Reduction of Thyroid Nodule Volume by Levothyroxine and Iodine Alone and in Combination: A Randomized, Placebo-Controlled Trial

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Context: Nodular goiter is common worldwide, but there is still debate over the medical treatment.

Objective: The objective of the study was the measurement of the effect of a treatment with (nonsuppressive) T4, iodine, or a combination of both compared with placebo on volume of thyroid nodules and thyroid.

Design: This was a multicenter, randomized, double-blind trial in patients with nodular goiter in Germany [LISA (Levothyroxin und Iodid in der Strumatherapie Als Mono-oder Kombinationstherapie) trial].

Setting: The study was conducted in outpatient clinics in university hospitals and regional hospitals and private practices.

Participants: One thousand twenty-four consecutively screened and centrally randomized euthyroid patients aged 18–65 yr with one or more thyroid nodules (minimal diameter 10 mm) participated in the study.

Intervention: Intervention included placebo, iodine (I), T4, or T4 + I for 1 yr. T4 doses were adapted for a TSH target range of 0.2–0.8 mIU/liter.

Outcome Measures: The primary end point was percent volume reduction of all nodules measured by ultrasound, and the main secondary end point was a change in goiter volume.

Results: Nodule volume reductions were −17.3% [95% confidence interval (CI) −24.8/−9.0%, P < 0.001] in the T4 + I group, −7.3% (95% CI −15.0/+1.2%, P = 0.201) in the T4 group, and −4.0% (95% CI −11.4/+4.2%, P = 0.328) in the I group as compared with placebo. In direct comparison, the T4 + I therapy was significantly superior to T4 (P = 0.018) or I (P = 0.003). Thyroid volume reductions were −7.9% (95% CI −11.8/−3.9%, P < 0.001), −5.2% (95% CI −8.7/−1.6%, P = 0.024) and −2.5% (95% CI −6.2/+1.4%, P = 0.207), respectively. The T4 + I therapy was significantly superior to I (P = 0.034) but not to T4 (P = 0.190).

Conclusion: In a region with a sufficient iodine supply, a 1-yr therapy with a combination of I and T4 with incomplete suppression of thyrotropin reduced thyroid nodule volume further than either component alone or placebo. (J Clin Endocrinol Metab 96: 2786–2795, 2011)
Treatment of uni- or multinodular goiter and/or thyroid nodules remains a significant challenge worldwide. A representative study in Germany determined the prevalence of thyroid nodules greater than 1 cm and goiters as 20 and 36%, respectively, for an age range 20–79 yr (corresponding approximately to 17 million inhabitants with thyroid nodules) (1). Ultrasound screening studies have revealed prevalences of goiter in Denmark of 23% (2) and 30% (3), whereas figures reported for the prevalence of thyroid nodules evaluated by ultrasound across Europe are 31% in Finland (4), 34.7% in France (5), and 33.1% in Italy (6). Corresponding data for North America are scarce; one publication (7) reported thyroid nodules in 67 of 100 normal subjects.

There are insufficient data on medical treatment of nodular goiter because the number of patients in the reported trials (8–18) has been consistently too low to demonstrate even moderate or clinically relevant effects on thyroid nodule volume [maximum number of patients: 123 (18)]. In addition, half of the previous studies on the efficacy of T4 treatment have used a fully TSH-suppressive regimen (TSH < 0.1) with high T4 doses (8–11, 13, 14), which is no longer acceptable because of frequent side effects. Other studies (12, 15–18) aimed to achieve a partially suppressed TSH value (upper limit 0.4). For these treatments, three metaanalyses (19–21) have shown a slight benefit with T4 therapy (vs. placebo).

Koc et al. (22) compared the effect of full TSH suppression (<0.1) with partial TSH suppression (0.4–0.6) and placebo, and they found a similar reduction of nodule volume in both treatment arms. Furthermore, there has been only one placebo-controlled trial (number of patients: 70) evaluating the therapy of nodular goiter with iodine (I) (12).

We therefore performed a national multicenter, prospective, double-blind, randomized, placebo-controlled assessment of the efficacy of T4, I, and T4+I for the therapy of nodular goiters, with a placebo (P) as control, for a period of 12 months [LISA (Levothyroxin und Iodid in der Strumatherapie Als Mono-oder Kombinationstherapie) trial] (23). In this study T4 doses were adapted to a TSH target range of 0.2–0.8 mU/liter under T4 and T4+I therapy.

Materials and Methods

Study objectives

The objective of this study was to evaluate whether the effect of a T4 +I combination is superior to either of the monotherapies (T4, I, or P) in a 12-month treatment of nodular goiter.

Primary objective

The primary objective was to compare the change in total volume of all nodules after 12 months of T4+I treatment with the change after 12 month of each of the reference treatments (one of the two active controls or placebo).

Secondary objectives

The secondary objective was to compare the change in goiter volume, number, and echogenicity of nodules after T4+I treatment with that after each reference treatment after 12 months therapy.

Sample size

The number of patients to be included in the study was determined based on previous figures collected from routine data of one of the centers. A change of 10% in total nodule volume corresponding to 0.06 in log total nodule volume was judged to be potentially relevant. Based on practice data, a SD of 0.2 log units was assumed as a rather conservative estimate of the variability of before and after differences in log thyroid volumes determined by the same physician with the same equipment. It was assumed that log total nodule volumes would reveal a similar measurement error. Taking into consideration a dropout rate of 15%, a number of 250 patients per group was fixed to be randomized to receive 212 evaluable patients per group.

Study centers and recruitment of patients:

Sixty German study centers participated (Supplemental Appendix I, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org), with an even geographical distribution across the country. Most of the physicians were members of the German Endocrine Society, and all experienced thyroidologists. The research protocol was approved by the ethic committees of the medical chambers of the concerned federal states; all participants gave written informed consent.

All (consecutively investigated) patients with nodular goiter, who were seen by the participating physicians and were expected to meet the inclusion and exclusion criteria after their previous medical history were screened.

Inclusion and exclusion criteria

Inclusion criteria included the following: Caucasian race; aged 18–65 yr; normal TSH value (range between 0.6 and 3.0 mU/liter); thyroid nodules in a normal-sized or enlarged thyroid; at least one nodule (>20% of volume with cystic change) with 1.0 cm diameter or greater; for nodules greater than 1.0 cm, the diagnosis must be performed according to the guidelines for diagnostic standards of thyroid disorders to exclude malignancy (24).

Exclusion criteria included the following: thyroid therapy within the last 3 yr; known focal or diffuse autonomous thyroid structure; presence of thyroid cysts; contraindication to iodine; concomitant treatment with iodine-containing medication (i.e., amiodarone) or use of iodine-containing contrast medium within the last 6 wk; presence of thyroid peroxidase antibodies (maximum twice the normal value) or known autoimmune thyrotopathy; symptomatic coronary heart disease; endocrine orbitopathy; former radioiodine therapy or surgery; any acute illness or allergy; known pregnancy at time of screening; dermatitis herpetiformis; or pathological laboratory results.
Important changes to inclusion criteria after trial commencements

Age limits changed from 18–55 to 18–65 yr; initial thyroid volume changed from enlarged to normal or enlarged [Amendment 2 (04-09-29)].

Randomization

Centerwise randomization sequences with variable block lengths were generated by the study statistician and sent to the pharmacy that produced unlabeled coded medication packages for the total follow-up period with sufficient medication for the titration process to guarantee concealment and blindness. However, because only licensed drugs were used, the patient but not the physician could have found out what group she/he is in by visiting a pharmacy and comparing his pills with the available drugs.

Visits

Five visits were performed: screening (V1), randomization (V2), and three follow-up visits under therapy after 3 (V3), 6 (V4), and 12 months (V5). Study procedures are listed in Supplemental Table 1.

At each visit sonography was performed with a 7.5- or 10-MHz transducer. Goiter and nodule volumes were calculated by the published method of Brunn et al. (25). All ultrasound images with measurements were photographed and archived as source data.

TSH was measured at V2, V3, V4, and V5 in a central laboratory (luminescence assay, Immulite 2000; Siemens, Erlangen, Germany) under regular external quality control.

Thyroid peroxidase antibodies and clinical laboratory values (at V1 and V5) were measured in the laboratories of the study centers.

Iodine concentration of spot urine was measured centrally at V2 and V5 using a sensitive and specific HPLC method (26).

Medication and adaption of T4 dose

The patients were randomized centrally and assigned at V2 to one of the following four parallel groups: P, placebo; I, 150 µg potassium iodide per day; T4, 75 µg levothyroxine per day; T4+I, combination of 75 µg levothyroxine and 150 µg potassium iodide per day.

At V2 through V5, blood for measurement of TSH was sent to the central laboratory. At V3 and V4, physicians and patients were advised to continue the current medication. After determination of TSH at V3, the central laboratory communicated the results to the Clinical Research Organization and proposed a dose adaptation in the T4 and T4+I arms (if TSH was out of aimed range) or the continuation of the dose (if TSH was in range) by identification of the next-numbered drug package to be used. In the T4 and T4+I arms, if TSH was less than 0.2 mU/liter, the T4 dose was reduced to 50 µg/d, whereas if TSH was greater than 0.8 mU/liter, the T4 dose was increased to 100 µg/d. In the I and P arm, the medication was not changed, but an adaptation was simulated to keep investigators and patients blind. At each follow-up visit, unused medication was collected and counted to estimate patient compliance.

In 38 patients, who stopped medication because of serious adverse events (e.g. hospitalization because of accidents, etc.), no causal relationship to the medication was assumed by the investigators.

Possible drug-related serious adverse events

Two patients developed atrial fibrillations: both belonged to the P group.

Quality controls

Monitoring

In accordance with International Conference on Harmonization Good Clinical Practice guidelines, the study was monitored by the CRO in regular intervals; the monitors had direct access to the investigator's source documentation to verify consistency and accuracy of the data recorded in the case record forms. The written ultrasound report of the thyroidologist was taken as source documentation.

Sonography

Volumetry by ultrasound is the primary objective of the trial; therefore, two thyroid phantoms with two lobes and six nodules of unknown volume (27) were shipped to the study centers, which were asked to measure the volumes in a blind manner. Of these measurements, total nodular volume per test lobe and lobe volume were calculated using the same formula as they were used for the primary and secondary outcome of the trial. The resulting estimates of the coefficient of variation were 10.9% [95% confidence interval (CI) 7.1–17.0%] or 11.1% (95% CI 6.9–18.2%) for differences of repeated measurements of total nodular volume or thyroid volume, respectively, by the same physician with the same equipment in the same thyroid phantom.

The TSH luminescence assay was regularly controlled by external quality controls.

Statistics

Baseline determinations were compared between randomization groups by one-way ANOVA or χ² tests. Total nodule volumes were log transformed. The primary outcome was calculated as the difference between the last observation within the 12-month follow-up period and the baseline observation of the same patient. This approach was chosen to preserve the intention-to-treat approach. It is equivalent to change from baseline to 12-month determination in which missing values were conservatively imputed by the last observation carried forward as it was defined in the study protocol. The primary analysis then consisted of the calculation of six pairwise t tests for direct comparison of treatment group. P values were adjusted for multiplicity of comparisons by applying the closure test procedure (28) to keep an experiment-wise type I error rate of 5%. A justification of this approach is given in the Supplemental Appendix II. In an additional post hoc analysis, a two-way ANOVA with the factors iodine and T4 was performed in the total analysis population to study the interaction of the two components for a better understanding of the effect of the combined therapy. We present the results by reporting adjusted P values along with raw (unadjusted) P values and estimates of percent change of total nodule volumes with unadjusted 95% CI for the illustration of effect sizes. Furthermore, sensitivity analyses were performed to study whether methodological decisions were crucial for the result of the trial (reported in Supplemental Appendix II and III).
Table 1: Patient characteristics of the LISA analysis population according to randomization groups, presented as absolute frequencies and percentages or arithmetic means with symmetric 95% CI

|                          | Placebo (n = 199) | Iodine (n = 198) | T4 (n = 206) | T4+Iodine (n = 191) | P value |
|--------------------------|-------------------|------------------|--------------|---------------------|---------|
| Male gender              | 52 (26.1%)        | 56 (28.3%)       | 59 (28.6%)   | 61 (31.9%)          | 0.651   |
| Age                      | 46.1 [44.6–47.5]  | 47.0 [45.6–48.4] | 47.1 [45.7–48.5] | 47.4 [46.1–48.8] | 0.570   |
| Family history           | 87 (43.7%)        | 74 (37.4%)       | 84 (40.8%)   | 68 (35.6%)          | 0.360   |
| Concomitant disease      | 120 (60.3%)       | 139 (70.2%)      | 128 (62.1%)  | 120 (62.8%)         | 0.180   |
| BMI                      | 27.0 [26.3–27.8]  | 27.3 [26.6–28.1] | 27.3 [26.6–27.9] | 27.0 [26.2–27.7] | 0.871   |
| Thyroid volume (ml)      | 18.6 [17.2–20.2]  | 18.2 [17.6–19.8] | 18.9 [17.4–20.5] | 18.8 [17.2–20.5] | 0.932   |
| Volume of nodules (ml)   | 1.67 [1.43–1.94]  | 1.72 [1.49–1.98] | 1.47 [1.26–1.72] | 1.96 [1.67–2.30] | 0.075   |
| Number of nodules        | 1.54 [1.42–1.67]  | 1.62 [1.51–1.74] | 1.67 [1.55–1.80] | 1.64 [1.50–1.78] | 0.512   |
| Largest nodule <20% cystic | 14.1%            | 17.7%            | 20.9%        | 22.5%               | 0.145   |
| TSH (mU/liter)           | 4.01 [2.90–5.11]  | 4.01 [2.90–5.11] | 4.01 [2.90–5.11] | 4.01 [2.90–5.11] | 1.000   |
| Iodine excretion (µg/liter) | 49.7 [43.0–57.6] | 59.5 [51.1–69.4] | 52.2 [46.4–58.8] | 53.7 [47.5–60.8] | 0.062   |

P values relate to one-way ANOVA (F tests) or χ² tests. BMI, Body mass index.

The secondary analysis on thyroid volume or number of nodules was performed with the same test strategy as the primary analysis. Thyroid volumes were log transformed. Echogenicity distributions were compared by χ² tests.

The association of total nodule volume changes, thyroid volume changes, and treatment effects with variables suggested to be influential on these outcomes was studied with multilevel models. We explored the involvement of the following variable: age, gender, family history, body mass index, baseline TSH greater than 1.0 mU/liter, baseline urine I-excretion I less than 100 µg/liter, baseline thyroid volume greater than 25 ml for men and greater than 18 ml for women, baseline nodular volume greater than 2 ml, the presence of multiple nodules at baseline, and less than 20% cystic largest nodules. Details of the statistical methodology are reported in Supplemental Appendix II.

Results

Analysis populations

One thousand two hundred forty-five consecutive patients with nodular goiter were screened. A total of 1020 patients in 60 centers were randomized (patient flow: Supplemental Fig. 1). Of the randomized patients, seven patients did not receive any dose of the study medication. In another 47 patients, the quantification of nodule sizes at screening or at baseline was insufficient or failed to demonstrate nodules of the required minimum diameter. These patients could not be used for analysis because no reliable reference value was available to determine the changes. Before breaking the blind, a data quality review showed a clustering of out-of-range values of the primary end point in two centers. Because an additional monitoring visit revealed an only fragmentary photographic documentation of sonography results and did not dispel doubts on the validity of measurements, the data of all 172 patients, recruited at these centers were not used for the analysis, after a blind decision of the steering committee.

Thus, the primary analysis was performed in the remaining 794 patients. However, a sensitivity analysis in all 1013 patients who received at least one dose of study medication was performed to study whether the inclusion of these patients would have changed the results. For exploration of potential predictors of outcome or effect modification, a complete case analysis population of 600 patients was used.

Patients

Patient characteristics are listed in Table 1: No significant differences were found with respect to demography, thyroid or other diseases, or initial iodine excretion. However, there was a nonsignificant trend toward higher initial iodine excretion in the iodine group and to smaller nodule volumes in the T4 group.

T4 dose adaptation and change in TSH levels

On average, the target ranges of T4 and T4+I treatment as defined in the study protocol were met after dose adaptation (Fig. 1A). Supplemental Table 2 shows the percentages of patients below, within, or above the TSH target range (0.2–0.8 mU/liter) according to visits and treatment.

Change in iodine excretion

Iodine excretion increased significantly over the complete study period in all four treatment groups (Fig. 1B and Table 2). The increase was largest in the two groups with iodine medication, and the differences of I to T4 and T4+I to P and T4 were significant.

Primary objective: change in total nodular volume

Figure 2 (black lines) and Table 2 show the average reductions of the total nodular volume. Significant reductions were observed in the three active treatment groups. However, a nonsignificant trend toward lower values was
even seen in P patients. Compared with the initial volume at V2 up to V5, mean volumes were reduced to \(-5.2\%\) under P, \(-9.0\%\) under I, \(-12.1\%\) under T\(_4\), and \(-21.6\%\) under T\(_4\)+I. Compared with P, nodular volume reductions were \(-17.3\%\) (95\% CI \(-24.8\%/-9.0\%\), multiplicity adjusted \(P < 0.001\)) in the T\(_4\)+I group, \(-7.3\%\) (95\% CI \(-15.0\%/+1.2\%\), \(P = 0.201\)) in the T\(_4\) group, \(-4.0\%\) (95\% CI \(-11.4\%/+4.2\%\), \(P = 0.328\)) in the I group. In direct comparison, the T\(_4\)+I therapy was significantly superior to T\(_4\) (\(P = 0.018\)) or I (\(P = 0.003\)). Figure 1C shows the development of the average decrease from visit to visit. The nodular volume reduction in the T\(_4\)+I group developed gradually and did not come to an end during the observation period. Individual changes were remarkably heterogenous (Fig. 3A). As a result of this high variability, between 42.2\% (P) and 26.7\% (T\(_4\)+I) of patients revealed increases in total nodular volumes, although the average volumes decreased (Supplemental Table 3).

Additionally the courses of all (1433) individual nodules were evaluated. Decreases of more than 50\% were
TABLE 2. Change of iodine excretion, nodule and thyroid volumes, and number of nodules from baseline to end of follow-up within 1 yr by randomization group

| Change from baseline (%) | Placebo (basis), % | *P*raw | *P*adjusted | *I* (basis), % | *P*raw | *P*adjusted | *T*4 (basis), % | *P*raw | *P*adjusted |
|--------------------------|-------------------|--------|-------------|----------------|--------|-------------|----------------|--------|-------------|
| Iodine excretion         |                   |        |             |                |        |             |                |        |             |
| P                        | 34.53             |        |             | 0.069          |        |             |                |        |             |
| [14.14; 54.92]           |                   |        |             |                |        |             |                |        |             |
| I                        | 63.84             |        |             | 0.069          |        |             |                |        |             |
| [39.49; 88.20]           |                   |        |             |                |        |             |                |        |             |
| T4                       | 27.16             |        |             | 0.594          | -36.68| 0.017       |                |        |             |
| [9.03; 45.28]            |                   |        |             |                |        |             |                |        |             |
| I+T4                     | 88.06             | 53.54  | <0.001      | 24.22          | 0.143 | 60.90       | <0.001         |        |             |
| [66.55; 109.57]          | [24.04; 83.03]    |        |             |                |        |             |                |        |             |
| Nodule volume            |                   |        |             |                |        |             |                |        |             |
| P                        | -5.2              |        |             | 0.328          |        |             |                |        |             |
| [-11.0; 0.9]             |                   |        |             |                |        |             |                |        |             |
| I                        | -9.0              | -3.96  | 0.328       |                |        |             |                |        |             |
| [-13.6; -4.1]            | [-11.4; 4.16]     |        |             |                |        |             |                |        |             |
| T4                       | -7.29             |        |             | 0.392          |        |             |                |        |             |
| [-15.04; 1.18]           | [-10.97; 4.67]    |        |             |                |        |             |                |        |             |
| I+T4                     | -17.26            | <0.001 | -13.85      | 0.011          | -10.76| 0.018       |                |        |             |
| [-27.1; -15.7]           | [-24.75; -9.03]   |        |             |                |        |             |                |        |             |
| Thyroid volume           |                   |        |             |                |        |             |                |        |             |
| P                        | -1.9              |        |             | 0.207          |        |             |                |        |             |
| [-4.4; 0.6]              |                   |        |             |                |        |             |                |        |             |
| I                        | -4.4              | -2.47  | 0.207       |                |        |             |                |        |             |
| [-7.2; -1.5]             | [-6.19; 1.39]     |        |             |                |        |             |                |        |             |
| T4                       | -5.22             |        |             | 0.162          |        |             |                |        |             |
| [-8.67; -1.63]           | [-6.63; 1.15]     |        |             |                |        |             |                |        |             |
| I+T4                     | -7.94             | <0.001 | -5.61       | 0.103          | -2.78 | 0.190       |                |        |             |
| [-12.8; -6.5]            | [-11.78; -3.93]   |        |             |                |        |             |                |        |             |
| Number of nodules        |                   |        |             |                |        |             |                |        |             |
| P                        | 0.070             |        |             | 0.488          |        |             |                |        |             |
| [-0.006; 0.147]          |                   |        |             |                |        |             |                |        |             |
| I                        | 0.035             | 0.035  | 0.488       |                |        |             |                |        |             |
| [-0.028; 0.099]          | [-0.134; 0.064]   |        |             |                |        |             |                |        |             |
| T4                       | -0.005            | -0.075 | 0.463       |                |        |             |                |        |             |
| [-0.091; 0.081]          | [-0.190; 0.040]   |        |             |                |        |             |                |        |             |
| I+T4                     | -0.097            | 0.103  | 0.264       |                |        |             |                |        |             |
| [-0.115; 0.062]          | [-0.213; 0.020]   |        |             |                |        |             |                |        |             |

Analysis is intention to treat; missing values are imputed by last observation carried forward. Pairwise *t* tests with nominal (raw) *P* values (upper entry) followed by *P* values resulting from a closure test that corrects for the multiplicity of comparisons (lower entry). Multiplicity corrected significant results are in bold. Comparisonwise 95% confidence intervals are in brackets.

seen in 8.5/9.5/7.6/11.3% of the nodules evaluated in the P/I/T4/T4+I group, respectively.

**Secondary objective: change in thyroid volume and number or echogenicity of nodules**

Figure 2 (gray lines) and Table 2 show the average reductions of the thyroid volume. As with total nodule volume, significant reductions compared with V2 were observed in the three active treatment groups but to a lesser extent. Reductions were significantly more pronounced with T4+I than with P or I and with T4 than with P. The thyroid volume reduction with T4+I and T4 developed gradually in a similar manner to the total nodule volume reduction but was less pronounced (Fig. 1D). Individual changes in thyroid volumes were heterogeneous but less variable than the changes in total nodular volumes (Fig. 3B). Nevertheless, in some patients thyroid volumes increased over the follow-up period.

Table 2 shows the change in number of nodules. The number increased with P or I and decreased with T4 and T4+I. However, changes from baseline or differences between groups were not significant. No group differences were found with respect to echogenicity.

**Association of baseline determinations with outcome or treatment effects**

None of the covariates studied was predictive of total nodular volume reduction (Fig. 4, left panel) or modified
the effect of T4+I therapy compared with placebo or iodine. Thyroid volume reduction (Fig. 4, right panel) was more pronounced in patients with large thyroids, i.e. baseline thyroid volume greater than 25 ml for men and greater than 18 ml for women (change to baseline of large thyroid compared with normal: −8.4%, 95% CI −11.4/−5.4%, \( P < 0.001 \)), with TSH greater than 1.0 (change to baseline TSH > 1.0 vs. TSH ≤ 1.0: −5.3%, 95% CI −8.1/−2.5%, \( P < 0.001 \)) and in older patients (change to baseline −1.8% per 10 yr of age, 95% CI −3.2/−0.3%, \( P = 0.016 \)). In patients with a larger body mass index, the reductions were smaller (change to baseline +1.6% per 5 kg/m\(^2\), 95% CI +0.2/+3.0%, \( P = 0.023 \)). These effects were independent of treatment. No covariate that modified the effect of T4 or T4+I therapy compared with placebo was found.

**Discussion**

This is the first sufficiently powered trial on the medical treatment of nodular goiter with nonsuppressive levothyroxine and/or iodine compared with placebo. It demonstrates that in formerly iodine-deficient Germany, the volume of benign nodules greater than 1 cm in diameter is significantly more reduced by only partly TSH-suppressive T4 doses in combination with iodine than by T4 alone, iodine alone or placebo (Table 2 and Fig. 2). The average decrease of volumes is smooth and continues to the end of the observation period (Fig. 1C). This could be a result of the low proliferation rate of thyroid epithelial cells or the slow growth of thyroid nodules (29). No significant ad-
vantage over placebo could be established for any of the other treatments.

Individual changes of nodular volume were remarkably heterogeneous (Fig. 3A). Although the coefficient of variation of thyroid volume changes was about the same as that anticipated on the basis of previous data, the coefficient of variation of nodular volume changes was more than double. Even with T4+I, nodular volume increased in 25% of patients, whereas 16% showed volume decreases greater than 50%, also suggesting heterogeneity of responses and/or pathophysiology (Supplemental Table 3).

The intraobserver variability of thyroid nodule volume measurements observed in parallel phantom measurements was high (11%), as previously demonstrated by Brauer et al. (30), thus providing good reason to investigate much higher numbers of patients per group than those enrolled in any previous (lesser powered) trials.

Of note for the design of future studies, several assumptions of our sample size calculation that were based on our experience with total thyroid volumes did not apply to nodular volumes. Due to the unexpectedly wide heterogeneity in nodule volume changes and the reduction of sample size through the exclusion of two centers, the trial was in fact underpowered to detect the assumed 10% change. However, due to the larger-than-expected mean reductions in the nodule volume (exceeding the lowering of thyroid volume reduction by more than twice), the study was sufficiently powered for both end points.

No simultaneous analysis of thyroid nodule and thyroid volume changes in response to treatment has been published to date. It is worth noting that several other factors discussed in the literature (such as family history, body mass index, initial thyroid or nodule volume, and multiplicity of nodules) were found not to be associated with the extent of nodule volume reduction (Fig. 4). Furthermore, no subgroup could be identified with larger or smaller treatment effects on nodular volume. In a post hoc analysis, we further studied whether changes in TSH levels and/or iodine excretion were mediators that could explain the heterogeneity in nodular volume changes or the differential treatment effect of T4+I. The analysis was inconclusive (data not shown). Thus, the mechanism underlying our findings could not be explained on statistical grounds.

One possible explanation is offered by the finding that the patients with thyroid nodules included in our trial were clearly iodine deficient (mean urinary iodine excretion 49.7–59.5 μg/liter, Table 1), whereas the recently surveyed German population met the World Health Organization criteria for sufficient iodine supply overall with a mean urinary iodine excretion of 132 μg/liter (32). This is an important argument for the iodine component of the T4+I treatment. Moreover, similar differences in iodine excretion may also be relevant to the etiology of thyroid nodules in other iodine-sufficient countries (33). Given the mean urinary iodine concentration of 164 μg/d determined from the National Health and Nutrition Examination Survey database (34) and assuming similar differences in urinary iodine concentration between the general population and patients with thyroid nodules in North America, patients with thyroid nodules in North America could also be largely iodine deficient [8.8 ± 0.4% of the National Health and Nutrition Examination Survey population were found to have an iodine excretion lower than 50 μg/d (and 28.2 ± 1.2% lower than 100 μg/d) in 2007–2008 (34)]. It would then be important to know whether in areas with better overall iodine supply than Germany, patients with thyroid nodules also constitute a subgroup with lower urinary iodine excretion and probably less efficient iodine conservation mechanisms, arising from some genetic predisposition.

Iodine medication normalized the iodine excretion in the two iodine-taking groups. Iodine excretion also increased in the T4 and placebo groups, probably due to a
greater awareness among the patients of the issue of nutritional iodine intake.

TSH adaptation worked in the two T4 groups as intended (Fig. 1A), suggesting the feasibility of subtle TSH-decreasing treatment with low T4 doses (Supplemental Table 2). Together with the similar findings of Koc et al. (22), this is important because it suggests that the complete suppression of TSH by high thyroid hormone doses, which owing to their various side effects are no longer acceptable, is not necessary.

Taken together, the results of this large trial on the medical treatment of nodular goiter will provide the clinician with additional valuable arguments for or against a medical therapy of the individual patient with a nodular goiter. Although limited by its 1 yr duration and lack of data regarding changes of the patient’s nodule-related symptoms, our study together with previous data (12) suggests to treat patients with thyroid nodules with T4 +I to limit nodule size and to prevent further thyroid nodules. Whether the finding that only the (nonsuppressive) T4 +I combination resulted in a significant thyroid nodule volume decrease can be explained by the additional iodine intake alone or an unknown genuine T4-I interaction will need further research.

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