Qualitative and Quantitative Impact of Protective Glucocorticoid Therapy on the Effective $^{131}$I Half-Life in Radioiodine Therapy for Graves Disease

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This aim of this retrospective study was to determine the impact of glucocorticoid therapy on the effective $^{131}$I half-life in radioiodine therapy for Graves disease. Methods: Three hundred fifteen consecutive Graves disease patients undergoing radioiodine therapy at our institution between August 2004 and January 2009 were enrolled. We investigated the influences of thyroid state (hypothyroidism, euthyroidism, hyperthyroidism), antithyroid drug dose before $^{131}$I therapy, thyroid-stimulating hormone receptor antibody (TRAb) level, and qualitative and quantitative factors of prednisolone therapy on the effective $^{131}$I half-life, applying univariate (paired $t$ test) and multivariate (multiple-regression) analyses. Results: Multivariate analyses revealed independent significant effects of the thyroid metabolic state ($P = 0.004$), antithyroid drugs ($P < 0.001$), presence of TRAb ($P = 0.004$), and glucocorticoids ($P = 0.046$) on thyroidal radioiodine half-life. Compared with euthyroidism, thyrotoxicosis and hypothyroidism reduced the effective half-life; high doses of antithyroid drugs and high TRAb levels had the same effect. Also, glucocorticoid therapy shortened the effective thyroidal radioiodine half-life in a dose-dependent manner. Pharmacologically, this effect is attributable to the prednisolone-induced increase of renal plasma $^{131}$I clearance and the resulting reduction of plasma $^{131}$I available for reuptake into the thyroid during radioiodine therapy. Conclusion: Oral treatment with prednisolone results in a reduction of effective thyroidal $^{131}$I half-life in Graves disease, especially at higher doses.

Key Words: Graves disease; radioiodine; endocrine ophthalmopathy; effective half-life; prednisolone

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In randomized trials, glucocorticoids have been shown to reduce the risk of endocrine ophthalmopathy (EO) after radioiodine therapy (RIT) (1). European and national state-ments on RIT in patients with Graves disease (GD) and EO recommend short courses of oral glucocorticoids during and after RIT (2,3). The German guidelines for treatment of GD with radioiodine propose low-dose glucocorticoid pulse therapy with 0.5 mg of prednisolone per kilogram in patients at risk of developing EO (3). In patients already presenting with EO-related symptoms, doses of 1.0–1.5 mg/kg are suggested. Although prednisolone has beneficial effects on the development or course of EO during RIT of GD, it is well established that glucocorticoids themselves change thyroid metabolism and triiodothyronine ($T_3$) and levothyroxine ($T_4$) levels and modulate the concentration of stimulating antithyroid antibodies (thyroid-stimulating hormone receptor antibody [TRAb]) (4–7). Therefore, the aim of our study was to investigate the influence of prednisolone on the thyroidal $^{131}$I half-life in GD patients and to assess this effect in comparison to other factors already known to change effective $^{131}$I half-life during the course of RIT in GD patients—namely the thyroidal metabolic state, antithyroid medication, and TRAb level (8–12). In addition, possible prednisolone-induced changes in $^{131}$I uptake and RIT outcome were reconsidered in this large patient group.

MATERIALS AND METHODS

Between August 2004 and January 2009, 315 consecutive patients (mean age ± SD, 52.4 ± 13.8 years; 253 women) treated with RIT for GD were included in this retrospective study. One hundred twenty-five patients received prednisolone (pred + group), and 190 underwent RIT without prednisolone (pred – group) (Table 1). The pred + group was further subdivided into low-prednisolone (predlow, 0.5 mg/kg; 72 patients) and high-prednisolone (predhigh, ≥1 mg/kg; 53 patients) groups. At RIT, 113 patients were diagnosed with euthyroidism because of antithyroid medication, 106 with subclinical hyperthyroidism (thyroid-stimulating hormone [TSH] suppressed, free triiodothyronine [$fT_3$] and free levothyroxine [$fT_4$] levels within reference range), and 52 with thyrotoxicosis (TSH suppressed, $fT_3$ or $fT_4$ levels elevated). Because of the effects of antithyroid drugs, 20 patients presented with subclinical (TSH elevated, $fT_3$ and $fT_4$ levels elevated).
levels within reference range) and 24 with overt (TSH elevated, fT3 or fT4 levels reduced) hypothyroidism. The numbers of the prednisolone subgroups within the metabolic groups are given in Table 1. For subsequent statistical calculations, the categoric variable metabolic state was transferred to a semi-quantitative ordinal sum score accounting for the TSH level (0, elevated TSH; 1, TSH within reference range; and 2, suppressed TSH) and fT3 and fT4 levels (0, fT3/fT4 levels reduced; 1, fT3/fT4 levels within reference range; and 2, fT3/fT4 levels elevated).

TRAB levels were measured before RIT using the receptor assay TRAK-Human (Brahms AG) (TRAb > 1.5 IU/L indicative for GD). The amount of daily antithyroid medication was normalized to the corresponding thiamazole equivalent, as proposed: 1 mg of thiamazole equals 1.6 mg of carbimazole equals 15 mg of propylthiouracil (13).

Patients with evidence of GD-associated EO were given 1–1.5 mg of oral prednisolone per kilogram of body weight; 0.5 mg of oral prednisolone per kilogram of body weight was administered to patients at risk of developing EO (i.e., cigarette smokers). Simultaneously starting with RIT, glucocorticoids were continued to patients at risk of developing EO (i.e., cigarette smokers).

Because it was previously hypothesized that glucocorticoids might reduce thyroidal ¹³¹I uptake, the 24-h therapeutic ¹³¹I uptake was compared between pred− and pred+ patients. Twenty-four-hour uptake and all subsequent daily ¹³¹I measurements were undertaken under standardized conditions using a RAM ION DigiLog ion chamber survey meter (Rotem Industries). Initial ¹³¹I activity was calculated before RIT according to the German guidelines, which recommend thyroid doses between 200 and 300 Gy in GD while accounting for concomitant diseases, especially EO (3).

The average RIT dose actually attained was calculated for all prednisolone groups separately. Therapy outcome was investigated 6.3 ± 1.7 mo after RIT. Patients presenting with persistent hyperthyroidism at this follow-up or still requiring antithyroid drugs at that time to achieve euthyroidism were regarded as nonresponders to RIT.

Group differences in radioiodine uptake and achieved radiation dose were tested using 2-sided t tests. Differences in the treatment outcome of the various prednisolone groups were analyzed with the Fisher exact test. The impact of the variables thyroid metabolic state, dose of pre-RIT antithyroid drugs, TRAb level, and prednisolone therapy on the effective ¹³¹I half-life was estimated in Statistica (version 6.0; StatSoft) using univariate (2-sided paired t tests) and multivariate (multiple-regression) analyses. The threshold chosen for significance was a P value of 0.05. At a P value less than 0.10, a statistical trend was reported. Pearson correlation estimating r was used for analyses of antithyroid drug amount and TRAb level versus the effective half-life. All group data are presented as mean ± SD.

To further illustrate from a clinical perspective the impact of pre-RIT antithyroid drugs and TRAb level on the effective ¹³¹I half-life, the data were additionally subdivided semiquantitatively to define categoric patient groups (Fig. 1).

### RESULTS

No significant age differences between the prednisolone groups were evident (pred−, 54.0 ± 14.0 y; pred+, 49.9 ± 13.9 y; predlow, 49.8 ± 13.5 y; and predhigh, 50.1 ± 12.4 y).

The overall therapeutic ¹³¹I uptake was 72.1% ± 19.2%.

In pred− patients, therapeutic uptake was 71.5% ± 20.7%, and in the pred+ group it was 72.9% ± 17.1% (predlow, 72.7% ± 14.6%; predhigh, 73.1% ± 20.2%). Comparisons between the prednisolone groups failed to demonstrate any difference.

The average radiation dose attained was 349 ± 146 Gy. The group-specific doses are listed in Table 2. Although significant differences were found when comparing pred− and pred+ (P = 0.005) groups and pred− and predhigh (P = 0.002) groups, statistics for pred− versus predlow and predlow versus predhigh groups failed to reach significance (P = 0.12 and P = 0.16, respectively). Within-group comparisons regarding therapy outcome (responder vs. nonresponder) demonstrated significantly lower doses in nonresponders in both the pred− (P < 0.001) and the pred+ (P = 0.03) groups.

At the follow-up, 276 patients (87.6%) were classified as RIT responders and 39 patients (12.4%) as nonresponders. In the pred− group, 162 (85.3%) were responders and 28 (14.7%) nonresponders; in the predlow group, 65 (90.3%) responded to RIT and 7 (9.7%) did not; and in the predhigh group, 49 (92.5%) were responders and 4 (7.5%) were not. Thus, the combined pred+ group comprised 114 responders (91.2%) and 11 nonresponders (8.8%). No significant difference in therapy outcome was evident between the groups.

### Univariate Analysis

**Thyroid Metabolic State.** The mean effective ¹³¹I half-life in euthyroid patients was 5.98 ± 1.43 d—a significantly

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**TABLE 1**

Metabolic Groups and Prednisolone Medication

<table>
<thead>
<tr>
<th>Group</th>
<th>Prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Euthyroidism (n = 113)</td>
<td>68 (60.2%)</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism (n = 106)</td>
<td>64 (60.4%)</td>
</tr>
<tr>
<td>Thyrotoxicosis (n = 52)</td>
<td>28 (53.8%)</td>
</tr>
<tr>
<td>Subclinical hypothyroidism (n = 20)</td>
<td>14 (70.0%)</td>
</tr>
<tr>
<td>Overt hypothyroidism (n = 24)</td>
<td>16 (66.6%)</td>
</tr>
<tr>
<td>All metabolic states (n = 315)</td>
<td>190 (60.3%)</td>
</tr>
</tbody>
</table>

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![Fig. 1](link)
longer half-life than that in the overt hypo- and both hyperthyroid subgroups—and a trend toward a longer effective $^{131}\text{I}$ half-life of euthyroid patients, as compared with subclinical hypothyroid patients, ($P = 0.07$) was noted (Fig. 1A). Group comparisons between hypo- and hyperthyroidism revealed no significant difference in effective half-life ($P = 0.37$). Subclinical hyperthyroidism led to a significantly longer effective half-life than thyrotoxicosis ($P = 0.001$), and the effective half-life did not differ significantly between subclinical and overt hypothyroidism ($P = 0.27$).

Antithyroid Drug Effects. Euthyroid patients were treated with $6.95 \pm 9.96$ mg of thiamazole equivalent per day, hypothyroid patients with $11.85 \pm 9.20$ mg per day, subclinical hyperthyroid patients with $9.89 \pm 9.85$ mg per day, and overtly hyperthyroid patients with $15.91 \pm 14.22$ mg per day. Statistically, euthyroid patients received less thiamazole equivalent than all other metabolic groups (euthyroidism vs. subclinical hyperthyroidism, $P = 0.03$; euthyroidism vs. thyrotoxicosis, $P < 0.001$; and euthyroidism vs. hypothyroidism, $P = 0.004$).

The radioiodine effective half-life was significantly dose-related to the pre-RIT thiamazole equivalent ($P < 0.001$). The 6 defined categories demonstrated a continuous decrease in effective radioiodine half-life with increasing antithyroid drug doses (Fig. 1B). Significant differences in effective half-life were found at thiamazole equivalents larger than 10 mg per day, as compared with no antithyroid medication. Pearson statistics revealed an overall negative correlation ($r = -0.27$) between antithyroid drug dose and effective $^{131}\text{I}$ half-life.

TRAb Level. In 6 subjects, no pre-RIT TRAb level was available. The effective half-life was significantly dose-related to the TRAb level ($P < 0.01$), with an overall negative correlation ($r = -0.21$). The 5 TRAb subgroups showed an effective radioiodine half-life reduction with increasing TRAb levels (Fig. 1C).

Prednisolone. The mean effective radioiodine half-life of pred− patients ($5.48 \pm 1.54$ d) was significantly longer than that of pred+ patients ($5.01 \pm 1.44$ d; $P = 0.007$) (Fig. 1D). A significantly shorter effective $^{131}\text{I}$ half-life ($4.76 \pm 1.44$ d) was found in the pred$_{\text{high}}$ group than in the pred− patients ($P = 0.002$), whereas the group comparison of pred− and pred$_{\text{low}}$ ($5.19 \pm 1.41$ d) did not reveal a significant difference ($P = 0.17$). Finally, a trend toward a shorter effective half-life in the pred$_{\text{high}}$ group than in the pred$_{\text{low}}$ group was evident ($P = 0.09$).

When the prednisolone groups were investigated with regard to the accompanying metabolic state, significant differences in effective half-life were still evident in the subgroups of euthyroid patients (pred− vs. pred$_{\text{low}}$ $P = 0.04$; pred− vs. pred$_{\text{high}}$ $P = 0.01$) and subclinical hyperthyroid patients (pred− vs. pred$_{\text{low}}$ $P = 0.26$; pred− vs. pred$_{\text{high}}$ $P = 0.02$), whereas in the hypothyroid and thyrotoxic patients no significant change in effective half-life due to prednisolone was found (Fig. 1E).


**TABLE 2**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Without prednisolone</th>
<th>With prednisolone</th>
<th>0.5 mg/kg prednisolone</th>
<th>≥1 mg/kg prednisolone</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>341 ± 141</td>
<td>382 ± 138</td>
<td>371 ± 147</td>
<td>407 ± 130</td>
<td>357 ± 141</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>239 ± 100</td>
<td>267 ± 80</td>
<td>267 ± 80</td>
<td>315 ± 131</td>
<td>320 ± 138</td>
</tr>
<tr>
<td>Overall</td>
<td>323 ± 140</td>
<td>375 ± 138</td>
<td>358 ± 141</td>
<td>398 ± 131</td>
<td>349 ± 146</td>
</tr>
</tbody>
</table>

Data are mean ± SD, given in grays.

**Multivariate Analysis**

The multivariate regression analyses revealed significant independent influences of the thyroid status \((P = 0.004)\), pre-RIT antithyroid drug dose \((P < 0.001)\), TRAb level \((P = 0.004)\), and prednisolone treatment \((P = 0.046)\) on the effective \(^{131}\)I half-life.

The multiple-regression analysis yielded the following equation:

\[
\text{Effective half-life} = \beta_1 \times [\text{metabolic state}] + \beta_2 \times [\text{antithyroid drug}] + \beta_3 \times [\text{TRAb}] + \beta_4 \times [\text{prednisolone}] + \text{intercept},
\]

where \(\beta_1 - \beta_4\) are the standardized regression coefficients \((\beta_1, -0.16; \beta_2, -0.22; \beta_3, -0.16; \text{and} \beta_4, -0.11)\) and the intercept was 6.41.

**DISCUSSION**

This study confirms that the metabolic thyroid state, antithyroid drugs, and the TRAb level change the thyroidal effective \(^{131}\)I half-life during RIT of GD (8–12). The multivariate analysis points to independent influences of these factors on the effective half-life.

Because glucocorticoids during RIT are recommended for GD patients presenting EO or those at risk of developing EO, the impact of glucocorticoids on thyroidal iodine metabolism and RIT outcome have also become relevant issues in recent years. When we compared the pred− with the pred+ groups using univariate and multivariate analyses, we found a significant and independent reduction in iodine half-life by glucocorticoids, mainly driven by high prednisolone doses. Furthermore, interactions of the administered prednisolone with the iodine uptake and RIT outcome were investigated. In our study, \(^{131}\)I uptake and treatment outcome did not differ significantly in the pred− and pred+ groups. However, others argued that glucocorticoids reduce the thyroid radioiodine 24-h uptake by increasing renal iodine clearance and decreasing thyroid-stimulating antibodies (6). Zingg and Perry demonstrated a decreased radioiodine uptake after application of steroids in comparisons before and after administration (14). However, their findings might alternatively be explained by stunning from the first \(^{131}\)I dose. After high doses of cortisone, Fredrickson et al. found a decreased 24-h uptake in euthyroid patients without thyroid diseases but not in GD patients (15). In healthy subjects, Hill et al. demonstrated a slower \(^{131}\)I intrathyroidal accumulation over 4–8 h after prolonged cortisone treatment but stated that the 24-h uptake was the same as at baseline (16). They concluded that iodine uptake was retarded but not inhibited by cortisone. In a placebo-controlled study in GD patients, betamethasone administered over 3 wk before RIT failed to demonstrate any difference in 24-h uptake, whereas the RIT success in terms of cessation of hyperthyroidism was impaired (5). Because no pre-RIT volume was measured and all patients received a standard \(^{131}\)I dose, it might be speculated that the finding by Gamstedt and Karlsson (5) was related to differences in attained grays per thyroid tissue. Comparing a pred+ \((0.4–0.5 \text{ mg of prednisone per kilogram, starting } 2–3 \text{ d after RIT})\) with a pred− group, Bartalena et al. found equivalent therapy outcomes after 1 y of follow-up (1). Jensen et al. found no difference in therapy outcome in pred+ GD patients \((25 \text{ mg of prednisolone per day, starting } 2 \text{ d before RIT})\), compared with pred− patients (9). Also, Chiovato et al. revealed no difference in therapy outcome in patients with prednisolone \((0.4–0.5 \text{ mg/kg})\) versus outcome in those without (17). Finally, a recent but small study points to an even better therapy outcome using prednisone \((1 \text{ mg/kg, starting } 1 \text{ d before RIT})\) (18). At least in our study, one reason for unaffected therapy outcome in pred+ versus pred− patients, despite a shorter effective radioiodine half-life, might be the relatively high attained total dose across all subgroups, resulting in a ceiling effect with regard to the differences in therapy outcome. However, the main body of published evidence, including our own, comparing patients administered glucocorticoids with those not administered glucocorticoids indicates an unaltered \(^{131}\)I uptake and an unchanged or better therapy outcome when prednisolone is administered at around the same time as RIT is initiated.

Two points might account for the shortened effective iodine half-life, especially under high prednisolone doses. First, because the iodine uptake is not altered by the glucocorticoids and T₃ and T₄ blood levels fall under glucocorticoids (4), organically bound intrathyroidal iodine and premature hormone precursors might be released into the extrathyroidal space at higher rates, as compared with a glucocorticoid naïve metabolic state. Second, however, the predominant reason is probably the diuretic effect of prednisolone itself, which
induces an increase in the glomerular filtration rate and a loss of sodium and potassium at doses between 30 and 70 mg/d (19–21). These effects do not occur after a single dose of glucocorticoids but are apparent when prednisolone is administered over several days (19). Furthermore, the diuretic effect of glucocorticoids is dose-dependent (19,20,22), relating to our finding of a pronounced decrease of the effective $^{131}$I half-life under higher prednisolone doses. With regard to the iodine metabolism, the iodide blood clearance is dominated by the thyroid uptake and renal excretion. Apart from intestinal resorption, the iodide blood pool is supplied by thyroidal iodide release (predominantly bound to T$_3$/T$_4$) and by iodide remnants of peripherally metabolized thyroid hormones. In RIT, the 2 latter processes contribute to the $^{131}$I blood pool after the 24-h uptake, because no gastrointestinal radioiodine is available for further resorption at that point. Then, one can view the radioiodine as mainly distributed in 3 compartments: blood pool, thyroid, and urine. During RIT, the extrathyroidal $^{131}$I blood pool is available for reuptake into the thyroid. Stun- ning effects during RIT are likely to impair these reuptake processes. However, similar stunning occurs in pred$^−$ and pred$^+$ patients, not accounting for the measured difference in effective $^{131}$I half-life between the patient groups. In addition, stunning only reduces, but does not totally inhibit, reuptake. Taken together, the measure of effective half-life is the net sum of intrathyroidal $^{131}$I decay, release of $^{131}$I-labeled thyroid hormones, and intrathyroidal iodide into the blood and uptake of available extrathyroidal $^{131}$I from the blood compartment. Because of the diuretic prednisolone effect, a shift of blood-pool $^{131}$I to the urine compart- ment takes place in pred$^+$, as compared with pred$^−$, patients, thus reducing the available amount of radioiodine for thyroidal reuptake. Indeed, in intraindividual compari- sons an increased urinary $^{131}$I excretion under glucocorticoids was demonstrated (15). In a longitudinal study, renal plasma $^{131}$I clearance rates increased during cortisone ther- apy, as compared with pre- and posttreatment periods (23). Ingbar et al. revealed a 3-fold higher renal iodide clearance in hypophysectomized rats treated with cortisone, com- pared with controls (24). Because this renal prednisolone effect does not occur immediately after the first dose, the 24-h uptake remains unaffected in both the pred$^+$ and pred$^−$ groups (19). Because the prednisolone-induced diu- resis is Additionally dose-dependent (19,20,22), we found not only a qualitative but also a quantitative prednisolone impact on the effective half-life. Consistent with this pro- posed pharmacophysiologic mechanism influencing the effective radioiodine half-life at an extrathyroidal site, the multivariate analysis identified the prednisolone adminis- 


differences in effective $^{131}$I half-life and, ultimately, the result- ing RIT dose. At least in those GD patients who undergo RIT with high prednisolone doses for EO, to reach thyroid doses equivalent to those attained in GD patients without glucocorticosteroid therapy an extra 10%–15% $^{131}$I activity should be considered.

**CONCLUSION**

Effective thyroidal $^{131}$I half-life is one of the key factors for the success of RIT in GD. Glucocorticoids are commonly given during RIT of GD to prevent or treat concomitant EO. When prednisolone is administered at around the same time as RIT is initiated, neither thyroidal 24-h uptake nor final therapy outcome is impaired. However, this approach sig- nificantly shortens the effective thyroidal $^{131}$I half-life in a dose-dependent manner, probably because of the diuretic properties of prednisolone. Multiple-regression analysis identified prednisolone treatment as an independent factor that interferes with thyroidal effective iodine half-life, as do the previously characterized factors thyroidal metabolic state, antithyroid drugs, and TRAb level.

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