Figure 2. The percentage mean change in thyroid volume following stimulation with 0.3 mg of recombinant human thyrotropin or placebo 24 hours prior to iodine 131 ($^{131}$I) therapy. *$P=.04$ between groups. †$P=.01$ between groups. ‡$P=.002$ between groups. §$P<.001$ compared with baseline. Error bars indicate SEM.**

### Thyroid Function

Overall, 25 patients had subclinical hyperthyroidism before treatment (14 in the placebo group and 11 in the thyrotropin group; $P=.60$). Three weeks after $^{131}$I therapy, 37 patients (20 in the thyrotropin group and 17 in the placebo group; $P=.15$) showed a transient decrease in serum TSH level below 0.30 mU/L. Thereafter, the thyroid function of these patients either normalized or decreased. No significant changes in serum levels of free $T_4$ and free $T_3$ indexes were observed 3 weeks following $^{131}$I therapy in either group (132.0±69.3 nmol/L in the thyrotropin group and 130.0±46.0 nmol/L in the placebo group) compared with baseline values.

Permanent hypothyroidism (Figure 4) developed in 16 patients (62%) in the thyrotropin group compared with 3 patients (11%) in the placebo group ($P<.001$), and consequently these patients were given levothyroxine. Overall, those who developed hypothyroidism had a significantly higher mean±SD retained thyroid dose compared with those who remained euthyroid ($14\,800\pm 5700\, \text{rad} \, [148.0\pm 57.0\, \text{Gy}]$ and $94\,300\pm 4300\, \text{rad} \, [94.3\pm 43.0\, \text{Gy}]$, respectively; $P<.001$). However, when stratifying according to randomization group, the difference was statistically insignificant ($15\,600\pm 5800\, \text{rad} \, [156.0\pm 58.0\, \text{Gy}]$ and $12\,810\pm 5610\, \text{rad} \, [128.1\pm 56.1\, \text{Gy}]$ in the thyrotropin group [$P=.17$] and $10\,710\pm 3430\, \text{rad} \, [107.1\pm 34.3\, \text{Gy}]$ and $78\,200\pm 2210\, \text{rad} \, [78.2\pm 22.1\, \text{Gy}]$ in the placebo group [$P=.13$]), but this is most likely explained by lack of statistical power. It is worth noting that those


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who developed hypothyroidism experienced a greater mean ± SD goiter reduction compared with those remaining euthyroid (69.0% ± 11.5% and 52.0% ± 16.0%, respectively; \( P = .005 \)).

Before treatment, thyroid peroxidase antibodies were present in 6 patients (5 in the thyrotropin group) and were found in an additional 8 patients 1 year after \( ^{131} \)I therapy (4 in the thyrotropin group). Of these 14 patients, 6 developed hypothyroidism during the observation period (all were pretreated with recombinant human thyrotropin). None had TSH receptor antibodies before treatment, but these appeared in 2 patients (both were in the thyrotropin group) during the follow-up period.

### ADVERSE EFFECTS

Adverse effects were significantly more frequent in the thyrotropin group (34 events occurred in the thyrotropin group and 12 events in the placebo group; \( P < .001 \)). These were especially related to hyperthyroid symptoms and thyroid growth (Table 3). None experienced any respiratory problems, and any complaints of cervical compression and/or pain remitted within 1 to 2 weeks after \( ^{131} \)I therapy, while hyperthyroid symptoms had disappeared within 3 weeks after \( ^{131} \)I therapy in nearly all cases. One patient in the thyrotropin group developed Graves disease and mild and transient thyroid-associated ophthalmopathy, which was treated successfully with methimazole and prednisolone for a short period.

### PATIENT SATISFACTION

No significant correlation was found between the individual visual analog scale scores and the initial goiter size (\( r = 0.003; P = .93 \)). In both groups, the goiter-related symptoms were significantly improved 3 months and 1 year after \( ^{131} \)I therapy (Table 4). No significant difference was found between the 2 randomization groups, neither at 3 months nor 1 year after therapy.
COMMENT

A few previous clinical studies have suggested that recombinant human thyrotropin prestimulation augments the effect of 

\[ ^{131}\text{I} \] therapy in patients with NNG. However, all of these studies have shortcomings related to either dose calculation, an inhomogeneous study population, lack of a control group, a short follow-up period, or a small study population.

To our knowledge, our study is the first large-scale, double-blind, placebo-controlled trial investigating the effects and adverse effects of pretreatment with recombinant human thyrotropin prior to 

\[ ^{131}\text{I} \] therapy in patients with benign NNG. We found a mean thyroid volume reduction of 62% in the thyrotropin group compared with 46% in the placebo group, corresponding to an increase of 35% in thyroid size reduction. Furthermore, we found that patient satisfaction was high, independent of whether recombinant human thyrotropin or placebo was given, which could be owing to a poor correlation between thyroid size and symptoms or perhaps a lack of sensitivity of the visual analog scale.

In concert with other studies not using recombinant human thyrotropin, we found an inverse correlation in the placebo group between the initial goiter volume and the relative goiter reduction after 1 year, which was not found in the thyrotropin group. That dose restriction was slightly higher in the latter group does not change this fact. Thus, recombinant human thyrotropin-augmented therapy may be independent of goiter size, possibly because of a more homogeneous distribution of 

\[ ^{131}\text{I} \]. This indicates that recombinant human thyrotropin may have a particular role in patients with large goiters. Furthermore, patients with a low thyroid RA IU seem to benefit more from recombinant human thyrotropin prestimulation, and we most likely underestimated the effect of recombinant human thyrotropin because patients with a thyroid RA IU below 20%—the very patients we anticipate to have the greatest benefit—were excluded.

We have previously shown that 0.3-mg recombinant human thyrotropin use 24 hours prior to 

\[ ^{131}\text{I} \] therapy increases the retained thyroid dose by 75% compared with placebo. Although a positive correlation between the retained thyroid dose after recombinant human thyrotropin stimulation and goiter volume reduction 6 months after 

\[ ^{131}\text{I} \] therapy was recently suggested, our study offers no confirmation of this. Consequently, the effect of recombinant human thyrotropin on goiter volume reduction cannot solely be explained by an increase in the applied thyroid dose but may be dependent on other factors mediated by recombinant human thyrotropin.

From our previous investigation of the impact of 0.9-mg recombinant human thyrotropin use on thyroid volume in healthy nongloutous individuals and of 0.3-mg recombinant human thyrotropin use in patients with NNG, we know that recombinant human thyrotropin causes an acute and temporary increase in thyroid size by approximately 35% and 24%, respectively. Considering that 

\[ ^{131}\text{I} \] therapy in some cases causes a transient goiter growth of 15% to 25% within the first week, its combination with recombinant human thyrotropin use may potentially lead to severe tracheal compression in susceptible individuals. In the present study, none of our patients experienced any respiratory problems, but whether there was an impact on the trachea is unknown because we did not perform tracheal imaging (computed tomography or magnetic resonance imag-
ing) or pulmonary function tests. An early measurement of the acute changes in goiter size after radioiodine therapy would have been informative but was not performed to avoid radiation exposure of the personnel.

A late adverse effect of 131I therapy is the development of hypothyroidism.1,20,24,25 In the present study, a 5-fold higher incidence was found, most likely due to a higher retained thyroid 131I dose and a more homogenous distribution of 131I.1,21 Because levothyroxine replacement therapy is usually straightforward, this should not be a major argument against recombinant human thyrotropin–augmented 131I therapy. A point favoring recombinant human thyrotropin use is that those patients who developed hypothyroidism also had a greater goiter reduction.

From this randomized, placebo-controlled, double-blind trial, we conclude that the use of 0.3 mg of recombinant human thyrotropin 24 hours prior to 131I therapy results in a more effective goiter volume reduction at the expense of a 5-fold higher frequency of hypothyroidism, a higher frequency of adverse effects, and lack of evidence of an improved patient satisfaction. Future studies should focus on including patients with large goiters and low thyroid RAIU because they may benefit the most from recombinant human thyrotropin pretreatment. Finally, the optimal dose and timing of recombinant human thyrotropin use in relation to 131I therapy remains to be determined, with the aim being the best balance between beneficial and adverse effects.

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