0021-972X/99/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 84, No. 2
*Printed in U.S.A.*

# Comparison of Radioiodine with Radioiodine plus Lithium in the Treatment of Graves' Hyperthyroidism*

FAUSTO BOGAZZI, LUIGI BARTALENA, SANDRA BROGIONI, GIOVANNA SCARCELLO, ALESSANDRO BURELLI, ALBERTO CAMPOMORI, LUCA MANETTI, GIUSEPPE ROSSI, ALDO PINCHERA, AND ENIO MARTINO

*Dipartimento di Endocrinologia e Metabolismo, Ortopedia e Traumatologia, Medicina del Lavoro (F.B., L.B., S.B., G.S., A.B., A.C., L.M., A.P., E.M.), University of Pisa, 56122 Pisa, Italy; and Reparto di Epidemiologia e Biostatistica, Istituto di Fisiologia Clinica (G.R.), National Research Council (C.N.R.), 56100 Pisa, Italy.*

**ABSTRACT**

Effectiveness of radioiodine for Graves' hyperthyroidism depends also on its intrathyroidal persistence. The latter is enhanced by lithium by blocking iodine release from the thyroid. One hundred ten patients with Graves' hyperthyroidism were randomly assigned to treatment with radioiodine or radioiodine plus lithium, stratified according to goiter size (≤40 or >40 mL) and evaluated for changes in thyroid function and goiter size, at monthly intervals, for 12 months.

Cure of hyperthyroidism occurred in 33 of 46 patients (72%) treated with radioiodine and in 45 of 54 patients (83%) treated with radioiodine plus lithium. The probability of curing hyperthyroidism was higher and its control prompter ($P = 0.02$) in the radioiodine-plus-lithium group. Patients with ≤40-mL goiters had similar persistence of hyperthyroidism (13%), but lithium-treated patients had hyperthyroidism controlled earlier ($P = 0.04$). Among patients with >40-mL goiters, hyperthyroidism was cured in 6 of 15 patients (40%) treated with radioiodine alone and in 12 of 16 patients (75%) treated with radioiodine plus lithium ($P = 0.07$), and cure occurred earlier in the latter ($P = 0.05$). Goiters shrank in both groups ($P < 0.0001$), more effectively and promptly ($P < 0.0005$) in the radioiodine-plus-lithium group. Serum free $T_4$ and $T_3$ levels increased shortly after therapy only in the radioiodine group ($P < 0.01$).

Lithium carbonate enhances the effectiveness of radioiodine therapy, in terms of prompter control of hyperthyroidism, in patients with small or large goiters. In the latter group, lithium also increases the rate of permanent control of hyperthyroidism. (*J Clin Endocrinol Metab* **84:** 499–503, 1999)

RADIOIODINE therapy is a well-established and effective treatment for Graves' hyperthyroidism. The primary goal of radioiodine therapy is to restore euthyroidism, although thyroid ablation and hypothyroidism may represent a desired therapeutic outcome, especially in the presence of ophthalmopathy (1–4). The effectiveness of radioiodine is affected by several factors, including previous treatment with antithyroid drugs, goiter volume, 24-h thyroidal radioactive iodine uptake (RAIU), and the rapid release of radioiodine after incorporation into thyroglobulin (Tg) (5–8). Iodine blocks the release of organic iodine from the thyroid gland, but it is not used as an adjunct to radioiodine because it reduces thyroidal uptake and recycling of radioiodine (9). Lithium blocks the release of organic iodine and thyroid hormone from the thyroid gland without affecting thyroidal RAIU (10–13). Accordingly, its use as an adjunct to radioiodine in the therapy of thyrotoxicosis was postulated, but information on this subject is limited (14, 15). To address this question, we undertook a blind, randomized, controlled study evaluating the efficacy of radioiodine therapy alone, and radioiodine combined with lithium, in Graves' hyperthyroidism. The results of this study indicate that the addition of lithium to radioiodine therapy is associated with a more prompt control of hyperthyroidism and, in patients with large goiters, with a higher degree of its permanent correction.

Received August 6, 1998. Revision received October 5, 1998. Accepted October 23, 1998.

Address all correspondence and requests for reprints to: Enio Martino, M.D., Dipartimento di Endocrinologia e Metabolismo, Ortopedia e Traumatologia, Medicina del Lavoro, University of Pisa, Ospedale di Cisanello, Via Paradisa, 2, 56122, Pisa, Italy.

* Presented in abstract form at the 24th European Thyroid Meeting, Munich, German, August 30-September 3, 1997. This work was supported, in part, by grants from the University of Pisa (Fondi d'Ateneo).

## Subjects and Methods

### *Study groups*

During the period 1994–1996, we enrolled 110 patients with newly diagnosed, untreated Graves' disease, age more than 20 yr, recent onset of hyperthyroidism (≤6 months), and nonsevere or absent Graves' ophthalmopathy. Patients with severe Graves' ophthalmopathy, previous treatment of hyperthyroidism with radioiodine or surgery, contraindications to glucocorticoids, or lithium treatment were excluded. Patients were stratified according to the baseline goiter volume (≤40 or >40 mL); although somewhat arbitrary, this value was suggested by a survey of the American Thyroid Association as ideal for radioiodine treatment (16). Patients were treated with methimazole for 3–4 months to restore euthyroidism and then randomly assigned to treatment with radioiodine (n = 55) or with radioiodine plus lithium (900 mg/day for 6 days, starting on the day of radioiodine administration) (n = 55). Methimazole was withdrawn 5 days before radioiodine therapy. The dose of radioiodine was: 7 MBq per gram of estimated thyroid tissue and corrected for the 24-h RAIU. Each patient received a short course of prednisone to prevent a possible progression of Graves' ophthalmopathy, as previously reported (17, 18). Prednisone was started 21 days after radioiodine treatment to avoid interference with radioiodine recirculation. One patient from the radioiodine and lithium group and 9 patients from the radioiodine group were excluded shortly after enrollment because they refused subsequent controls. The study was approved by the institutional review committee, and all patients gave informed consent.

### *Evaluation*

Baseline evaluation included ophthalmologic examination, evaluation of thyroid function, thyroid scan, 24-h RAIU, thyroid ultrasonography, white cell count, differential count, hematocrit, mean corpuscolar volume, platelet count, BUN, creatinine, serum electrolytes, urine analysis, and electrocardiogram. Thyroid ultrasonography was performed by 1 examiner (F. Bogazzi), who did not know the treatment administrated to the patient; thyroid volume was determined at 0, 7, 14, and 30 days and 2, 3, 6, and 12 months. Serum free $T_4$ (FT4) and T3 (FT3), and Tg levels were measured at 0, 7, 14, and 30 days after radioiodine and then every month for all of the follow-up period. Patients were considered cured when they became stably euthyroid or developed permanent hypothyroidism. Euthyroidism was considered stable when it persisted for at least the 12 months after the first evidence, implying that patients who became euthyroid at 12 months were followed for an additional 12 months. Hypothyroidism or persistent hyperthyroidism after radioiodine treatment were corrected within 3–4 weeks, by administration of T4 or methimazole, as appropriate. A second dose of radioiodine was administered to patients with persistent hyperthyroidism at the end of the follow-up period. Serum lithium level was measured at the 6th day of treatment. Possible symptoms of lithium toxicity were looked for by a questionnaire filled out by each patient 15 days after radioiodine treatment.

### *Evaluation of thyroid function and volume*

Thyroid function was assessed by measuring serum FT4 and FT3 (Lisophase kits, Laboratori Bouty, Sesto S. Giovanni, Italy) and serum TSH (Auto-DELFIA Wallac, Gaithersburg, MD). The normal ranges were: serum FT4, 0.6–1.8 ng/dL (8.4–23.2 pmol/L); FT3, 0.25–0.55 ng/dL (3.8–8.4 pmol/L); and TSH, 0.4–3.7 mU/L. Serum TSH-receptor antibody was determined by radioreceptor assay (TRAK assay, BRAHMS Diagnostica, Berlin, Germany; normal values, less than 5U/L). Serum Tg (Sorin Biomedica, Saluggia, Italy; normal value < 3–30 mg/L), serum anti-Tg antibody (Sorin Biomedica; undetectable in normal controls), and serum anti-TPO antibody (Serodia, Tokyo, Japan; undetectable in normal controls) were also determined by commercial kits. Urinary iodine excretion was measured using an autoanalyzer apparatus (Technicon, Rome, Italy). The median urinary iodine excretion in our area is 110 $\mu$g/L. Serum lithium concentration was measured by a standard chemical method; therapeutic levels for psychiatric disorders ranged from 0.6–1.2 mEq/L. Thyroid volume was measured by ultrasound using a 7.5 MHz linear transducer and calculated by the ellipsoid model: width × length × thickness × 0.52 for each lobe (19, 20).

### *Statistical analysis*

Baseline values were expressed as mean ± SD (or ± SE, where specified) for quantitative variables. The baseline characteristics of the two groups were compared by unpaired *t* test and by $\chi$-square test. The control of hyperthyroidism in the two groups was represented using survival curves at 12 months, estimated by the Kaplan-Meier method. Comparisons between nonremission curves were performed by the Mantel-Cox (MC) test and by the Breslow-Gean-Wilcoxon (BGW) test. The $\chi$-square test and Fisher exact test were used to compare nonremission rates at 12 months. Differences between the two groups in thyroid volume, serum FT4, FT3, and Tg levels (at each interval during the study period) were evaluated by ANCOVA, taking baseline value as covariate. The time trend within each treatment was evaluated by ANOVA with repeated measures. Multiple comparisons with basal values were performed by the modified Dunnett's test (21).

## Results

There were no significant differences in the baseline clinical and biochemical characteristics of the two groups (Table 1). Most patients came from iodine-deficient areas, as assessed by the low urinary iodine excretion (Table 1). Cure of hyperthyroidism was achieved in 33 of the 46 patients (72%) treated with radioiodine alone and in 45 of the 54 patients (83%) treated with radioiodine plus lithium (Table 2). Patients treated with radioiodine plus lithium had a higher probability of being cured than patients treated with radioiodine alone ($P = 0.03$, by MC test), although the 2 groups did not significantly differ at the end of the study ($P = 0.16$) (Fig. 1). In addition, the probability of controlling hyperthyroidism during the first months after radioiodine treatment was higher in the radioiodine-plus-lithium group ($P = 0.02$, by BGW test). Among the patients with ≤40-mL goiters (31

**TABLE 1.** Baseline characteristics of the two groups of patients with Graves' hyperthyroidism

| | | Radioiodine group | Radioiodine plus lithium group |
|---|---|---|---|
| No. of patients (M/F) | | 46 (9/37) | 54 (10/44) |
| Mean age (range) (yr) | | 51 (24–87) | 45 (23–74) |
| Onset of hyperthyroidism (months) | | 5.7 ± 2.1 | 6.1 ± 2.3 |
| Smokers (percent) | | 62 | 63 |
| Radioiodine dose (MBq) | | 521 ± 148 | 556 ± 141 |
| Ophthalmopathy (present/absent) | | 27/19 | 33/21 |
| Thyroid volume (mL)[a] (range) | | 35 ± 21 (10–94) | 38 ± 22 (11–106) |
| Serum FT4 (ng/dL) | | 2.1 ± 2.0 | 2.6 ± 2.4 |
| Serum FT3 (ng/dL) | | 0.7 ± 0.6 | 1.0 ± 0.9 |
| Serum TSH (mU/L) | | 0.4 ± 0.9 | 0.6 ± 1.0 |
| Serum TSH-receptor antibody (U/L) | | 32 ± 54 | 40 ± 113 |
| Positive TSH-receptor antibody (percent) | | 65 | 67 |
| Serum AbTg (mU/mL) | | 197 ± 508 | 295 ± 590 |
| Serum AbTPO (mU/mL) | | 333 ± 577 | 271 ± 398 |
| UIE ($\mu$g/L) (range) | | 51 ± 37 (18–175) | 54 ± 35 (10–167) |
| Hyperthyroid patients at the time of radioiodine (percent) | (all) | 41 | 54 |
| | (≤40 mL) | 32 | 50 |
| | (>40 mL) | 60 | 62 |

Values are means ± SD. AbTg, antithyroglobulin antibody; AbTPO, antithyroperoxidase antibody. Normal values are: FT4: 0.65–1.8 ng/dL (8.4–23.2 pmol/L); FT3: 0.25–0.55 ng/dL (3.8–8.4 pmol/L); TSH: 0.4–3.7 mU/L; serum TSH-receptor antibody: <5; Ab-Tg: negative; Ab-TPO: negative; thyroid volume 7 ± mL. To convert serum free $T_4$ hormone values to pmol/L, multiply by 1.287. To convert serum free $T_3$ values to pmol/L, multiply by 1.536. To convert MBq to mCi, divide by 37. UIE: urinary iodine excretion; in our area the median value is 110 $\mu$g/L. *P* values for differences between the two groups were ≥ 0.172.

[a] Thyroid volume was measured by ultrasound.

**TABLE 2.** Outcome of therapy in the two groups after 12 months

| | ALL | | ≤40-ml Goiter | | >40-ml Goiter | |
|---|---|---|---|---|---|---|
| | Radioiodine | Radioiodine + lithium | Radioiodine | Radioiodine + lithium | Radioiodine | Radioiodine + lithium |
| | (n = 46) n (percent) | (n = 54) n (percent) | (n = 31) n (percent) | (n = 38) n (percent) | (n = 15) n (percent) | (n = 16) n (percent) |
| Hyperthyroid | 13 (28) | 9 (17) | 4 (13) | 5 (13) | 9 (60) | 4 (25) |
| Hypothyroid | 26 (57) | 35 (65) | 21 (68) | 28 (74) | 4 (27) | 7 (44) |
| Euthyroid | 7 (15) | 10 (18) | 6 (19) | 5 (13) | 2 (13) | 5 (31) |

Figures *in parentheses* indicate the percent of patients in each group. Patients who were not euthyroid were given methimazole (if hyperthyroid) or $T_4$ (if hypothyroid). Hyperthyroidism was defined by the increase in serum free $T_4$ and/or free $T_3$ concentrations and undetectable serum TSH concentration; hypothyroidism was defined by the decrease in serum free $T_4$ and increase in serum TSH concentrations.

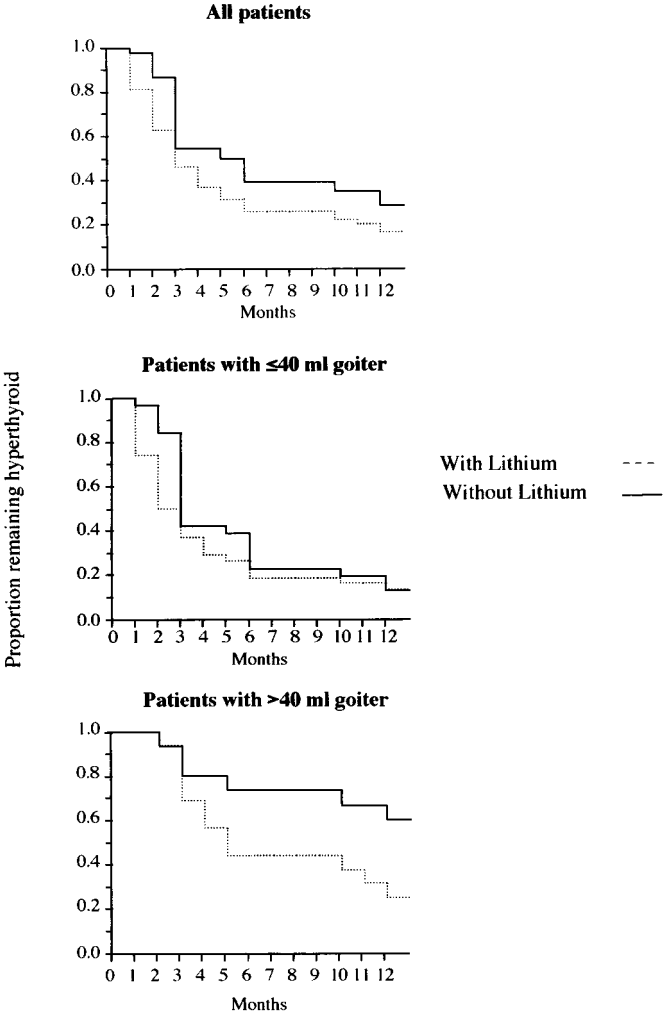


FIG. 1. Kaplan-Meier estimates of the proportion of patients who remained hyperthyroid. The overall outcome of the two groups of patients was assessed by the MC test ($P = 0.03$, *top panel*; $P = 0.18$, *middle panel*; $P = 0.05$, *lower panel*). The rapidity of cure (*i.e.* the prompt control of hyperthyroidism) was assessed by the BGW test ($P = 0.02$, *top panel*; $P = 0.04$, *middle panel*; $P = 0.08$, *lower panel*). All patients in each group completed the 12-month period of observation.

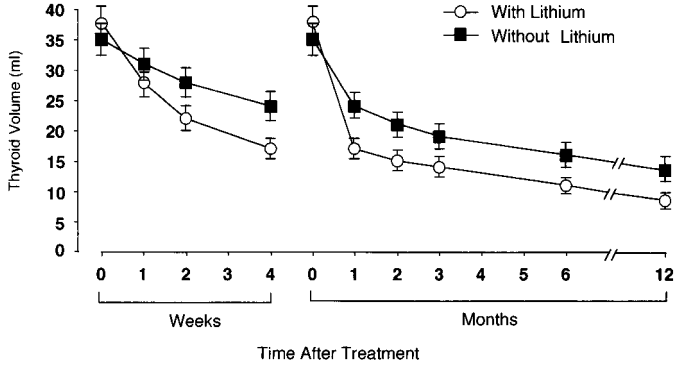


FIG. 2. Mean changes, from baseline, in the thyroid volume. *Bars* indicate the SD. All patients in each group completed the 12-month period of observation.

treated with radioiodine and 38 with radioiodine plus lithium), 4 (13%) and 5 (13%), respectively, had persistent hyperthyroidism (Table 2). However, patients treated with radioiodine plus lithium had a more rapid control of hyperthyroidism ($P = 0.04$, by BGW test) (Fig. 1). Among the patients with >40-mL goiters, hyperthyroidism was cured in 6 of the 15 patients (40%) treated with radioiodine and in 12 of the 16 (75%) treated with radioiodine plus lithium ($P = 0.07$) (Table 2). Patients treated with radioiodine plus lithium had a higher probability of controlling hyperthyroidism promptly than did patients treated with radioiodine alone ($P = 0.05$, by MC test; $P = 0.08$, by BGW test) (Fig. 1).

Goiter volumes were similar in the two groups at baseline (35 ± 21 mL in the radioiodine group, 38 ± 22 mL in the radioiodine-plus-lithium group, $P = 0.48$). Goiter shrinkage occurred in both groups during the study period ($P < 0.0001$) (Fig. 2) and was more pronounced, at each time, in the radioiodine-plus-lithium group ($P < 0.0005$). Among patients with >40-mL goiters, adjunct of lithium was followed by a reduction of goiter size from 66 ± 21 mL to 15 ± 9 mL ($P < 0.0001$); this reduction was greater than that observed after radioiodine alone, in which the goiter shrank from 58 ± 17 mL to 28 ± 11 mL ($P < 0.005$). Goiter shrinkage was significantly different in the two groups at 7 days ($P = 0.03$), during, and at the end of the study period ($P < 0.005$, at each time). Patients with ≤40-mL goiters had similar goiter volume at the end of the study (8 ± 6 mL in the radioiodine group, 7 ± 6 mL in the radioiodine-plus-lithium group). Goiter shrinkage occurred in both groups ($P < 0.0001$), but it occurred earlier, and it was higher at 7, 14, 30, 60, and 90 days after therapy, in the patients treated with radioiodine plus lithium ($P < 0.0005$, $P < 0.002$, $P < 0.002$, $P < 0.002$, and $P = 0.02$, respectively).

Patients treated with radioiodine had a significant increase in serum FT4 [from 2.1 ± 2.0 ng/dL to 2.8 ± 1.7 ng/dL ($P <$ 0.01)] and FT3 [from 0.7 ± 0.6 ng/dL to 0.9 ± 0.7 ng/dL ($P <$

0.01)], 1 week after radioiodine therapy (Fig. 3). Such an increase was not observed in the patients treated with radioiodine plus lithium. Serum Tg was measured in anti-Tg-negative patients (n = 10 in the radioiodine group, n = 17 in the radioiodine-plus-lithium group). Serum Tg levels, after 1 week, increased from 320 ± 467 ng/mL to 705 ± 887 ng/mL in the radioiodine group ($P \sim 0.05$), whereas they did not change in the radioiodine-plus-lithium group (Fig. 3).

Mean serum lithium concentration was 0.3 ± 0.1 mEq/L in the lithium-treated patients, below the therapeutic range. Only 1 of the 54 patients experienced mild nausea, which did not require treatment discontinuation. No patients had a worsening of eye signs during the follow-up study.

## Discussion

Radioiodine therapy is a well-established treatment for Graves' hyperthyroidism. Its efficacy can be affected by several factors, including the short persistence of radioiodine in the thyroid gland. In hyperthyroid Graves' patients, RAIU is enhanced by TSH-receptor antibody (22); however, radioiodine is also rapidly discharged because of its increased turnover. The effectiveness of radioiodine therapy may be reduced by pretreatment with propylthiouracil but not with methimazole (23). Lithium can significantly affect the kinetics of iodine by reducing its release from the thyroid gland, thus increasing its retention (11, 24). However, lithium is not commonly used to potentiate the therapeutic effect of radioiodine therapy. Beneficial effects of lithium, in combination with radioiodine, were reported in cases of thyroid carcinoma (25–27) and in only one nonrandomized study in Graves' disease (14, 15). The latter study, carried out in patients with 35- to 55-g goiters, indicated that the addition of lithium to radioiodine did not produce a higher rate of cure after a 3-yr follow-up period (15). The results of our study showed that radioiodine plus lithium allows a more rapid control of hyperthyroidism than radioiodine alone. This effect was evident both in patients with small (≤40 mL) goiters and in those with large (>40 mL) goiters. In the latter subgroup, the addition of lithium was also associated with a greater degree of cure of hyperthyroidism. However, in this subgroup of patients, the recurrence or persistence of hyperthyroidism was high, and it reached 60% in those treated with radioiodine alone. This might be explained, at least in part, by the fact that most patients came from iodine-deficient areas. In patients with large goiters, but contraindications to thyroidectomy (*i.e.* cardiac disorders), lithium might represent a useful adjunct to radioiodine to achieve, more rapidly, a permanent control of hyperthyroidism. In this regard, an additional important effect of lithium addition was the lack of serum FT4 and FT3 surge which was observed shortly after radioiodine therapy. This effect might be related to radioiodine-induced destruction, as suggested by the concomitant rise in serum Tg concentrations, or to the prevention of thyroid hormone surge after antithyroid drug withdrawal. This effect might be particularly beneficial in older patients with an underlying cardiac disease. The combined treatment with radioiodine plus lithium might also be favorable for Graves' ophthalmopathy, because of the lower risk of recurrence of hyperthyroidism, which is known to affect negatively the course of eye disease (4).

Finally, the addition of lithium was associated with an overall greater shrinkage of large goiters, which occurred especially during the first weeks after radioiodine treatment. Thus, although thyroidectomy remains the first-choice treatment in Graves' patients with large goiters, the use of lithium may increase the efficacy of radioiodine therapy also in patients with large goiters.

Side effects of short-term lithium therapy were virtually absent. We, therefore, suggest the adjunct of lithium to radioiodine therapy for Graves' hyperthyroidism in patients with large goiters and contraindications to thyroidectomy, and in patients with active ophthalmopathy or cardiac disorders (irrespective of goiter size).

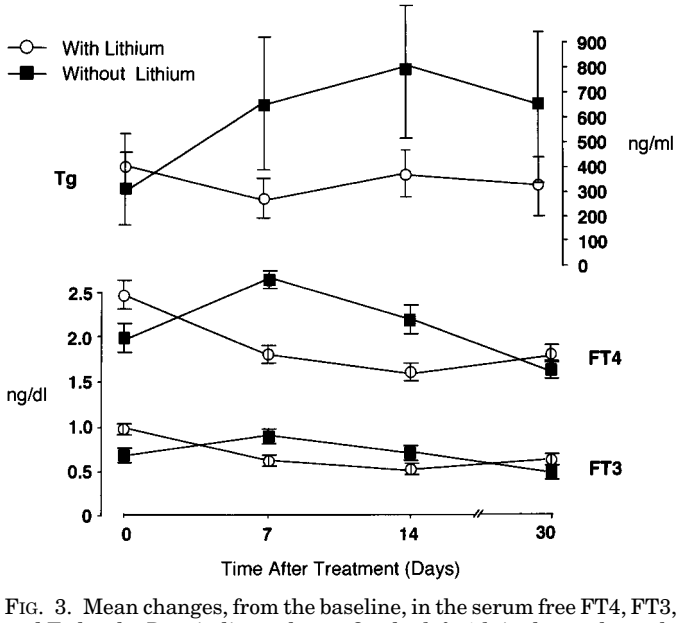


FIG. 3. Mean changes, from the baseline, in the serum free FT4, FT3, and Tg levels. *Bars* indicate the SE. On the *left side* is shown the scale for serum FT4 and FT3; and on the *right side*, for serum Tg. Serum Tg was measured in anti-Tg-negative patients.

## References

1. **Glinoer D, Hesch D, LaGasse R, Laurberg P.** 1987 The management of hyperthyroidism due to Graves' disease in Europe in 1986. Results of an international survey. Acta Endocrinol (Copenh). [Suppl] 185:9–37.
2. **Nagayama Y, Izumi M, Nagataki S.** 1989 The management of hyperthyroidism due to Graves' disease in Japan in 1988. Endocrinol Jpn. 36:299–314.
3. **Solomon B, Glinoer D, LaGasse R, Wartofsky L.** 1990 Current trends in the management of Graves' disease. J Clin Endocrinol Metab. 70:1518–1524.
4. **Bartalena L, Marcocci C, Pinchera A.** 1997 Treating severe Graves' ophthalmopathy. Bailliere's Clin Endocrinol Metab. 11:521–536.
5. **Marcocci C, Gianchecchi D, Masini I, et al.** 1990 A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism. J Endocrinol Invest. 13:513–20.
6. **Tuttle RM, Patience T, Budd S.** 1995 Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid. 5:243–247.
7. **Kendall-Taylor P, Keir MJ, Ross WM.** 1984 Ablative radioiodine therapy for hyperthyroidism: long-term follow-up study. Br Med J. 289:361–363.
8. **Peters H, Fischer C, Bogner U, Reiners C, Schleusener H.** 1997 Treatment of Graves' hyperthyroidism with radioiodine: results of a prospective randomized study. Thyroid. 7:247–251.
9. **Sternthal E, Lipworth L, Stanley B, Abreau C, Fang S-L, Braverman LE.** 1980 Suppression of thyroid radioiodine uptake by various doses of stable iodine. N Engl J Med. 303:1083–1086.
10. **Temple R, Berman M, Carlson HE, Robbins J, Wolff J.** 1972 The use of lithium in Graves' disease. Mayo Clin Proc. 47:872–878.

11. **Temple R, Berman M, Robbins J, Wolff J.** 1972 The use of lithium in the treatment of thyrotoxicosis. J Clin Invest. 51:2746–2756.
12. **Robbins J.** 1984 Perturbations of iodine metabolism by lithium. Math Biosci. 72:337–347.
13. **Mori M, Tajima K, Oda Y, Matsui I, Mashita K, Tarui S.** 1989 Inhibitory effect of lithium on the release of thyroid hormones from thyrotropin-stimulated mouse thyroids in a perfusion system. Endocrinology. 124:1365–1369.
14. **Turner JG, Brownlie BEW, Rogers TGH.** 1976 Lithium as an adjunct to radioiodine therapy for thyrotoxicosis. Lancet. 1:614–615.
15. **Brownlie BEW, Turner JG, Oveden BM, Rogers TGH.** 1979 Results of lithium-$^{131}$I treatment of thyrotoxicosis. J Endocrinol Invest. 2:303–304.
16. **Wartofsky L.** 1997 Radioiodine therapy for Graves' disease: case selection and restrictions recommended to patients in North America. Thyroid. 7:213–216.
17. **Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A.** 1989 Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med. 321:1349–1352.
18. **Bartalena L, Marcocci C, Bogazzi F, et al.** 1998 Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med. 338:73–78.
19. **Brunn J, Blocjc U, Ruf J, Bos I, Kunze WP, Scriba PC.** 1983 Volumetrie der schilddrusenlappen mittels real-time sonographie. Dtsch Med J. 287: 1206–1207.
20. **Vitti P, Martino E, Aghini-Lombardi F, et al.** 1994 Thyroid measurement by ultrasound in children as a tool for the assessment of mild iodine deficiency. J Clin Endocrinol Metab. 79:600–603.
21. **Glantz AS.** 1992 Primer of biostatistics. New York: McGraw-Hill Inc.
22. **Marcocci C, Valente WA, Pinchera A, Aloj SM, Kohn LD, Grollman EF.** 1983 Graves' IgG stimulation of iodide uptake in FRTL-5 rat thyroid cells: a clinical assay complementing FRTL-5 assays measuring adenylate cyclase and growth-stimulating antibodies in autoimmune thyroid disease. J Endocrinol Invest. 6:463–471.
23. **Imseis RE, Vanmiddlesworth L, Massie JD, Bush AJ, Vanmiddlesworth NR.** 1998 Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab. 83:685–687.
24. **Berens S, Bernstein R, Robbins J, Wolff J.** 1970 Antithyroid effects of lithium. J Clin Invest. 49:1357–1367.
25. **Briere J, Pousset G, Darsy et Guinet P.** 1974 The advantage of lithium in association with 131I in the treatment of functioning metastasis of the thyroid cancer. Ann Endocrinol. 35:281–282.
26. **Gershengorn MC, Izumi M, Robbins J.** 1976 Use of lithium as an adjunct to radioiodine therapy of thyroid carcinoma. J Clin Endocrinol Metab. 42:105–111.
27. **Pons F, Carriò I, Estorch M, Ginjaume M, Pons J, Milian R.** 1987 Lithium as an adjunct of iodine-$^{131}$ uptake when treating patients with well-differentiated thyroid carcinoma. Clin Nucl Med. 12:644–647.